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Rapport in het kort

Gezondheidswinst door beleidsmaatregelen voor chemische stoffen in consumentenproducten

Beleidsmaatregelen op chemische stoffen in consumentenproducten leiden tot minder blootstelling aan deze stoffen bij mensen. Maar in hoeverre zijn deze maatregelen effectief om gezondheidseffecten te verminderen? Voor het eerst is van negen stoffen in consumentenproducten berekend hoe groot de gevolgen zijn voor de gezondheid. Inderdaad mag voor de meeste van deze stoffen worden verwacht dat minder Nederlanders negatieve gezondheidseffecten zullen ondervinden. Dit blijkt uit onderzoek van het RIVM en TNO Kwaliteit van Leven, in opdracht van het ministerie van Volksgezondheid, Welzijn en Sport (VWS).

De gezondheidswinst is uitgedrukt in 'Disability Adjusted Life Years' (DALY's). Het aantal DALY's is het aantal gezonde levensjaren dat een bevolking verliest als gevolg van ziekte of vroegtijdig overlijden.

Het onderzoek heeft ook duidelijk gemaakt dat het niet zonder meer mogelijk is gezondheidseffecten voor de bevolking te berekenen, ondanks uitgebreide kennis en ervaring met de risicobeoordeling van stoffen. Bepaalde schadelijke effecten die in proefdieren zijn waargenomen, zijn zeer geschikt voor risicobeoordeling en normstelling, maar zijn niet direct te vertalen naar 'ziekte' bij mensen. Ook het tijdstip waarop een 'ziekte' zich manifesteert is moeilijk vast te stellen. Soortgelijke berekeningen zouden vooral gebruikt moeten worden om prioriteiten bij maatregelen te stellen: onderscheid wordt gemaakt tussen beleidsmaatregelen die erg weinig en die veel gezondheidswinst opleveren. Behalve DALY's zijn andere aspecten van belang voor het beleid, zoals de afname van de blootstelling aan de stof, het aantal betrokken consumenten, maatschappelijke consequenties en de perceptie van het risico bij de consument.

Trefwoorden: chemische stoffen, consumentenproducten, blootstelling, gezondheidswinst, risicobeoordeling, wetgeving.

Abstract

Health impact assessment of policy measures for chemicals in non-food consumer products

Policy measures are responsible for the reduction of consumer exposure to chemicals in consumer products. The effectivity of these policy measures in terms of actually reducing human health effects, is however unknown. It is the first time that, for nine chemicals used in consumer products, the impact on human health as a result of policy measures has been quantified. In most cases, the implementation of policy measures indeed can reasonably be expected to lead to a smaller population having fewer adverse health effects. This conclusion was based on a cooperative study of RIVM and TNO Quality of Life, under the authority of the Ministry of Health, Welfare and Sports.

The human health gain was expressed in terms of the 'Disability Adjusted Life Years' (DALY). The number of DALYs is determined by the sum of the number of years of life lost and the number of years living with disability for the population of interest.

The study also showed that adequate prediction of the health effects in the population is quite difficult, even though extensive knowledge and experience in the field of chemical risk assessment is available. Some observed adverse health effects in laboratory animals, which are highly suitable for the use in risk assessment and limit setting, cannot be directly translated to an 'illness' in humans. Moreover, the time of onset of the 'illness' is hard to define. Therefore, it is advised to policy makers to use health impact assessments only for priority setting amongst policy measures; making the distinction between policy measures that contribute very little or very much to health impacts. In addition, it is advised to consider other aspects next to the use of DALYs. For instance, providing information on the reduction of exposure, the frequency of health effects, and perception of the risk by consumers is considered very important.

Key words: chemicals, consumer products, exposure, health, gain, risk assessment, policy measures, legislation.

Preface

We like to thank the supporting committee for their contribution in the discussions, valuable ideas and suggestions for improvement:

Dr. M.E.J. van der Weiden	Ministerie van VWS
Dr. ir. P.C. Bragt	Voedsel en Warenautoriteit (VWA)
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Samenvatting

De Nederlandse bevolking gebruikt dagelijks tal van consumentenartikelen die chemische stoffen bevatten. Tijdens het gebruik kunnen mensen aan deze stoffen blootgesteld worden. Bescherming van de consument vindt plaats door middel van het uitvoeren van risicoreducerende beoordelingen binnen verschillende wettelijke kaders, en eventueel daarop volgende risicoreductiemaatregelen, zoals een limiet voor of een verbod van een bepaalde stof. Risicoreducerende maatregelen worden soms ook genomen vanwege maatschappelijke of politieke commotie, ongewenste blootstelling van een potentieel gevoelige groep, of het voorkomen (of terugdringen) van ongewenste chemische stoffen in consumentenproducten.

Het ministerie van VWS wil graag weten welke veranderingen in blootstelling en gezondheid van de Nederlandse bevolking het gevolg zijn van risicoreducerende beleidsmaatregelen voor chemische stoffen in non-food consumentenproducten. De effectiviteit van dergelijke maatregelen is tot op heden nog nooit gekwantificeerd.

Het doel van dit project was om de totale gezondheidswinst te berekenen van genomen of nog te nemen maatregelen voor het terugdringen van chemische stoffen in non-food consumentenproducten. Vanaf het begin van het project was duidelijk dat dit een zeer ambitieuze opdracht was.

Eerst is een inventarisatie gemaakt van eerder uitgevoerde studies, waarbij op het terrein van voeding, milieu, en arbeid een gezondheidswinstberekening is gemaakt gericht op chemische stoffen. De aanpak of methodiek uit deze studies bleek echter niet bruikbaar om de totale gezondheidswinst te berekenen voor non-food consumentenproducten.

Vervolgens is geprobeerd voor een beperkt aantal stoffen en stofgroepen de potentiële gezondheidswinst ten gevolge van een beleidsmaatregel uit te rekenen. Bij de selectie van stoffen werd gestreefd naar spreiding in:

1. toxische eigenschappen van stoffen (Carcinogeen, Mutageen, Reproductietoxisch en Sensibiliserend: CMRS);
2. categorieën van consumentenproducten (zoals cosmetica, textiel, doe-het-zelf-producten, schoonmaakmiddelen, wasmiddelen);
3. het bijbehorende blootstellingspatroon (kortdurend/incidenteel of chronisch).

Verder speelden beschikbaarheid van blootstellings- en toxiciteitsgegevens (humane of dierexperimentele) mee bij de keuze van de stof, en – uiteraard – het van toepassing zijn van een wettelijke beleidsmaatregel (reeds genomen of in voorbereiding).

Uiteindelijk werden negen stoffen of stofgroepen gekozen. Tussen haakjes is aangegeven op welke producten de geëvalueerde beleidsmaatregelen betrekking hadden. Acrylamide (cosmetica), azokleurstoffen (textiel en tatoeages), dichloormethaan (doe-het-zelfproducten), formaldehyde (spaanplaat, textiel en cosmetica), lampolie (voorkoming

van vergiftiging na drinken), nikkel (legeringen voor producten met huidcontact), nitrosamines (spenen, ballonnen en cosmetica), tolueen (lijm, en verf die verspoten wordt) en Vluchtige Organische Stoffen (VOS; verven en lakken).

Ondanks dat de gevolgde methodiek voor het vaststellen van het effect van de beleidsmaatregel voor de negen stoffen/stofgroepen in detail van elkaar verschilden, bestond deze telkens uit de volgende vier stappen:

1. Bepaling van de blootstelling:

Hierbij werd gebruik gemaakt van gemeten data of anders van aannames over de hoeveelheid stof in het product, frequentie en duur van blootstelling, enzovoort. De omvang van de blootgestelde populatie werd ook geschat. Om een beeld te geven van de totale context van de beleidsmaatregel werd waar mogelijk ook de blootstelling via andere bronnen aan de betreffende stof geschat.

2. Uitvoering van een risicobeoordeling:

Hierbij wordt een inschatting gegeven van het verschil in de veiligheidsmarge voor en na de beleidsmaatregel; dat wil zeggen de marge tussen het (no) effect niveau en de geschatte blootstelling voor en na de beleidsmaatregel.

3. Bepaling van de gezondheidswinst:

Met behulp van de informatie uit de stappen 1 en 2 werd geprobeerd de incidentie van het effect of de ziekte vast te stellen voor en na de beleidsmaatregel.

4. Normering van de gezondheidswinst in DALY's:

De gezondheidswinst werd uitgedrukt in 'Disability Adjusted Life Years' (DALY's), wat staat voor het aantal gezonde levensjaren dat een populatie verliest door ziekte en sterfte, uitgedrukt in eenheid per jaar. Met behulp van DALY's kunnen ziekten onderling vergeleken worden als het gaat om hun invloed op de gezondheid van de mens. In deze maat komen drie belangrijke gezondheidsaspecten terug, te weten 'kwantiteit' (levensduur) en 'kwaliteit' van leven, en het aantal personen dat een effect ondervindt.

In dit rapport wordt voor de eerste keer de (potentiële) verandering in blootstelling en gezondheid van een genomen maatregel voor een chemische stof in een consumentenproduct kwantitatief berekend. De mate waarin dit mogelijk is, is afhankelijk van beschikbare gegevens en beschikbare kennis.
De totale impact op de gezondheid van beleidsmaatregelen voor stoffen in consumentenproducten zal zeker hoger zijn dan de som van de geselecteerde stoffen in de voorbeelden in dit rapport omdat er slechts een negental cases in dit project zijn onderzocht.

Resultaten uit de voorbeeldstudies laten zien dat de beleidsmaatregelen voor alle bestudeerde stoffen tot een behoorlijke afname van de blootstelling aan deze stof leiden. Hierbij werd wel in een aantal gevallen verondersteld dat na de beleidsmaatregel de resterende blootstelling verwaarloosbaar is (en dus als nul wordt beschouwd).
Voor de Nederlandse populatie leidde deze blootstellingsreductie in de meeste gevallen tot een afname in het potentieel aantal mensen met negatieve gezondheidseffecten. Op basis van berekeningen van de potentiële gezondheidswinst, uitgedrukt in DALY's, werd het effect van een maatregel bekeken.

De huidige nikkelwetgeving ten aanzien van contacteczeem lijkt succesvol, want zij levert een potentiële gezondheidswinst van 3000 DALY op. Hierbij moet overigens bedacht worden dat de totale ziektelast aan contacteczeem ongeveer 30.000 DALY's bedraagt. Voor beleidsmaatregelen met kortdurende, incidentele blootstelling aan de chemische stof zoals bij doe-het-zelf producten (dichloormethaan, tolueen, VOS) werd voor elk een gezondheidswinst van rond de honderd DALY's gevonden. In het geval van lampolie-intoxicatie was het effect van de maatregel een afname in het aantal meldingen hoewel dit slechts resulteerde in een gezondheidswinst van één DALY. Het aantal berekende DALY's voor beleidsmaatregelen gericht op kankerverwekkende verbindingen loopt uiteen van nihil (formaldehyde), een paar (nitrosamines, gebaseerd op dierstudies), tot in de honderd (acrylamide) of duizenden (azokleurstoffen en nitrosamines, gebaseerd op humane data). Deze verschillen in aantallen DALY's worden veroorzaakt door de mate van blootstelling, de potentie van de kankerverwekkende verbinding, de grootte van de gebruikerspopulatie van het type product of, zoals in het geval van de nitrosamines, de gebruikte toxiciteitsgegevens. Ter vergelijking, de berekende jaarlijkse ziektelast in Nederland (Nationaal Kompas) voor zeven soorten kanker samen bedraagt ongeveer 400.000 DALY's.

Het gebruik van het DALY-concept voor deze gezondheidswinstberekening kan voor waardevolle inzichten zorgen in het beoordelen van de effectiviteit van mogelijke verschillende interventies.
Tijdens de uitvoering van dit project is echter ondervonden dat de ervaring en uitgebreide kennis van de risicobeoordeling van stoffen niet direct omgezet kan worden in een methodiek (of systematiek) die de gezondheidseffecten van blootstelling adequaat kan voorspellen. Het blijkt soms moeilijk om voor bepaalde effectparameters die wél bruikbaar zijn in de normstelling en risicobeoordeling van chemische stoffen, een vertaling te maken naar 'ziekte' bij de mens.
In veel gevallen bleek de betrouwbaarheid van de gezondheidswinstberekening niet erg hoog in de door ons bestudeerde case-studies. Afhankelijk van de stof en maatregel wordt de betrouwbaarheid van de gezondheidswinstberekening in meer of mindere mate beïnvloed door onzekerheden in de drie onderliggende stappen: de blootstellingschatting, de effectbeoordeling en de extrapolaties naar DALY waardes. Geadviseerd wordt daarom om deze en vergelijkbare berekeningen alleen als onderbouwing van beleid te gebruiken als er sprake is van absoluut gezien grote gezondheidswinst of grote verschillen tussen maatregelen. Daarnaast wordt aangeraden naast DALY's ook andere parameters zoals afname van blootstelling of incidentie en risicoperceptie in de evaluatie of de afweging voor het nemen van een beleidsmaatregel mee te nemen.

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Summary

Using consumer products, the Dutch population is potentially exposed to many chemicals. Protection of consumers is managed by performing risk assessments in different legal frameworks. If necessary, risk reduction strategies are set up resulting in limitations or bans of chemicals in specific products. Risk reduction measures are sometimes also initiated for other reasons: social or political commotion, exposure of a (potentially) sensitive target population, or prevention of the presence of undesirable substances in consumer products.

The Ministry of Health, Welfare and Sport likes to know the effect of risk reduction measures on exposure and health of the Dutch population. Up till now, the impact on human health of the implementation of these policy measures is not quantified.

The principal starting point for this project is to quantitatively estimate the potential health gain resulting from policy measures taken in the past and to be taken in the future for chemicals in consumer products. From the start of this project it was clear that this goal was very ambitious.

At first, an inventory of existing studies in the food, environmental and occupational field was performed in an attempt to explore the possibility of extrapolating study results to consumer products. The approach or methodology used were not useful to quantify the total health impact of all policy measures on chemicals in consumer products.

Next, it was tried for a selected number of chemicals to quantify the potential health gain as a result of policy measures. Cases were selected aiming at a distribution in:

1. various toxic properties (Carcinogenic, Mutagenic, Reproduction toxic, Sensitizing: CMRS);
2. categories of consumer products (cosmetics, textiles, do-it-yourself products, cleaning agents, detergents, and so on);
3. the corresponding exposure times (acute or chronic).

Furthermore, the availability of exposure data, and presence of sufficient (human or animal) toxicological data were of importance in choosing substances, and – of course- the presence of legislation (present or in the future),

Ultimately, the following nine substances were chosen. Between brackets it is indicated for which product the policy measure is implemented. Acrylamide (cosmetics), azo-dyes (textile and tattoos), dichloromethane (do-it-yourself products), formaldehyde (chipboard, textiles and cosmetics), lamp oil (prevention of intoxication), nickel (nickel releasing alloys in products in contact with skin), nitrosamines (teats and soothers, cosmetics and balloons), toluene (adhesives and spraying paint) and Volatile Organic Compounds (VOC; paints and varnishes).

The methodology used for the quantification of the effect of the policy measure differed in detail between the various substances, but always consisted of the following four steps:

1. Estimation of the exposure:

Measured or estimated (assumed) data on the amount of substance in the product, frequency and duration of exposure, and so on, were used. The size of the exposed target population was also estimated. To give an idea of the context of the policy measure, the exposure to the substance through other sources was also estimated if possible.

2. A risk assessment was performed:

An estimation is given on the difference in margin of safety before and after the policy measure, meaning the margin between the (no) effect level and the estimated exposure before and after the policy measure.

3. Estimation of the health gain

With the information from steps 1 and 2, an effort was made to establish the change in incidence of effect/disease before and after the implementation of the policy measure.

4. Expression of the health gain in DALYs:

The health gain was expressed in 'Disability Adjusted Life Years' (DALYs) which is equivalent to the number of healthy life years lost by disease in a population. When using DALYs, various diseases can be compared for their influence on public health. This index reflects three important aspects of public health: 'quantity' (length of life) and 'quality' of life, and the number of people affected.

In this report, for the first time the (potential) health impact of an implemented policy measure on a chemical in a consumer product is quantitatively determined. To what extent this is possible is dependent on the availability of data and existing knowledge.
It should be noted that the total health impact of all consumer product policy on chemicals will undoubtedly be higher than the sum of health impacts of the selected examples, presented in this report, because only nine cases were included.

Results from these case studies show an effect on the levels of exposure, which was in most cases largely decreased. It should be reminded that the '% decrease' is often 100% because it was assumed that exposure after the measure was negligible (and thus counted as zero).
For the Dutch population this exposure reduction resulted in most of the cases in a decrease in the potential number of people with health effects. On the basis of the calculations of the potential health gain, expressed in DALYs, the effect of a policy measure is assessed.
The so-called Nickel Directive regarding contact eczema seemed to result in a successfully high level of health gain, resulting in a health gain of 3000 DALYs. It is noted that the burden of disease of contact eczema in the Netherlands (in 2003) was about 30,000 DALYs. Furthermore, the cases of acute exposure by substances in DIY products (dichloromethane, toluene, VOCs) resulted in a health gain of about 100 DALYs each of derived health gain. In the lamp oil case, the effect of the implementation of the measure was a decrease in the number of intoxications, which resulted in a burden of disease of about one DALY. The number of DALYs derived for the carcinogenic substances differ from zero (formaldehyde), few (nitrosamines, based on animal data), to hundreds

(acrylamide), thousands (azo dyes) or ten thousands (nitrosamines, based on human data). These differences in range of DALYs are caused by the level of exposure as well as the potency of the carcinogenic substance, or by the size of the target population of the type of product. For comparison, the yearly burden of disease in the Netherlands for 7 different cancers is about 400,000 DALYs.

The use of the DALY-concept for this kind of health impact assessment can provide valuable insight in the effectiveness of possible different interventions allowing the comparison of different health effects.
During this exercise, it has been experienced that the practice and extensive knowledge on risk assessment of chemicals cannot be directly transformed into a system that aims to predict the health impact of current exposures. It became apparent that it is sometimes difficult to extrapolate certain effect-parameters, which are useful in standards and risk assessment, to ‘disease’ in humans.
In most cases, the reliability of the health impact assessment was not very high in the studied cases in this report. Dependent on the case under study, the reliability is more or less affected by uncertainties in the three basic underlying steps, i.e. in the exposure assessment, the effect assessment and in assigning the DALY values.
It is therefore advised, that Health Impact Assessments based on presently applied methodology should only be used to support policy decisions for situations where for a single measure a (very) high health impact is estimated, or, where to prioritize among possible measures, those that show large absolute differences in health impact.
Next to the health gain (in number of DALYs), other parameters such as the decrease in exposure, decrease in incidence, change in risk perception, are informative and important in the evaluation or consideration of taking policy measures.

1. Introduction

The Dutch population is potentially exposed to many chemicals through contact with non-food consumer products. Protection of consumers against effects of harmful substances is regulated in different legal frameworks (see section 3.1 for more information). Within these frameworks risk assessments are conducted to decide if measures are needed to prevent or reduce risk for consumers. These might initiate risk reduction strategies resulting in limitations or bans of chemicals in specific products. Risk reduction measures are sometimes also initiated for other reasons: social or political commotion, exposure of a (potentially) sensitive target population, prevention of the presence of undesirable substances in consumer products, or prevention of establishing a precedent.

Risk assessments are initially based on worst case assumptions and scenarios since a precautionary approach is inherent in the goal of many risk assessments (e.g. in the case of authorisation of substances). This applies to both assessments of exposure and health effects. Appropriate exposure data for substances in consumer products are often scarce, which increases uncertainty and may result in unrealistic exposure scenarios. Assessment of adverse health effects caused by specific chemicals is commonly based on toxicological data from animal experiments, as data on effects in humans are often not available. Subsequently, these observations in animals are extrapolated to humans using safety factors (e.g. for inter- and intraspecies extrapolation). Safety factors are applied within the concept of public health protection to avoid adverse effects.

In real life today, serious health consequences observe in the Netherlands due to exposure to dangerous chemicals in consumer products are not known and most probably uncommon. The largest contribution to reduce adverse health effects has probably already been achieved in the past. One reason could be that the current the regulatory system is functioning effectively; meaning that the most toxic substances are prohibited or exposure conditions leading to risk situations are prevented. The regulatory system results in a limited potential for most chemicals present in consumer products to cause serious illness. On the other hand, there may be an under-recognition of health effects because there is no systematic monitoring system for this. This under-recognition especially might be the case for long-term effects because of inability to recognize health effects induced by these chemicals in general.

The main aim of the regulatory system is to prevent adverse health outcomes. According to the Product Safety Regulation all consumer products should be safe. Industry is primarily responsible for the safety of consumer products, while the government supervises the industry. It is, however, often unclear which substances are present in products, and what the possible health effects of chemicals in products might be for the consumer. In the nearby future, new European chemicals regulation REACH (Registration, Evaluation, Authorisation and restriction of Chemicals) will be implemented, in which chemicals need to be registered if produced in quantities exceeding 1 tonne per year. Substances used in different kinds of consumer products should therefore be more clearly identifiable in the future.

Policy regulates exposure to chemicals via consumer products by bans or marketing restrictions. However, regulation is not the only way for policy to intervene; an information campaign might for example also be a way to prevent undesirable exposures. The effectiveness of legislation can be checked by monitoring. In addition, surveillance and enforcement by the Dutch Food and Consumer Product Safety Authority (VWA) will result in a better compliance of the law and might deliver information that can be used to adjust policy measures if needed.
See also Figure 1.

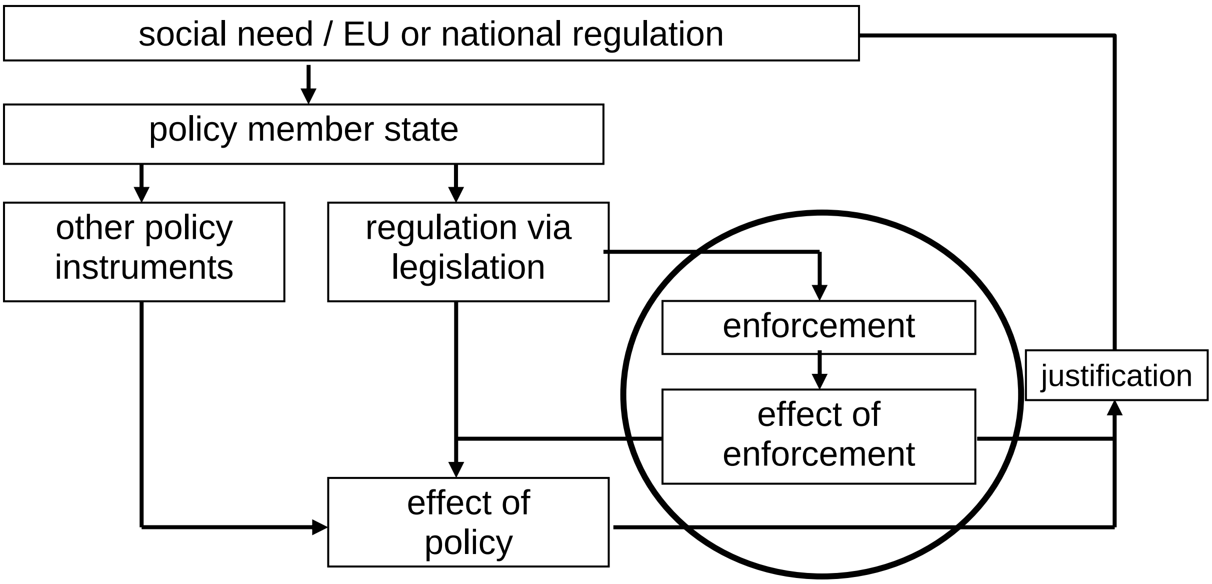

Figure 1. Effect of the total policy cycle (adapted from VWA, 2005)

Potential impact of regulatory or other measures installed to reduce or annihilate risks of adverse health effects due to exposure to harmful chemicals can be predicted by a Health Impact Assessment (HIA). HIA is a combination of procedures, methods and tools by which a policy, programme or project may be judged as to its potential effects on the health of a population, and the distribution of those effects within the population (definition by WHO, 1999).

Expressing health impact in Disability Adjusted Life Years (DALYs) is facilitating the comparison of a range of diverse health effects, weighing severity and duration of the effects. In the National Institute for Public Health and the Environment (RIVM) report, ‘Our food, our health’ (Van Kreijl et al., 2004), the potential impact of a more healthy diet and microbiologically and chemically safer food on the health of the Dutch population was estimated and expressed in terms of DALYs. The Dutch Ministry of Health, Welfare and Sports (VWS) asked RIVM and Food and Chemical Risk Analysis (TNO, Quality of life) to perform a similar exercise in the field of non-food consumer products, thereby focussing on CMRS (carcinogenic, mutagenic, reproductive toxic, and sensitising) substances. In the past and in the future, measures were and will be taken to protect consumers from contact with chemicals in cases where risk cannot be excluded. Policy makers like to know and quantify the outcome (effect on exposure and health) of these measures resulting in enhanced insight in the consequences of such actions. Up till now, the quantitative impact on human health of the implementation of these measures is unknown, because such analyses were never performed.

The purpose of this project is to estimate quantitatively the overall potential health gain resulting from risk reduction measures taken in the past and to be taken in the future with respect to the presence of specific chemicals in non-food consumer products. In the next section, the approach of the project will be explained.

2. General approach

The principal starting point for this project is to quantitatively estimate the potential health gain resulting from risk reduction measures taken in the past and to be taken in the future for chemicals in consumer products. However, because it was very clear from the start of this project that this goal was very ambitious, this project was directed towards an exploration of possible approaches.

At first, an inventory of existing studies on health impact assessments was performed in an attempt to explore the possibility of extrapolating study results to the field of consumer products. Secondly, it was examined whether it is possible to actually quantify the potential health gain with respect to risk reduction measures on chemicals in consumer products. Since it is the first time that a health impact assessment (HIA) is performed for chemicals in non food consumer products, it was decided to perform a HIA for a selected number of cases to get insight in the scientific and practical principles and problems, the implementation of a methodology, and to get an idea of the order of magnitude of possible health gain.

The lay-out of this report follows these two different lines.

In chapter 3 some background information on several relevant issues. In chapter 3, information on different Directives and legislation concerning chemicals in consumer products is summarized (section 3.1). Also an overview on existing methods for health impact assessments for chemicals is provided (section 3.2).
The first approach is described in chapter 4, which contains the information obtained by performing a literature search to make an inventory of existing studies on quantification of health gain concerning chemicals in consumer products.

The second approach can be found in chapter 5, where the health impact assessment on the selected chemicals and products is described. At first, some details are given on the approach (section 5.1), including the indicators used in the case studies, the use of the DALY approach regarding cancer or acute effects in this report, and some general assumptions. In section 5.2, the selection of the chemicals is explained. Section 5.3 consists of a short summary of the results of each case study, which are described in detail in the 9 appendices. These case studies can only be used in the context of this report, and should not be read separately. Section 5.4 gives an overview of all case studies.
In chapter 6, the overall discussion is given, followed by the conclusions (chapter 7) and recommendations (chapter 8).

3. Background Information

3.1 Legislation framework for substances in non-food consumer products

Several different legal frameworks exist for chemical substances in consumer products. In the General Product Safety article 18a of the Warenwet it is stated that it is prohibited to sell products of which the trader knows or might expect that they are a danger to the safety or health of humans, taking into account the expected use. This is also based on a European Directive, the European General Product Safety Directive 2001/95/EC.

Furthermore, substances can be classified based on their hazardous properties such as mutagenic, carcinogenic, or toxic for reproduction according to criteria in the Annex VI of the Directive 67/548/EEC. Substances classified as carcinogenic or toxic to reproductive are divided into three categories, where category 1 means that there is evidence for the specified effect in humans, category 2 means that the effect is possible in man, but proven in animals, and category 3 means that there is some concern for man and evidence in animal data. These so called CMR substances can be found on Annex I of the Dangerous Substance Directive 67/548/EEC. The European Union is considering substituting the current criteria for classification and labelling by the Global Harmonisation System (GHS).

The list with classified chemicals (Annex I of Directive 67/548/EEC) is used by some other Directives, resulting in a ban or concentration limit of the use of CMR substances classified in category 1 or 2. It is included in the Biocides Directive, the Preparation Directive (1999/45/EC) and the Limitations Directive (76/769/EEC).
A preparation is understood to mean a mixture of chemicals substances, which includes as consumer products, detergents and disinfectants. The Preparations Directive states that substances classified as category 1 or 2 are not allowed in gaseous preparations in higher concentrations than 0.02% vol/vol. For substances classified as category 3 the limit is 0.2%. In other preparations the limit is 0.1% w/w for category 1 and 2 substances and 1% for category 3 substances.
Under the Limitations Directive on the approximation of the laws, regulations and administrative provisions of the Member States relating to restrictions on the marketing and use of certain dangerous substances and preparations, there is a provision that regulates that CMR category 1 and 2 substances or preparations containing such a substance may not be sold to the general public. This provision does not apply to articles containing CMR category 1 or 2 substances. In a relatively small number of cases the rules for classification, packaging and labelling are insufficient to reduce risks and must be supplemented by rules to restrict marketing and use under this Limitations Directive. In this Directive 76/769/EEC, the 'Market and Use' Directive, bans or limitations for the

marketing and use of dangerous substances and preparations are entered. Substances regulated in the Limitations Directive are listed in the Annex I to that Directive which also specifies the restrictions on marketing and use applying in each particular case. This directive sets a number of general requirements as to chemical substances in preparations intended for delivery to the general public such as nickel in jewellery, phthalates in toys and child care products, and a ban on cadmium and substances classified by EU as carcinogenic, mutagenic and reprotoxic category 1 and 2. Substances are included because of occupational circumstances (cement with a high chromium VI content), or because of public health (for example cadmium as pigment or stabilizer in plastic) or because of the environment (for example organotin-containing paint for sea ships).
This European legislation is implemented in corresponding Dutch Acts e.g. 'Warenwet' (consumer products), 'Wet milieugevaarlijke stoffen (WMS)' and 'Wet milieubeheer'.

The concept legislation of REACH is now accepted by the European Parliament. The new chemicals legislation should regulate all chemical substance within the European Union and will replace over 60 existing directives and regulations. Among them The Directive for Existing Chemicals, the Directive for New Chemicals, the Council Directive (76/769/EEC) relating to restrictions on the marketing and use of certain dangerous substances and preparations. With REACH an integrated system is implemented for the **R**egistration, **E**valuation, **A**uthorisation (grant permits) and Restrictions of **CH**emical substances. Starting point of the proposal is that in the future not the governments, but industries are responsible for delivering information to assess if use of certain chemicals might be a risk for man or environment.
The goals of the REACH proposal are:

1) protection of man and environment,
2) improvement of the competitive position and innovation capacity of European industry,
3) more unity in the existing EU regulations for chemical substances,
4) more transparency in the properties and risk of use of substances, and
5) promotion of alternative testing of substances without animals.

For more information see also the site on risks and substances of the RIVM (http:/www.rivm.nl/rvs/). More information on all different Dutch legislations might be found on the website www.overheid.nl (further on 'wet- en regelgeving', where can be searched on the name of a specific chemical).

3.2 Selecting a way of assessing health impact assessment

To monitor the health status of a population or to evaluate the consequences of policy actions, several approaches can be envisaged. Over the past decades, reports about the population health status have changed focus. Traditionally mortality has been a dominant indicator of health. With the increasing life expectancy, public health attention shifted towards morbidity and health-related quality of life, in addition to mortality (Melse et al., 2000). This has led to the development of indicators comining mortality and morbidity into so called composite health measures'.

During the past twenty years, a variety of these health indicators has been developed. They are referred to as ‘Healthy Life Expectancy (HLE)’, ‘Health/Disability-Adjusted Life Expectancy’ (HALE/DALE), ‘Quality Adjusted Life Years’ (QALYs), ‘Disability Adjusted Life Years’ (DALYs), or ‘Healthy Year Equivalent’ (HYE). The majority of these new combined health indicators have been developed to provide a ‘common currency’ to be able to compare health effects or health outcomes of very different nature. They have been used in the description of population health status (Melse et al., 2000; Murray and Lopez, 1996), as well as in the assessment of the health benefits gained from a variety of interventions, both in the clinical and in the more general public health setting. Application of these parameters in health impact assessment with respect to chemicals, if possible at all, is still in its infancy.
Technically, these composite health measures can be divided in two groups. The first one is derived from life expectancy and indicates how many years a person can expect, on the everage, to live in good health (as defined by a selected health measure). Examples are the HLE and HALE/DALE. These measures are mostly used as indicator for overall health status. The second group presents the absolute numbers of years gained or lost by a certain disease, a risk factor or an intervention. Examples are the QALY, HYE and DALY. These measures are mostly used to assess and compare the contribution of specific factors or actions to health gain or loss. The basic data needed for both are the same: age-specific mortality rates and age-specific prevalences/incidences of the health effect selected. The measures mentioned are explaned below in more detail (see also (Van der Maas and Kramers, 1997; Anand and Hanson, 1997; Arnesen and Nord, 1999; Neeling, 2003):

- HLE: **H**ealthy **L**ife **E**xpectancy (also called Health Expectancy) represents the number of years a person can expect, on the average, to live in good health. It is calculated by subtracting from the life expectancy the average number of years lived in an unhealthy state (so-called Sullivan method). For the definition of this ‘unhealthy state’ many different health measures can be taken, theoretically. In practice, items from health interview surveys on perceived health or disabilities are often used.
- HALE/DALE: **H**ealth **A**djusted **L**ife **E**xpectancy (formerly called/started as **D**isability **A**djusted **L**ife **E**xpectation) is conceptually the same as HLE. It differs in practice, however, because it uses as many different figures on disease occurrence as possible, as well as weighting factors for the severity of these diseases. Therefore it is a lot more complex than the HLE and availability of data is one of the major problems calculating HALEs.
- QALY: **Q**uality **A**djusted **L**ife **Y**ear, represents disease-specific **health gain** by taking into account both quantity and the quality of life generated by healthcare interventions. It is calculated by combining the years gained by an intervention and a measure of the quality of the life-years gained.
- HYE: **H**ealthy **Y**ear **E**quivalent, applies lifetime health profiles instead of disease specific quality parameters. It was developed (Mehrez and Gafni, 1989) for similar purposes as the QALY but it addresses some fundamental problems of the QALY. In theory it is superior to the QALY approach but practical implementation is considered doubtful.

- DALY: **D**isability **A**djusted **L**ife **Y**ear, represents **health loss** connected to a specific disease, a specific risk factor (e.g. smoking, air pollution). In relation to an intervention (e.g. promoting healthy nutrition), it rather indicates **health gain**, like the QALY. It is calculated as the sum of years of life lost (YLL) and years lived with disability (YLD) weighted for severity of the disability (or disease) in question, all related to the specific disease etc. in question. In terms of concept and calculation DALY and DALE are each other's counterpart.

Selection of the DALY approach for this study
Among the composite health measures mentioned above, the DALY seems best suited for the purpose of this report, i.e. for comparing estimated health losses of quite different nature. Historically, the DALY was first developed for comparing the impact of various diseases at the population level (Murray and Lopez, 1996, 1997). Later, it was also used to assess the impact of major risk factors such as smoking, alcohol and environmental issues (WHO, 2002; Van Oers, 2002; De Hollander et al., 2006). Recently, it was used to assess the impact of unhealthy nutrition habits, of food contamination as well as of interventions aiming at improving these (Van Kreijl et al., 2004/2006).
So, although originally developed as a measure for assessing population health, the exploration and use of the DALY concept in integrated risk assessments has been started. As summarised above, the DALY depicts the 'burden of disease' caused by premature mortality (as YLL) and morbidity (as YLD) as a summation into one figure. YLL is calculated as the number of years lost by premature mortality, by subtracting the age at death from a predefined ('ideal') life expectancy. YLD is calculated from the number of years lived with a disease (from epidemiological data), combined with a weighting factor for the severity of the disease. The weighting factors are derived by expert panels, and have a range between 0 (perfect health-no disability) to 1 (death- maximum health loss, severest disability). When DALYs are calculated for risk factors or interventions, the procedure is to estimate the fraction of a disease (e.g.) lung cancer) that can be attributed to the risk factor (e.g. smoking). An example is presented in Box 1.

Box 1.
A person develops lung cancer at the age of 45 and dies of it at the age of 59. The average life expectancy is set to 80 years. The number of years of life lost, YLL= 21 (80-59) and with a DW factor of 0.44 for lung cancer the number of years lived with disability, YLD=6.2 {0.44 x (59-45)}. So the total health loss for this person is calculated by YLL+YLD sums up to 27.2 DALY. By using age-specific mortality and morbidity data together with the population size, this calculation can be carried out for populations instead of individuals. The result is an absolute number of DALYs for a population which is useful for copmparison purposes rather than as a number per se.

The DALY concept has been criticized on several points. However, a full discussion on this topic is beyond the scope of this report but the interested reader is referred to, for example, Arnesen and Nord (1999). Reliability of expert derived Disability Weights (DWs), availability of epidemiological data, forced consistency between epidemiological

measures and the choice of secondary (not directly clinically-related) endpoints are among the more frequently addressed topics (Anand and Hanson, 1997; Arnesen and Nord, 1999).
The use of DALYs to assess health risks from chemical exposures, especially when based on other than human data, presents an extra problem, which would however be common to any approach of a uniform health measure. For example translating information about 'liver damage' from animal experiments into human liver disease and subsequently into DALYs, or employing DALYs to express effects within the (experimental animal) reproductive toxicological field provide major obstacles. These issues will become evident in the description of the case studies.
Finally, a common theme in public health policy-making (see also the next section on REACH) is to take combined health measures like the DALY one step further by translating them into monetary units in order to convert cost-effectiveness analyses into cost-benefit analyses. Many conflicting views do exist, based on methodological and technical as well as on practical and ethical grounds, about the (im)possibilities to make such conversions. Because of this ongoing discussion, as recently reviewed by Gyrd-Hansen (2005), and the additional uncertainties involved, this issue will not be further addressed in this report. Furthermore, comparing different scenario's with DALYs as the common endpoint makes translation into monetary values redundant, because comparisons are directly made towards differences in health loss. In some of the examples discussed below we use the (monetary) values as reported including the accompanying assumptions made.

4. Inventory of existing health impact assessments

Before performing a HIA ourselves on case substances, a broad and quick search in literature and internet was performed to investigate what was done up till January 2006 on quantification of health gain due to measures taken to reduce exposure to hazardous chemicals in non-food consumer products. It became apparent that in this specific area no previous studies could be found. However, several studies were performed assessing health impact in the environmental setting, considering for example transport, noise or air pollution. In some specific cases, a chemical or chemicals were used as point of departure, such as lead or indoor air pollution (WHO, 2004). More recently, studies were carried out for food (Van Kreijl et al., 2004/2006) and in the occupational field (Hoeymans et al., 2005; Baars et al., 2005). Some of these studies are summarized and their problems and shortcomings mentioned, together with their usefulness for the current exercise is described. Of particular interest in this context are the REACH impact reports. More than thirty studies have been carried out in order to analyse the impact of the proposed new chemical legislation. Some of the studies analysed the impact of REACH on society whereas other studies limited their scope to the impact of REACH on the business sector. It is tried to estimate (quantitatively) the direct and indirect impact of benefits and costs. A search was performed on this subject, in scientific literature databases as well as on internet (EU sites, governmental organizations and so on). In the following sections some of the afore-mentioned studies are summarised.

4.1 REACH impact studies

By the end of 2003 the European Commission (EC) submitted a proposal for a new regulation in the field of chemical substances, REACH, to the Council and the European Parliament. The EC as well as a number of member states and organizations have commissioned studies to assess the impact of REACH. The focus of these studies ranges from impact on health, nature, environment to industry. To enable comprehensive discussions on the impact of REACH, the consultants 'ECORYS' and 'OpdenKamp Adviesgroep' were invited to draft a compilation of all available studies in a single synthesis study. This study served as the starting point of a 'Workshop REACH Impact Assessment' held in October 2004 organized by the Dutch Government in its capacity as President of the European Union. This same study, 'The impact of REACH' (EC, 2003) and the relevant contributions concerning health benefits (including occupational health) are also at the basis of the conclusions in this paragraph.
Different views on how, if possible at all, to value health benefits expressed in DALYs into monetary units, are among the dominating factors determining the range of the calculated net benefits expressed in euro's. For reasons presented above we will restrict the benefits to the DALY level wherever possible. First an apparent inconsistency seems to occur in chapter 3 of the report on the Impact of REACH on society (EC, 2003). With

regard to benefits for society, clear arguments are presented why it is hard to quantify beforehand the size of any health benefits, like for example: *REACH is to be introduced due to the lack of knowledge about the hazard of chemical substances. It is unknown how many substances are hazardous, which substances will disappear from the market and which risks will be reduced. Besides that, the size of the effects of chemical substances on health and the environment is not precisely known.*

Despite the general conclusions presented, the report continues with detailed estimates on health benefits from other studies resulting finally in an estimate of approximately 50 million DALYs. The uncertainties in these estimates are addressed as follows, quote:

'The four most important reasons for the strong range of estimates are the assumptions made with regard to:

a. The extent to which exposure to chemical substances results in health damage.
b. The extent to which REACH is effective and reduces this exposure.
c. The economic evaluation for health by people.
d. The value that has to be attached to the survival or extinction of a species in nature'

When the uncertainties in cost estimates (Pearce and Koundour, 2003) are included in the calculations of the real benefits of REACH, it becomes obvious that at present cost-benefit analysis of REACH is a precarious undertaking. For the same reason most reports, including the 'Extended Impact Assessment' of the European Commission, emphasize that all figures produced should not be regarded as true cost-benefit analysis but as an indication about the potential scale of REACH.

In addition, estimations are presented on the impact of REACH on occupational health. Although there are differences in opinion to what extent, if any, these occupational health benefits should be added to the general health benefits and although not strictly based on the DALY concept, they will be briefly discussed hereafter.

Table 1. Reduction by REACH of specific disease cases per year in the EU (RPA and Statistic Sweden, 2003; Ecorys, 2004)

	Lowerbound *	Upperbound *
Skin Diseases	1350	12.000
Respiratory Diseases	275	1380
Eye Disorders	50	50
CNS (nervous) disorders	50	485
Cancers	2167	4333

* Lowerbound: assumption that one third of the diseases can be avoided. For cancer this results in 2167 cases, which represents 0.23% of the total cancer mortality per year in the EU. Upperbound: assumption that two thirds of the diseases can be avoided. For cancer this means 4333 cases or 0.47% of the total cancer mortality in the EU.

As indicated in Table 1, in the occupational setting five diseases were analyzed in particular, i.e. skin diseases, respiratory diseases, eye disorders, CNS (nervous) diseases and cancers. As a result it was concluded that prevention of cancer would by far be the

most important benefit of REACH. The most important assumptions made were the effectiveness of REACH (1/3 to 2/3 decrease of health effects by unknown chemicals) and the value of human life (low and best value). As a result, calculating roughly with a value YLL=5 per cancer case, as was also applied in ‘Our food, our health’ (Van Kreijl et al., 2004), this would result in additional occupational benefits in the range of 10835 to 21665 DALYs for Europe.
More recently, a further report on the impact of REACH on occupational health was published (Pickvance et al., 2005) with a focus on skin and respiratory diseases. For asthma, they conclude on 40,000-80,000 new cases per year in the European Union (consisting of
25 countries). The proportion affected by REACH is about 50% (based on literature data from different countries, ranging from 28 to 84%). For chronic obstructive pulmonary disease (COPD) a similar calculation has been performed. As a conservative estimate, it is assumed that 5% of the adult population has COPD of which 10% could be controlled under REACH, resulting in an affected incidence of 10,000 a year. For skin disease (occupational dermatitis), the European incidence was estimated at 400 million a year, of which 50% could be potentially preventable by REACH. That 50% is based on six references ranging from 50% to 98%). Health-related quality of life costs were discussed as well as productivity and health service costs.

Table 2. Incidences of asthma, COPD and dermatitis and the assumed effect of REACH (from Pickvance et al., 2005)

	Incidence: nr. of cases / million / year	**Proportion of cases avoided by REACH**
Asthma	200	50%
COPD	500	10%
Dermatitis	200	50%

Careful analysis of the studies discussed in the ECORYS report and the references therein reveal that essentially all health estimates provided are based on one single publication i.e. the original publication by Murray and Lopez (1997). At that time they produced estimates about the burden of disease associated with so called agro-chemical exposure, resulting for ‘established market economies’ in percentages as share of all DALYs of respectively 0.6% (conservative estimate of 5% of the total burden) to 2.5% (liberal estimate of 20% of the total burden). The degree in imprecision in these assumptions by itself indicated that we do not have a robust feel for the impact of chemicals on general health of the population. For example another report (Smith et al., 1999) suggested that the World Bank may have underestimated the burden of disease that is attributable to environmental chemicals by around 150%.
At present it seems not possible to update these original estimations because in current Global Burden of Disease reports ‘agro-chemical exposure’ is no longer applied as a classifier. An approach as suggested in one of the UK Consultations paper’s (2003) is subdividing the reduction of risks to human health into three categories: 1) through occupational exposure,

2) through exposure via the environment (food, water and air) and 3) exposure from consumer products. Although this subdivision makes sense, the report states that quantifying the risk reduction for human health is at present impossible due to a lack of information required and/or uncertainties in available information.
In conclusion, the impact studies prepared for the development of REACH are all based on a very small scientific basis. This information does not provide appropriate quantitative information that is directly applicable for the estimation of health effects due to chemical exposure from consumer products. Moreover, as discussed, several studies explicitly are warning that our present information on chemicals and their hazards not even allow a rough estimate of public health benefits to be made.

4.2 Our food, our health

In the RIVM report 'Our food, our health' (Van Kreijl, 2004/2006), one of the subjects is to address the adverse effects of chemical compounds in our food. It is emphasized that all figures (calculated and summarized in Table 4.8 of the above mentioned report) should be regarded as approximates because the underlying numbers on mortality and morbidity were at best rough estimates. As examples, two separate classes of chemicals will be discussed below.

Allergenic compounds.
2% of the adult population develops some kind of food allergy. It was assumed that 10% is unavoidable and results in continuous complaints. This resulted in a prevalence figure of 32000 (0.2% of 16 million). The selected disability factor was 0.03, which is similar to the factor for light/moderate asthma, which was considered most appropriate in this case. This results in a total health loss of 0.03 x 32.000= ~1000 DALYs

Carcinogenic compounds (process contaminants and nitrosamines).
For all three carcinogenic compounds addresses in 'Our food, our health' recent estimates of additional cancer cases due to the exposure to these compounds were used. For nitrate exposure, the figure applied was approximately 100 additional cancer cases, for acrylamide this figure was 75-130 extra cancer cases, and for polycyclic aromatic hydrocarbons (PAHs) 1-2 additional cancer cases was calculated based on extrapolation. Since for most cancers the DALYs lost by premature mortality would strongly outweigh the DALYS lost by loss of quality of life, it was decided to use only years of life lost for the cancer associated chemicals and to apply an average value for YLL of 5 years per cancer case. For these carcinogenic compounds this resulted in a total of 400-1200 DALYs to be gained.
Other contributions from other substances were considered to be relatively small, so the order of magnitude to be maximally gained is estimated in the range of 2200 DALYs.

Table 3. Substances and groups of substances presenting additional risks: type of effect(s) and potential health gain through avoidance of exposure (adjusted Table 4.8 from ‘Our food, our health’, 2006).

Group of substances	**Type of effect**			**DALYs to be gained**
	Acute	**Carcinogenic**	**Allergenic**	**Designated as order of magnitude due to the uncertainty**
Various proteins in foods			Shellfish, fish, milk, nuts, wheat	Ca. 1,000
Mycotoxins		Aflatoxins		Aflatoxin B1 <1
Phycotoxins	DSP, ASP			Ca. 10-70
Phytotoxins	Anisatin			<1
Nitrate/ nitrite		nitrosamines		Nitrosamines Ca. 100-500
Growth promoters	Clenbuterol			Ca. 1
Process contaminants		Polycyclic aromatic hydrocarbons		PAHS 5-10
		Acrylamide		300-700

ASP= amnesic shellfish poisoning
DSP= diarrheic shellfish poisoning
Anisatin: nerve toxin found in incorrectly prepared star anise tea

4.3 Some other health impact assessments

It became clear from a literature search that at present very few studies have been trying to connect the DALY concept with the exposure to chemical substances. If it was performed, most of them are connecting environmental pollution and health effects. Nothing was specifically found on health impact assessments or health gain studies concerning chemicals and consumers or chemicals in consumer products. More recently, some studies were performed in the field of occupational health. From the studies found, some are in short described hereafter.

The environmental burden of disease
Environmental factors can affect health and quality of life in various ways. Air pollution is associated with respiratory or cardiovascular diseases, noise exposure can lead to annoyance, and exposure to certain forms of radiation can cause the development of cancer. It is difficult to compare these problems, since they differ in type and scope.Therefore it can be useful to quantify the health impact of the environment in an integrated measure.

The World Health Organization (WHO, 2004) made a document on the burden of disease attributable to selected environmental factors and injuries among Europe's children and adolescents. Included factors in this report were outdoor and indoor air pollution, lead, water sanitation and hygiene. For example, for lead it was reported that it is the cause of 1.4% of all DALYs in Europe (for 2001) among children of age 0-4 years.
In order to gain some perspective on the dimensions of this environment-related health loss in the Netherlands, DALYs were calculated for the health effects of air pollution, noise, radon, natural UV-radiation and indoor dampness for the years 1980, 2000 and 2020. According to study on the environmental burden of disease, in the Netherlands, roughly 2 to 5% of the disease burden (as calculated for 49 (groups of) diseases) can be attributed to the effects of (short-term) exposure to air pollution, noise, radon, total natural UV and dampness in houses for the year 2000. When the more uncertain long-term effects of PM_{10} (Particulate Matter with an aerodynamic diameter smaller than 10 μm) exposure are included, this percentage can increase to slightly over ten percent, assuming no threshold. Long term PM_{10} can be regarded as an indicator for a complex mixture of urban air pollutants.The levels of PM_{10} are decreasing over time; therefore the related disease burden is also expected to decrease. Noise exposure and its associated disease burden will probably increase up to a level where the disease burden is similar to that attributable to traffic accidents. These rough estimates do not provide a complete and unambiguous picture of the environmental disease burden; data are uncertain, not all environmental-health relationships are known, not all environmental factors are included, nor was it possible to assess all potential health effects. The effects of a number of these assumptions were evaluated in uncertainty analyses. (Knol and Staatsen, 2005)

The occupational burden of disease
For the Dutch Ministry of Social Affairs and Employment, a feasibility study on burden of disease assessment was performed (Hoeymans et al., 2005) to give an impression of health loss caused by working conditions. Workers enjoy better health than non-workers, but work can also cause health loss. This assessment model approach, corresponding to the burden of disease estimates used in the model of the Public Health Status and Forecasts, represents a new approach in occupational health. This model has as its starting point occupational diseases and not the potentially health-threatening factors associated with working conditions - common in occupational health. Disease burden estimates can answer such questions as how bad a particular working condition is compared to other health risks, how much of this disease burden is preventable and what measures are the most profitable. The report of Hoeymans et al. (2005) describes a framework to estimate the occupational burden of disease. Using examples of back pain, hearing impairment, stress-related illnesses and complaints of arm, neck and shoulder, the possibilities and impossibilities offered by occupational burden of disease estimates were illustrated. Of these four complaints, hearing impairment is responsible for most of the health loss, expressed in DALYs. In theory, then, most health benefits can be gained by the prevention of a hearing impairment.
Disease burden calculations require a lot of data, if they are to be meaningful. However, as shown in the examples, part of the information is still seen to be lacking, e.g. data on the

prevalence of some occupational diseases and exposure to working conditions. This feasibility study showed that calculations on the occupational burden of disease are not only possible, but also useful, provided that extra investments are made. (Hoeymans et al., 2005). In another study, health effects and burden of disease due to exposure to chemicals at the workplace were explored (Baars et al., 2005). Exposure to chemicals at the workplace can account in part for the occurrence of 10 selected diseases. For asbestos-related illness, chronic toxic encephalopathy (CTE) and toxic inhalation fever, chemicals are responsible for 100% of the diseases. Chemical exposure at the workplace contributes about 25-30% to the occurrence of contact eczema and rhinitis plus sinusitis, and less than 10% in the case of four other selected diseases. For nine investigated diseases the burden of disease was approximately 47,000 DALYs, including about 1,900 deaths, due to exposure to chemicals at the workplace. The largest contributions are formed by mesothelioma, lung cancer, asthma, and chronic obstructive pulmonary disease. The margin of uncertainty in the results is very large, mainly caused by the scarce and incomplete data, and was estimated at about a factor of 5. It was not possible to estimate the burden of disease due to reproductive disorders following occupational exposure to chemicals. However, results of recent research in this area indicate concern. (Baars et al., 2005).

Two interesting papers by Jolliet and co-workers need some attention (Crettaz et al., 2002; Pennington et al., 2002). Their approach will be discussed in some detail in Appendix 1 because of its potential to provide generic health effects estimates like for example *'number of years lost/mg intake'* of a specific chemical. The application of what they call screening-level estimates of the potential consequences associated with an exposure to a given chemical for use in life cycle assessment (LCA) may be also applicable for some first/rough estimates related to consumer products, although the approach is not undisputed as will be explained in the appendix.

4.4 Conclusions on generic health impact assessment for chemicals

- Not until recently, studies are performed in an attempt to quantitatively assess the health impact of certain measures, changes or interventions with regard to chemicals.
- Within the field of composite health measures until now the DALY seems to be the most suitable tool to try to estimate the health benefits to be gained by regulating the chemical composition of consumer products, although serious problems are also associated with its use and interpretation.
- Application of the DALY concept in chemical risk assessment is still in its infancy, making explicitation of the assumptions important.
- The impact studies applying the DALY concept as prepared for the development of REACH are all founded on a very narrow scientific basis. This information does not provide appropriate quantitative information that is directly applicable for the estimation of health effects due to chemical exposure from consumer products.

5. Health impact assessment based on case studies

5.1 Approach

There is at present no general information available to be used to perform a general analysis on the total health gain of measures on chemicals in consumer products. Therefore, it was proposed to start performing HIA on a selected number of case studies. This enables us to develop methodology and define possible problems, and to see if this leads to useful and reliable results. These case studies will demonstrate the potentials, the limitations and uncertainties involved in assessing the health impact. They can also give some indication on the order of magnitude of health gain or decrease of health loss by an implemented measure.

5.1.1 A basic approach for the case studies

For all case studies, the point of departure is the measure implemented or to be implemented for the chemical in a specific product or exposure scenario. In assessing the impact of an implemented measure (in the past or the future), the effect of the measure will be determined defining the differences in the following indicators:

1. Estimation of the exposure:

Measured or estimated (assumed) data on the amount of substance in the product, frequency and duration of exposure, and so on, were used. The size of the exposed target population was also estimated. To give an idea of the context of the policy measure, the exposure to the substance through other sources was also estimated if possible.

2. A risk assessment was performed:

An estimation is given on the difference in margin of safety before and after the policy measure, meaning the margin between the (no) effect level and the estimated exposure before and after the policy meeasure.

3. Estimation of the health gain

With the information from steps 1 and 2, an effort was made to establish the change in incidence of effect/disease before and after the implementation of the policy measure.

4. Expression of the health gain in DALYs:

The health gain was expressed in ‘Disability Adjusted Life Years’ (DALYs) which is equivalent to the number of healthy life years lost by disease in a population. When using DALYs, various diseases can be compared for their influence on public health. This index reflects three important aspects of public health: ‘quantity’ (length of life) and ‘quality’ of life, and the number of people affected (see section 3.2).

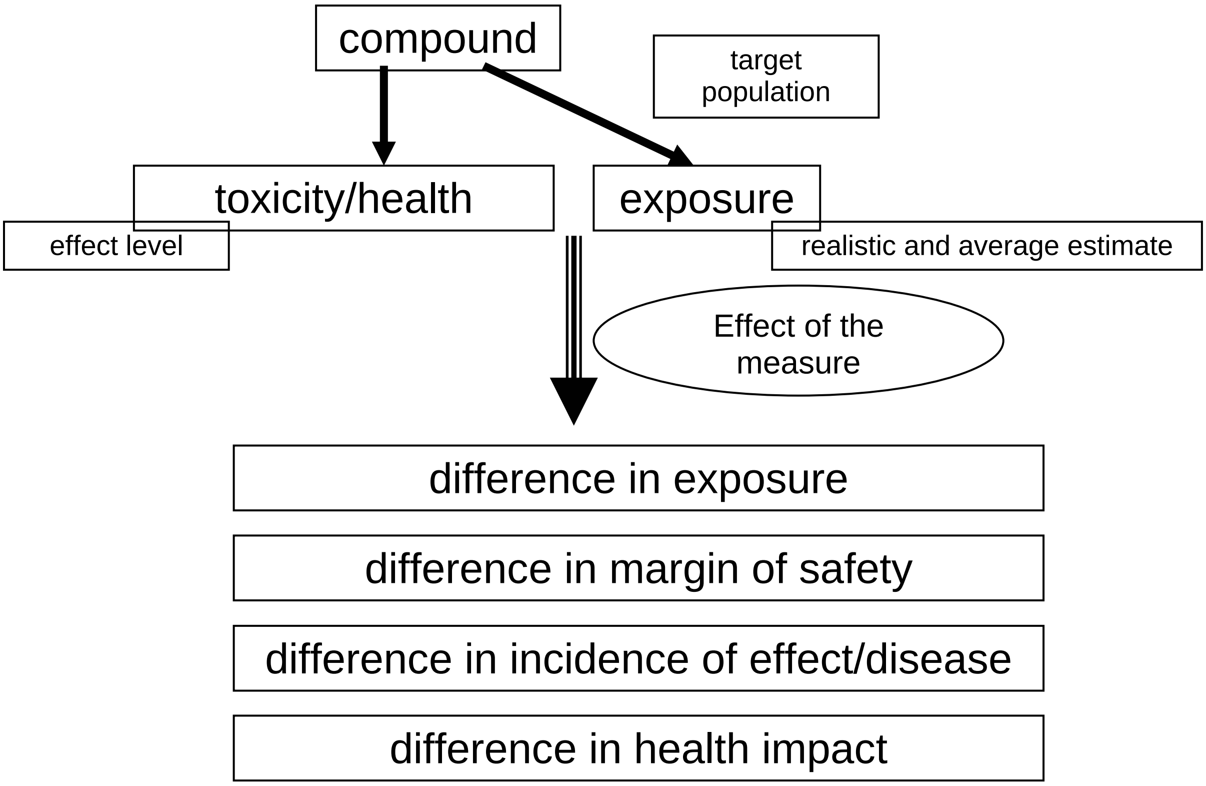

Figure 2. Indicators for effect of a policy measure on substances in consumer products

The first indicator, a decrease in exposure to the chemical in question, might already be a positive result of the implementation of the measure. This provides insight in the effect of the measure which might be very useful and a good parameter for evaluation of a measure. It is however not a direct indicator for a change in health effects. A decrease in incidence of an effect or disease, and/or a decrease in health loss can be considered an impact of health.

The methodology employed is basically similar to that used for risk assessment of chemical substances. As a start an exposure scenario is described, in which it is tried to be as realistic as possible (and not worst case as a starting point). All necessary assumptions, choices and sources are reported carefully, including information on uncertainties. Furthermore, a target population will be chosen and described.
Secondly, a human health hazard assessment is performed, using information as much as possible from scientifically reviewed reports from organizations or frameworks. Taking into account the scenario or product for which the measure was taken (or will be taken in the future), a specific endpoint or endpoints are selected and a No Observed Adverse Effect Level (NOAEL) is derived.
A risk assessment is described, as performed in another report or review in a specific framework or performed in the case report. Finally, a DALY calculation is performed (see section 3.2 and 5.1.2 for explanation of the DALY concept). A description of the

conversion of effect into disease is given and the weight factor is presented. For all steps, the calculation has been described as transparent as possible.

Exposure
Searches on exposure estimates for the different substances were performed in scientific databases and on internet. Furthermore, when analytical data were available from scientific papers, from the Dutch Food and Consumer product Safety Authority (VWA) or other sources, they were used. For the present exercise, it was necessary to obtain data on exposure to the chemical before and after the measure. When the measure was implemented recently or would be implemented in the future, in many case studies it was assumed that the exposure after the measure would be zero. Measured data were preferred above a calculation method or a mathematical model. If no analytical data were available, the exposure was estimated using a calculation or the model program ConsExpo. Information on frequency of use, time periods, and/or amounts etc is needed for estimation of change in exposure. This information was based on data if possible, otherwise assumptions were made based on expert judgment.
In risk assessment for authorization purposes, exposure estimates are almost always worst case estimates, which is a natural and desirable choice. In the situation of a health impact assessment, it is more favourable to have true exposure distributions. Whenever possible, normal procedures used for risk assessment have been adjusted to obtain estimates of average exposures over the population and over a time period. However, depending on the exposure scenario (product type), it might be possible that short term (peak) exposures are interesting as well, when risk is only found at peak levels and not average levels.
In all case studies, if possible, information on exposure from other sources and via other exposure routes were included, i.e. the measure is placed in context of the total aggregate exposure if possible.
Information on the *target population* was obtained through different sources. Generally, if exposure is through cosmetics or clothing, it was assumed that the total Dutch population is the target population. Dependent on the case study involved, information was used from Statistics Netherlands (CBS), product producers, hobbyist or trade associations and so on.

Toxicity
For most substances selected, reviews or reports from international organizations or legal frameworks were available. These data were used for the toxicity profile and for risk assessment, because they are already reviewed in European or international organizations. It was highly preferred to use human data, however, this was not possible in the majority of the case studies. In the case of data from animal studies, the critical effect found was linked to a corresponding (clinical) disease in humans. This is necessary to be able to calculate a DALY. In the case of carcinogenic substances, in risk assessment a linear dose-response is assumed. This is an easy way for calculation, and in the case of prevention it is on the safe side. For some more background on carcinogenicity and DALY approach, see section 5.1.2.1.

5.1.2 The DALY approach in this report

Health gain can be expressed in many different ways (for more information see section 3.2). In this report, the health gain or reduction of health loss will – as far as possible- be expressed in DALYs (Disability Adjusted Life Years). The DALY concept is presented by Murray en Lopez (1996) for the World Health Organization (see for use of this concept also WHO, 2005a). This burden of disease, or loss of health (measured in time units) is composed of two components: [1] the loss of quantity of life (years lost due to premature death), and [2] the loss of quality of life (years spent with a disease). The years spent with a disease are weighed according to the severity of the condition, using weighing factors. This renders the years spent with a disease comparable with those lost due to death. For example, if a disease has a weighing factor of 0.5, this means that a year spent with this disease is considered equivalent to half a year lost due to premature death. In this way, the lost life years and the disease year equivalents are enumerated as DALYs. Lost DALYs can be calculated for various diseases using statistical information about mortality rates and incidences/prevalences/seriousness, and can also be calculated for the risk factors based on the fraction of one or more diseases which can be explained by that risk factor (or attributed to the risk factor). The weighing factors have been determined as part of a separate study, and have a value between 0 (no health loss) and 1 (maximum health loss, equivalent to death) (Van der Maas and Kramers, 1997).
The DALY concept was introduced from the area of public health sector. Weighing factors and other information were directed at and developed for health effects in humans. It contrast, toxicological effect of chemical substances cannot always directly be linked to a clinical defined disease. In fact, in most case studies only information on toxicological effects in animals are available.
Quantification of health gain in a population (in DALYs) is a method to give insight in the burden of disease of that population. It should be taken into account that this methodology makes it possible by means of weighing factors for each disease to compare essentially incomparable issues. For example, it implicates that the summed disease burden of 114 people having influenza in a certain year (weighing factor 0,01) is similar to the summed burden of 2 persons having AIDS (weighing factor 0.57). It will be clear that the DALY-concept in its approach leaves out important aspects of a disease, and should be handled with care.

For this study, the choice was made to calculate the ‘to be prevented’ DALYs *per year*. For endpoints with a long incubation period such as cancer this might be somewhat misleading.
In some cases, this problem could have been solved using lifetables (Miller and Hurley, 2003; Veerman et al., 2007). However, this more sophisticated approach also is much more time consuming.

Specific attention is given in the following section on the use of a DALY calculation in the case of carcinogenicity as endpoint, and in the case of an endpoint related to short-term exposure.

5.1.2.1 *Health impact calculation in DALYs for carcinogenicity*

In 'Our food, our health' (Van Kreijl et al., 2004), for carcinogenicity it was assumed that each case will only result in premature death and an average loss of five life-years. This assumption was made on the basis of most common cancers and only on mortality. This did not take into account the years lived with disease, which normally account for 20-25% of the total DALY for cancers (which can be calculated from information in Kramers and Melse, 1998). This is more or less the same order of magnitude as proposed by Jolliet and co-workers (YLL=6.7) (Crettaz et al., 2002) as mentioned in section 4.4. In this project, we used a value of 8 years per cancer case, which is based on a more thorough calculation of an average DALY per average cancer case (see Table 4). It is still only based on 65% of the cancers. Using more recent data reported July 2007 on the National Public Health Compass (www.nationaalkompas.nl), an average DALY per cancer case of 9 can be calculated. Because of the small difference (8 or 9), especially in relation with ranges caused by other uncertainties, in all case studies (some of them already started with in 2005) considering cancer as an endpoint 8 is used as an average DALY per cancer case. In many case studies investigated for this report, it is not possible to establish the specific cancer possibly caused by the compound in humans. For the calculation most often animal experiments are used, in which liver tumours were found, which are not always relevant for humans. In case studies where there is specific information on the relevant type of cancer caused by the substance in humans, the number for DALY/cancer case could be chosen specifically.

Table 4. Incidence of various types of cancer in the Netherlands in 1994 and their corresponding DALYs

Cancer	Incidence [1]	DALYs [2]	DALY/ (incidence) cancer case (1997) [3]	Incidence 2003 (NKR)	DALY/(incidence) cancer case (2003) [7]
Lung	8,831	123300	14.0	9014	15.0
Breast (F)	10,050	83700	8.3	11758	7.1
Colorectal	8,052	60500	7.5	9898	7.0
Stomach	2,380	26600	11.2	1962	11.4
Prostate	6,315	24400	3.9	7902	3.8
Esophagus	959	14300	14.9	1434	14.1
Skin [4]	4,698	11800	2.5	6700	2.2
Total incidence (% of all cancers)	41,285 [5] (65%)	34,4600	**8.3**	48666	**8.7**
Average DALY per cancer case [6]				**8**	**9**

1 Data from the Dutch cancer registry (Visser et al., 1997).

2 Data from Melse et al. (2000).

3 DALY per cancer case calculated by dividing DALYs by the corresponding incidence.

4 Basal cell carcinoma (which shows the highest frequency) is not recorded in the Dutch cancer registry.

5 Other important cancers are cancer of the pancreas, endometrium, ovary, urinary tract and larynx, and Non-Hodgkin lymphoma (17% of the total incidence).

6 Weighted for the relative contribution of each cancer to the total cancer incidence. In view of the large uncertainties in the underlying assumptions, it is rounded off to an integer value (8.3 to 8).

7 For the DALY calculation in the final column, data from the most recent National Public Health Compass were used (http://www.rivm.nl/vtv/object_document/o1676n18840.html)

5.1.2.2 Health impact calculations in DALYs for acute effects

A specific problem which is of interest for assessing health impact of certain consumer chemicals in this report is that of the weighing of short-term conditions. Because the DALY is based on disease *years,* it is logical to weigh chronic conditions as 'one year spent in condition X'. In the case of short-term conditions, it is possible (a) to weigh the condition as if it were to last a full year, and then to correct the result according to the actual duration (as a fraction of a year), or (b) to adapt the weighing to represent 'a year which includes an episode of, for instance, influenza' (the 'year profile approach'). The first approach is used by Murray and Lopez (1996), De Hollander et al. (1999) and De Hollander (2004) for environment-related health loss, as well as by Mangen et al. (2004) for foodborne infections. It makes a more precise calculation possible. The second approach is that used by the Centre for Public Health Forecasting (Van der Maas and Kramers, 1997) and CVZ (Health Care Insurance Board 2003) and has the advantage that account is taken of the fact that the disease will be resolved relatively quickly. In the example of the foodborne infections both calculation methods arrive at results in the same order of magnitude.

For some of the chemicals, the most important exposure occurs over a shor period of time. Using this short-term exposure frame, it is necessary to find a weighing factor corresponding to the specific situation. A method to establish a weighing factor for a specific situation is the use of the EuroQol instrument. Using this method, the health status of a population is described using 6 dimensions, which vary in severity over three levels. The dimensions are: mobility, self care, daily activities, pains and other complaints, anxiety/depressions, and cognition. These dimensions describe the functional state of health of a certain individual with a certain disability. A score of 1 equals full health. A EuroQol score of 111111 will consequently result in a disability weight of 0. A score of 2 equals to a disability weight of 0.0833. A EuroQol score of 222222 will result in a disability weight of 0.5 (since all dimensions were scored as being half). A EuroQol score of 333333 will result in a disability weight of near 1. For more information see Table 5. When using the disability weight factor in the DALY calculation, a correction for the time period should also be included.

Table 5. EQ-6. Dimensions with their 3 levels (no problem, some problems, many problems).

Dimension	Level	Score
mobility	No problems in walking about.	1
	Some problems in walking about.	2
	Confined to bed.	3
self care	No problems with washing or dressing self.	1
	Some problems with washing or dressing self.	2
	Unable to wash or dress self.	3
usual activities	No problems with usual activities (e.g. work, study, housework, family or leisure activities).	1
	Some problems with usual activities.	2
	Unable to perform usual activities.	3
pain / discomfort	No pain or discomfort.	1
	Moderate pain or discomfort.	2
	Extreme pain of discomfort.	3
anxiety / depression	Not anxious or depressed.	1
	Moderately anxious or depressed.	2
	Extremely anxious or depressed.	3
cognition	No problems with cognitive functioning (e.g. memory, concentration, coherence, IQ)	1
	Some problems with cognitive functioning	2
	Extreme problems with cognitive functioning	3

EuroQol (6 Dimensies) (EQ-6D). For more details see a report by VTV (in Dutch) (Van der Maas and Kramers, 1997) and Hoeymans et al., 2005a.

5.1.3 General assumptions

In the exposure scenario's, some basic and general assumptions are taken into account:
- in principal, estimates are made for the Dutch situation/population
- life expectancy is rounded to 75 year
- the average body weight is 70 kg (when relevant other body weights were chosen)
- restriction to Dutch data as much as possible (unless otherwise reported)
- the DALY is expressed per year, assuming a steady state population

5.2 Selection of cases for the health impact assessment for chemicals in consumer products

As explained above, a selected number of case studies was analysed to get a better feeling for the methodology and problems, and to see if this leads to useful and reliable results.

In collaboration with the Ministry of Public Health, Welfare and Sports and the Food and Consumer Product Safety Authority (VWA) a number of criteria for the case studies have been worked out.
Cases were selected on the basis of the following criteria:

- The selected cases should cover a number of =categories of consumer products (cosmetics, textiles, do-it-yourself products, cleaning agents, detergents, and so on)
- The selected cases should cover various CMRS properties (Carcinogenic, Mutagenic Reproduction toxic, Sensitizing).
- The cases should involve different exposure times (acute or chronic).
- For each case the presence of legislation is necessary (present or in the future).
- The cases should be associated with existence of exposure data.
- The cases should be associated with presence of sufficient (human) toxicological data.

For more information on the candidate substances see the table in Appendix 2.

The following substances in consumer products were chosen taking the above mentioned criteria into account (in alphabetical order):

- acrylamide (measure in cosmetics)
- azo-dyes (measures in textile and tattoos)
- dichloromethane (measures for do-it-yourself products)
- formaldehyde (measures for chipboard, textiles and cosmetics)
- lamp oil (measures for reducing the risk of intoxication)
- nickel (measures for nickel releasing alloys in products in contact with skin)
- nitrosamines (measures for teats and soothers, cosmetics and balloons)
- toluene (measure in adhesives and spraying paint)
- VOC (measures in paints and varnishes)

5.3 Results of the individual cases

Nine different case studies, i.e. nine substances or substance groups are worked out in detail. For these substances one or more legal measures were implemented or will be implemented in the future. The extensive reports can be found in the Appendices 3 to 11. Here, the main characteristics of the different case studies are summarized briefly.

5.3.1 Acrylamide

Since 2002 according to the Cosmetics Directive (76/768/EC and 2002/340/EC, the use of polyacrylamides is permitted if the concentration of the monomer is less than 0.1 mg/kg product for non-rinse body care products, and 0.5 mg/kg product in other cosmetics. Acrylamide is included because of its carcinogenic properties, the comparison with its presence in food and the present regulation in cosmetics.

Exposure

Polyacrylamide is used in several cosmetic formulations at concentrations ranging from 0.05-2.8%. Residual levels of acrylamide can range from <0.01 to 0.15%. In the calculation a level of 2% was used for polyacrylamide, with a maximum monomer level of 0.01% in the polymer, which results in a dermal exposure level of 0.36 µg/kg bw/day. After the measure, assuming complete compliance, the exposure levels would be 0.004

µg/kg bw/day. Background exposure from drinking water, smoking and mostly food was estimated to be 0.6 µg/kg bw/day.
Description of toxicity
Acrylamide has been shown to be neurotoxic, it is a skin irritant and skin sensitizer, it is mutagenic and causes cancer (tumours in thyroid, adrenals, testes) in animal studies when exposed to high doses. It is amongst other classifications classified as carcinogenic category 2 (67/548/EC). For peripheric neuropathy a NOAEL could be derived of 500 µg/kg bw/day from a chronic rat study. A cancer risk estimate was recently established by the Dutch Health Council. A tumor incidence of 0.5 per 1000 at 1 µg/kg bw/day was used as a starting point.
Health gain
For induction of tumors, a decrease in additional tumor incidence as a result of acrylamide exposure via cosmetics is calculated to be 180 per 10^6 persons before and 2 per 10^6 persons after measures are taken. Using a standardised DALY of 8 for each person developing tumors, a target population of 16 million Dutch people exposed to cosmetics, and a life expectancy of 75 years, the measure results in a health gain of about 300 DALYs.
Reliability
Target population using cosmetics was assumed to the total Dutch population. 'Real' exposure estimates were supposed to be half of the reasonable worst cases estimates calculated in the Existing Chemicals Risk Assessment Report (RAR, 2002). Toxicity has been reviewed extensively, but data could not be based on human data. A recent evaluation of the carcinogenicity assuming a linear dose response is used for effects assessment and DALY calculation. It is unknown whether the average DALY for cancer is representative for the cancer potentially induced in humans.
(For more information see Appendix 3.)

5.3.2 Azo dyes
Azo dyes are used as colouring agent in textiles and tattoo liquids. This case is included because of daily prolonged dermal contact. Furthermore, the VWA has some measured data because of the enforcement of legislation. A ban of the use of azo dyes is regulated in Council Directive 76/769/EC from 1996 on.
Exposure
The exposure to azo-dyes from tattoos could not be estimated because of lack of data. For textiles, 2 out of 22 aromatic amines were selected for the exposure assessment, namely benzidine and 2,4-toluenediamine. Textiles in clothes and on toys are included. The target population is the total Dutch population (clothes) or infants of average age of 10.5 months (toys). The dermal exposure from textiles was estimated using assumptions on product amount, skin contact factor, leachable amount, frequency, skin absorption, and prevalence of the azo colourants. Besides dermal exposure, an exposure assessment was performed for children chewing on textile toys (oral exposure). The presence of azo dyes still present in textiles could be estimated as 15% (which in the past was 25%) as observed by the VWA for leather, or it might be assumed that the presence is zero. Calculations resulted in 8.0 ng/kg bw/day benzidine and 0.21 ng/kg/day 2,4-toluenediamine before the measure and 4.8 or 0 ng/kg bw/day benzidine and 0.12 or 0 ng/kg bw/day 2,4-

toluenediamine after the measure. For toys the concentrations amounted 0.04 ng/kg/day 2,4-toluenediamine before, and 0.025 ng/kg bw/day 2,4-toluenediamine after the measure (no data on benzidine in toys).

Description of toxicity

Some azo dyes might be converted into carcinogenic aromatic amines, among them benzidine and 2,4-toluenediamine. Exposure to these compounds result in animal studies to cardiovascular, haematological, renal, hepatic and genotoxic effects. Bladder cancer was observed in animal studies, and a relation was also found in human epidemiological studies. The negligible risk level (NRL), corresponding to one in a million additional cancer risk, derived for benzidine using human data is 0.004 ng/kg bw/day, which is also used for 2,4-toluenediamine. However, when using animal data, the NRLs would amount 3.2 and 5.6 ng/kg bw/day for benzidine and 2,4-TDA, respectively. The most conservative one, the human NRL, would be used in risk assessment, and is also taken forward here.

Health gain

DALYs were calculated using the additional calculated risk times 16 million subjects, what resulted in a total of 35,000 cases before the measure. Based on an average of 8 DALYs per cancer case and divided by 75 for the life expectancy, the number of DALYs before the measure is 3700. The health gain obtained by the measure is respectively 1500 or 3700 DALYs per year, assuming a decrease of 1.7 fold in exposure or a decrease in exposure to zero.

Reliability

Calculations were performed with 2 azo dyes, out of 22, of which some with carcinogenic properties. Those 2 were predominantly used in textiles, and were among the most potent azo dyes. In the exposure scenario's many assumptions were made, introducing a lot of uncertainty. Furthermore, the risk assessment is performed using the NRLs based on human data, while the NRLs from animal data are about a factor 1000 higher, resulting in almost zero DALYs. (For more information see Appendix 4.)

5.3.3 Dichloromethane

Dichloromethane (DCM) is an example of a volatile organic solvent used in paint strippers and glue removers in the do-it-yourself sector. Under Directive 76/765/EC a proposal for total restriction on the marketing and use of DCM based paint stripper is made.

DCM is classified as Xn (harmful) and R40 (carcinogen category 3).

Exposure

The exposed population is that part of the Dutch people that in free time works in DIY using paint stripper or glue remover, which is estimated to be about 150,000 people. The present exposure is calculated using ConsExpo 4 and the statistical program PROAST which resulted in an exposure distribution ranging from 50 ppm to 5000 ppm with an average of 660 ppm. The exposure after the proposed measure is assumed to be zero.

Description of toxicity

Short term exposure to DCM might lead to central nervous system (CNS) depression, elevated carboxyhaemoglobin (COHb) levels, eye sensitization and skin irritation. Absence of CNS effects was found at levels lower than 514 ppm in human volunteers. Furthermore, since the vapour density of DCM is high, concentrations might be higher closer to the ground, resulting in a possible higher risk for children.

For risk assessment Acute Exposure Guideline Levels (AEGLs) were used which were derived using animal and human data.
Long term exposure to DCM in mice resulted in lung and liver tumors. Therefore, DCM was classified as a carcinogenic compound. However, recent investigations on metabolism in mice and humans made clear that DCM is a mouse specific carcinogen. Carcinogenicity is therefore not taken into account as critical endpoint.
Health gain
The exposure after the proposed ban was assumed to be zero. Related health effects after acute exposure will disappear. The number of DALYs was calculated by comparing AEGLs with the modeled exposure distribution and by using the EuroQol method for weighing factors. This resulted for paint stripper and glue remover together in a health gain of about 140 DALYs.
As the possible carcinogenic effects are regarded (recently) as not relevant for humans, there was no risk for consumers before the measure, and no health gain to achieve.
Reliability
In the exposure calculation assumptions were made on target population (size of subpopulations), frequency of usage, release area, and so on, introducing a margin in the outcome. On the effect side, assumptions were made on the severity of the effects (slight or moderate/heavy CNS depression), and on the duration of the acute effects.
(For more information see Appendix 5.)

5.3.4 Formaldehyde
Formaldehyde is found in several consumer products. Legislation is introduced for chipboard (Dutch 'Warenwet', 1987; 10 mg/100g), textiles (Dutch 'Warenwet', 2001; 120 ppm), and cosmetics (EU Directive 76/768/EC in 1995; 0.2% and 5% for nail hardeners) and for oral hygiene products (EU Directive 76/768/EC in 1998; 0.1%). This case was included as a case of a carcinogenic compound, with exposure from multiple consumer products.
Exposure
The exposure to formaldehyde indoors caused by the presence of chipboard was chosen from a large amount of literature. The exposure before the measure was 250 $\mu g/m^3$ and after 55 $\mu g/m^3$.
For the exposure to formaldehyde through textile, an amount of 20 ppm in textile was used for exposure in the past, and an average of 17 ppm for exposure after the measure. Further assumptions on weight, skin contact, washing and frequencies were made, resulting in an exposure to 6 µg/kg bw/day before and 5 µg/kg bw/day after the measure.
Formaldehyde is used in cosmetics as a conservative, up to 1500 ppm which could result in an exposure of 0.2 mg/kg bw/day.
Description of toxicity
After inhalatory exposure, formaldehyde is causing cancer, but only at the site of entry, more specifically inducing nasal tumours when exceeding a concentration of 1.2 mg/m^3. The mechanism is based on the induction of irritation and cytotoxicity in the upper airways. Because of this mechanism, the use of linear extrapolation to estimate human cancer risk is considered not possible.

After dermal exposure, the critical effect is skin sensitization. Contact dermatitis might be induced after direct contact with more than 2% formaldehyde solution.

Health gain

Exposure to formaldehyde via plywood is not high and prolonged enough to induce the local nasal tumours. For dermal exposure to formaldehyde via textiles, the MOS calculations indicate no concern for sensitization, thus no DALY is calculated for contact dermatitis. For cosmetics, the data available are not sufficient to make a calculation. Therefore, no DALY could be calculated.

Reliability

Exposure estimates for indoor air used are based on foreign studies. Although the representativeness of the estimates might be restricted, large deviations are not expected. For textiles, exposure data before and after the measure were available, but probably worst case, with unknown distribution. For exposure estimates concerning cosmetics, many assumptions have to be made, introducing uncertainties. Considering the mechanism for carcinogenicity, the use of linear extrapolation to estimate human carcinogen risk will lead to erroneous conclusions. For dermal effects, human data were used to derive thresholds for elicitation of allergic contact dermatitis in sensitized subjects.

(For more information see Appendix 6.)

5.3.5 Lamp oil

This case was chosen because the incidence of lamp oil intoxications as monitored by the Dutch Poison Information Centre (NVIC) was reduced after the measure. In 1997 a ban on coloured and scented lamp oil with some regulations on the viscosity was set up in the EU, and is included in the 'Warenwet'. This case was included as an example substance for acute toxicity effects, and concerns the misuse of a product.

Exposure

The exposure was described by reported cases of intoxications at the NVIC. The ban resulted at first in a decrease of reported cases. The highest reported number of cases was reported in 1997 of 254, against the lowest number in 2002 of 87, resulted in a decrease taken for calculation of 167. However, after a few years, the number of intoxications with lamp oil increased again, the reason not known.

Description of toxicity

Effects after ingestion with lamp oil are acute effects as vomiting, nausea and shortness of breath. In more serious cases the intoxication results in chemical pneumonitis.

Health gain

The health gain was calculated using the EuroQol method, because of the acute character of the effects. This resulted in 1 DALY health gain as a consequence of the measure.

Reliability

Numbers of reported cases of intoxications at NVIC were used as a basis. It is not known if and how large the percentage of underreporting is. Furthermore, in the Netherlands, no fatal cases were ever reported, in contrary to Germany.

(For more information see Appendix 7.)

5.3.6 Nickel

Allergy to nickel-containing products is a frequently occurring problem. A limit of 0.5 µg/cm^2/week for the release of nickel from nickel-containing alloys was introduced in Denmark in 1991. The so-called Nickel Directive 94/27/EC was adopted in 1994 in the EU. This case was included because human data were already available on the impact of the measure. The toxicological endpoint of this case is skin sensitization.

Exposure

The total Dutch population is exposed to nickel which is present in jewellery, watches, frames, buttons, buckles and so on. After the measure was implemented, it is assumed that the exposure to nickel is low enough to prevent new sensitization. This would result in a decrease of newly sensitized persons.

Prevalence

Using the prevalence numbers (for women 20% and for men 5%) against the population of boys and girls born annually (about 100,000 each), 24,000 would become sensitized. 30% reduction of newly sensitized persons was assumed based on a few epidemiology studies, resulting in a yearly decrease in incidence of 7,300. A result of the measure would also be a decrease in elicitation, meaning a prevention of having complaints of the contact dermatitis. It was assumed that 10% of the population having a nickel allergy really has complaints. 12.5 % (nickel allergy prevalence) x 16 million x 10% = 200,000, again assuming a 30% reduction results in a reduction of 60,000 subject with no complaints.

Description of toxicity

Nickel is a skin sensitizer. The induction (sensitization) requires intense exposure. Elicitation of nickel dermatitis in already sensitised persons may occur at very low concentrations. Data gathered after the Danish legislation limiting nickel release from consumer items came into force suggest that the majority of the population are protected against nickel exposure by a release rate of 0.5 µg Ni/cm^2/week for items in close and prolonged contact with the skin.

Health gain

Constitutional eczema was assigned a disability weight of 0.07 which is used for contact eczema.

To prevent sensitization of a new subject, a number of DALYs can be calculated. This applies assuming all sensitized people have complaints. It is however assumed that people try to avoid exposure resulting in no or less suffering. It was assumed (guessed estimate) that 10% still has complaints including avoidance behaviour, resulting in
7,300* 60 * 0,07 * 0.1 = 3,066 DALYs.

For the elicitation of nickel contact dermatitis, it was assumed that only 10% of the sensitized people really have complaints (guessed estimate). The number of DALYs ‘gained’ by the measure is then: 60,000 * 0.07 = 4200 DALYs.

In total, depending on the possible avoidance of nickel exposure, 7000 DALYs could be gained by the implementation of the Nickel Directive.

Reliability

In this case, investigations in a human population were performed with the goal to assess the result from the implemented measure. Still, choices needed to be made from the available four studies, and assumptions were made on the population size. The decision on the assumption of avoidance behaviour influences the final health gain. Furthermore, the

health gain in DALYs is calculated per year, whereas total health gain over a period of time might be even higher.
(For more information see Appendix 8.)

5.3.7 Nitrosamines

Nitrosamines are present in rubber consumer products such as household gloves, slippers, electric cords, toys, teats, and so on. Nitrosamines are also present in food (cured meats, fish, beer) and in tobacco smoke. In 1992 a measure was taken that introduced a migration limit of 0.01 mg nitrosamines /kg product and 0.1 mg precursors/kg product from teats and soothers (Directive 93/11/EC; Food and Commodities Act). The Netherlands has even more strict national legislation on teats and soothers.
The Cosmetics Directive (76/768/EC) states that cosmetic products shall not contain nitrosamines or secondary dialkanolamines (from 1993 on). Another measure is taken for nitrosamines present in balloons. From May 1th 2004 on a warning should be present on the labels to not take balloon into the mouth but only inflate with a balloon pump. In 2006 this is extended with a maximum level of 0.01 mg nitrosamines /kg rubber and 1 mg nitrosatable substances/kg rubber.
This case study is included because nitrosamines belong to different product groups (and thus combined exposure), are carcinogenic, and measures were implemented some time ago. It is a group with many different compounds, which makes it a complex problem.
Exposure
For teats and soothers the target population are young children (0-4 years of age). Nitrosamine concentrations were measured by the VWA before and after the measure was implemented. Exposures were calculated using specific parameters for different age groups of children and for teats and soothers separately. The exposures before were in the order of magnitude of 1 ng/kg bw/day to 8 ng/kg bw/day for the youngest babies. As a result of the measure the exposure was reduced with 95% (rubber teats) to 99% (soothers).
For cosmetics the target population is the general public. For different cosmetic products and for children, men and women, the exposure was calculated. Exposure concentrations for adults are around 5 ng/kg bw/day before the measure, and decreased to about 1 ng/kg bw/day after the measure.
For balloons, the exposure is about 0.001 ng/kg bw/day for children of age 3 to 4.
Background exposure caused by diet (cured meat, sea food, beer, cheese) amounts about 60 ng/kg bw/day in 1980, which was decreased in 1990 to less than 15 ng/ kg bw/day. Added exposure by smoking amounts on average 15 ng/kg bw/day.
Description of toxicity
Endpoint of concern for the group of nitrosamines is carcinogenicity. Several individual nitrosamines are classified as carcinogenic, category 2. More than 300 different N-nitroso compounds have been tested, and show a wide variety in carcinogenic potency. In order to get an impression of the possible health gain, a 'reference' nitrosamine was chosen (N-nitroso dimethyl amine = NDMA) and evaluated. NDMA is most commonly detected. Oral exposure to NDMA results in liver tumours in animal studies. Inhalatory exposure results in carcinogenic effects in the nasal passage. Cancer risk value was assessed on 1.5×10^{-3} per µg/kg bw based on animal studies. Based on human studies, the unit relative risk (RR) per ng/kg bw/day NDMA calculated was 1.175 (95% CI 1.02 – 1.35),

for stomach cancer but assumed to be the same for colorectal cancer. This risk was eventually based on one study with sufficient information to derive a unit risk, but other studies with less detailed information yielded similar results.

Health gain

Legislation on nitrosamines in teats and soothers resulted in a decrease of exposure in the target population of very young children to almost zero. This led to an average health gain in DALY of 0.2 (animal data) – 750 (human data) using a DALY of 8 for each cancer case.

Legislation on nitrosamines in balloons resulted in a decrease in exposure of about 3%, which did not result in any DALY.

Legislation on nitrosamines and their precursors in cosmetics resulted in a decrease in exposure of about 84%. Weighted averaged over total life, reduction in cosmetics contribute for 99% of the total DALY, being nearly 14 and 50,000, based on animal and human data, respectively.

Reliability

Uncertainties are introduced in this case by the complex group of nitrosamines, exposure information on generally only one or few nitrosamines, and the choice of working with one reference compound in the calculations. NDMA is used as a reference compound because of ubiquitous exposure to it, but it is a relatively potent carcinogen, causing an overestimate of health gain.

Some measurements were present for before and after measures, and refereed assumptions were included in the calculations.

Another point of concern is caused by the use of linear extrapolation of the endpoint carcinogenicity. This might introduce another overestimation of the calculated health gain. Furthermore, there is a large difference between health effects and gain based on the use of animal or human data.

(For more information see Appendix 9.)

5.3.8 Toluene

Toluene is present in paints, varnishes, adhesives, glues, and inks for pens. It is chosen because of its reproduction toxic potential. In 2005, an amendment was added to EU Directive76/769 with a limit of 0.1% for toluene in adhesives and spraying paints. Toluene can be found on Annex I (Directive EU directive 2005/59/EC) classified as reproduction toxic.

Exposure

Effects are calculated for hobbyists who model to scale. They use glue and spray paint potentially containing toluene. The population is assumed to be 5,000 in the Netherlands having a frequency of one event per week. Based on product information, an average concentration was assumed of 15% in glue in the tertile using glue with the highest toluene levels, in the other glues the concentration is already below the set limit, and 12.5% in paint. The exposure before the measure to toluene from glue and spray paint was calculated and amounted 0.16 mg/kg bw per event (3.75 mg/m^3) and 26 mg/kg bw per event (620 mg/m^3) by inhalation and 0.005 mg/kg bw per event and 0.89 mg/kg bw per event for dermal exposure. After implementation of the measure, the exposure should

decrease from 0.2 mg/kg bw/event to 1.1 µg/bw kg per event for glue and from 27 mg/kg bw per event to 0.2 µg/kg bw per event for spray paint.
Background exposure ranges from 4 µg/m^3 for outdoor air to 30 µg/m^3 for indoor air.
Description of toxicity
Toluene causes headache, dizziness and eye irritation in humans with a NOAEC of 40 ppm (150 mg/m^3). After repeated exposure nasal toxicity was found at a dose of 600 ppm (2,280 mg/m^3). Effects on hearing and colour sight were reported, resulting in a LOAEC of 35 ppm (human) for colour vision impairment. Toluene exposure in a developmental toxicity study resulted in lower foetal and birth weight with a NOAEC of 600 ppm. In humans, a risk of late spontaneous abortions was associated with exposure to toluene at levels around 88 ppm (330 mg/m^3).
Health gain
No data are available on the relationship between acute exposure to toluene and the occurrence of reproduction effects.
Using 5000 subjects as the target population, and 0.1 as weighing factor for visual impairment, the resulting DALYs from the decrease in percentage of toluene in spray paint amount 12, based on reversible neurological effects.
Reliability
Reliability of exposure assessment is affected because of large uncertainties in number of exposed people, lack of actual exposure data, and limited reliability of exposure models and the input information used. Calculations were performed using average assumptions as much as possible, however, peak exposure would possibly give headaches or dizziness. For severity and duration of potential health effects, assumptions had to be made. (For more information see Appendix 10.)

5.3.9 VOC

Legislation on VOC contents in paints is planned in the future because of concern on levels in the environment and because of health problems in occupational settings. Purpose of Council Directive 2004/42/CE is to limit in 2 phases (2007 and 2010) the emissions of organic solvents from paints and varnishes to reduce contribution of VOCs to the formation of tropospheric ozone. Furthermore, The Ministry of Social Affairs and Employment implemented legislation saying that workers are no longer allowed to use solvent-based paint for indoor painting (from January 2001). This case is included because of the possibility that these measures have implications on consumer health as well.
Exposure
The target population is the DIY population, which is assumed to consist of 4 million people. At the moment, the percentage of solvent-based paint used is about 75%, this will decrease to 40% (in 2010) and further to 0% (after implementation of substitution duty to consumers).
A daring approach was used for assessing the exposure of VOCs from paints. For solvent-based paints, the mixture of white spirit was used with its average characteristics and properties as the sole organic solvent compound present in paints. It was assumed that the content of VOC was on average 40% before the measure, 10% after the measure or zero after substitution. For water-based paint, 3 compounds ethylene glycol, propylene glycol,

and 2-(2-butoxyethoxy)ethanol were chosen as representatives present in concentrations of on average 10%. In phase II (2010) it should be decreased to 3%.

Description of toxicity

For VOCs in solvent-based paints, it was chosen to use data from white spirit as the sole organic solvent present (an ATSDR and EHC document is available). For the present case, the CNS effects and irritation are relevant. A LOAEL of 600 mg/m^3 on irritation was derived from human data. For consumers, the long term effects being chronic toxic encephalopathy (CTE) are assumed to be not relevant because consumers are not exposed to high levels for prolonged periods of time.

Headaches were found in a human study to occur at 18-48 mg/m^3 for ethylene glycol, while for propylene glycol skin irritation and sensitization were found. For DEGBE, the lowest NOAEL was 39 mg/m^3 in a sub acute inhalation study in rats based on increased relative liver weights.

Health gain

The health gain for VOCs in solvent-based paint was calculated using white spirit, EuroQol for a weighing factor, which resulted in about 90 DALYs per year with more or less worst case assumptions. For the glycol ethers and DEGBE, the possible toxic effects were shown at exposure levels exceeding levels occurring before measures are taken, and thus there was no concern, resulting in a health gain of zero.

Reliability

The choice for some example substances, and the use of white spirit for the total VOCs introduces a large uncertainty. Furthermore, the exposure estimates chosen were not average values but maximum exposure values. They were chosen on the assumption of an expert distribution based on literature plus modelling.

(For more information see Appendix 11.)

5.4 Overview of case results

In the Tables 6 to 10, the information from the cases studies given above is summarized. Table 6 gives the information on the different measures for all case substances, Table 7 gives an overview on the estimated decrease in exposure, Table 8 describes the estimated decrease in incidence of effect and finally the estimated health gain for all investigated case studies can be found in Table 9. In Table 10, an overview of the reliability of the health gain assessment is provided.

Starting point for all case studies were the implemented or to be implemented measures for the different case substances. In Table 5, an overview of these measures is provided.

Table 7 shows all exposure levels estimated, calculated or obtained from literature. It should be reminded that the '% decrease' is often 100% because it was assumed that exposure after the measure would be zero. However, in one case when measured data were available, a large decrease could be found as well (nitrosamines). Legislation sometimes mentions allowable levels of a substance (formaldehyde), sometimes it is a total ban

resulting in zero exposure by this type of product. In all case studies (in which calculations could be performed) a decrease was found, which in itself is considered a gain.
Background levels were most often taken from literature sources as EU Risk Assessment Reports, ATSDR documents or Dutch Health Council reports. They were included to give an idea of the contribution of the exposure of the consumer products to the total exposure. One can see, for example, that in the case of the nitrosamines, the total exposure in the baby group consists almost totally of the exposure from teats and soothers. In contrast, in adults the background exposure from food is largest, equalling about 10% resulting from exposure to cosmetics.
For the more acute exposures (in the cases of dichloromethane, toluene and VOC), the percentage against (the more chronic) background levels was not calculated.

In Table 8 an overview is given of the incidences in number of affected subjects in all case studies. Again, in almost all case studies in which calculations could be performed a decrease in incidence was found.
For formaldehyde in cosmetics and azo dyes in tattoos, no reliable estimates could be derived. For formaldehyde in both chipboard, and textile, the (calculated) incidence was already zero before the measure, resulting in no decrease after implementation of the measure. The highest incidence is estimated for headache caused by VOC substances. However, this is based on calculations which are of worst case character. The Nickel Directive results in a fairly high decrease in incidence of nickel sensitized people, which was based on some epidemiological studies. For lamp oil, the information is also based on human information, reports on intoxications. For carcinogenic effects of nitrosamines the two very different estimates are based on animal or human data. For both acrylamide and toluene there was a moderate incidence before and a low or no incidence after the measure.

In Table 9 the overall result is shown for the estimated health gain in DALYs. In this table, the adverse health impact is expressed in DALYs to get more insight in the differences and consistencies between the different case studies.
Based on this table, it is seen that the so-called Nickel Directive resulted in a successfully high level of health gain. Furthermore, the cases of acute exposure by substances in DIY products (dichloromethane, toluene, VOCs) resulted in a health gain of about 100 DALYs each of derived health gain. The number of DALYs derived for the carcinogenic substances differ from zero (formaldehyde), few (nitrosamines, based on animal data), to hundreds (acrylamide), thousands (azo dyes) or ten thousands (nitrosamines, based on human data). These differences in range of DALYs are caused by the level of exposure as well as the potency of the carcinogenic substance, or by the size of the target population of the type of product. Toluene was included as a reprotoxic compound, however, the level and character (acute) of the exposure by this type of product was assessed in the Existing Chemicals program as a concern for CNS effects, but at no concern for the endpoint of reprotoxicity.

In Table 10, the reliability of the exposure assessment, toxicity profile, DALY calculation and an overall estimation is given, based on expert judgement.

For exposure, the reliability provides information if the calculated (mean) exposure for the target population is a good estimate for the true mean exposure of the target population. Dependent on the specific cases, the reliability was assessed taking into account components such as availability of measurements, use of similar analytical methods, number of assumptions made in the exposure assessment, foundation of the used model, and so on.
For the toxicity profile, in many cases animal data are used for the final assessment, introducing an uncertainty factor in the necessary extrapolation of animals to humans. The assumption used for carcinogenicity that tumour formation follows the rule of linearity also introduces uncertainty. Furthermore, the choice of a marker compound (as done for nitrosamines, azo dyes and VOC) affects the reliability of the effects assessment.
In the reliability of the calculation of the DALY, the choice of a weighing factor for effects it taken into account which could sometimes not be directly related to a disease. For many cases, a DALY of 8 for cancer was used (see more information in section 2.4). Furthermore, the estimation of the target population is included.
In the final column (overall), an overall estimation of the reliability of the estimated health gain expressed in DALYs was made, taking into account reliabilities of exposure assessment, toxicity profile and DALY calculation. More discussion on the reliability of the performed case studies can be found in the discussion (see section 6.5).

Table 6. Information on chemical, product, legal measure and health effect in all case studies.

Compound	Product	Legal measure	Year	Measure	Toxicology
acrylamide	cosmetics	Cosmetics Directive (76/768/EC and 2002/304/EC)	2002	0.1 mg polyacrylamides/kg product (non-rinse) 0.5 mg/kg products in other cosmetics	carcinogenicity neurotoxicity
azo dyes	textiles	Council Directive 76/769/EC	1996	ban	carcinogenicity
	tattoos				
dichloromethane	DIY	Directive 76/765/EC	proposal	total restriction in paint stripper/glue remover	acute neurotoxicity
formaldehyde	chipboard	Dutch 'Warenwet'	1987	10 mg/100g	carcinogenicity
	cosmetics	EU Directive 76/768/EC	1995 1998	0.2% for cosmetics and 5% for nail hardeners 0.1% oral hygiene products	sensitization
	textile	Dutch 'Warenwet'	2001	120 ppm	sensitization
lamp oil	household	Directive 76/769/EC Dutch 'Warenwet'	1997 2000	ban on coloured and scented lamp oil	acute poisoning
nickel	jewellery	Nickel Directive 94/27/EC	1994	migration limit 0.5 µg/cm^2/week	sensitization
nitrosamines	teats/soothers	Directive 93/11/EC (Food and Commodies Act)	1992	migration limit of 0.01 mg nitrosamines/ kg product an d 0.1 mg precursors/kg product	carcinogenicity
	cosmetics	Cosmetics Directive 76/768/EC	1993	not contain nitrosamines or secondary dialkanolamines	
	balloons*		2004	warning not to take into the mouth and limit of 0.01 mg/kg rubber	
toluene	DIY	Directive 76/679/EC	2005	limit of 0.1% toluene in adhesives and spraying paints	acute neurotoxicity
VOC	DIY	Council Directive 2004/42/CE	2001-2007-2010		acute neurotoxicity

* The Ministry of Health, Welfare and Sports, and the suppliers or importers of balloons in the Netherlands made an agreement to put a warning on the labels: 'Warning! For safety reasons do not take balloons into the mouth and only inflate with a balloon pump'. This warning should be present on the labels from May 1st 2004. In 2006 additional legislation became into effect, setting a maximum level of nitrosamines and nitrosatable substances in balloons.

Table 7. Overview of exposure estimates of all investigated case studies.
Values are given before and after the measure, the resulting decrease, background values and the exposure through the product (before the measure) compared to the background.

Compound	Product	Toxicology	Exposure before the measure	Exposure after the measure	% decrease	Background exposure	Consumer exposure (% of background)
acrylamide	cosmetics	carcinogenicity neurotoxicity	0.36 µg/kg bw/day	0.004 µg/kg bw/day	99	0.6 µg/kg bw/day	60
azo dyes	textiles	carcinogenicity	8 ng/kg bw/day benzidine 0.2 ng/kg bw/day 2,4-TDA	0 - 5 ng/kg bw/day benzidine 0 - 0.1 ng/kg bw/day 2,4-TDA	62-100[1] 40-100[1]	n.d.	n.d.
	tattoos		-	-	-	-	-
dichloromethane	DIY	acute neurotoxicity	660 ppm (average)	assumed to be zero	100[1]	n.a.	n.a.
formaldehyde	chipboard	carcinogenicity	0.25 mg/m^3	0.06 mg/m^3	78	-	-
	cosmetics	sensitization	not known	0.2 mg/kg bw/day	-		-
	textile	sensitization	6 µg/kg bw/day	5 µg/kg bw/day	17		-
lamp oil	household	acute poisoning	n.a.[2]	n.a.[2]	n.a.[2]	n.a.[2]	n.a[2].
nickel	jewellery	sensitization	n.a.[3]	n.a.[3]	n.a.[3]	n.a.[3]	n.a.[3]
nitrosamines	teats/soothers*	carcinogenicity	8 ng/kg bw/day	0.39 ng/kg bw/day	97	20 ng/kg bw/day **	85
	cosmetics**		5.3 ng/kg bw/day	1.2 ng/kg bw/day	85		20
	balloons***		0.001 ng/kg bw/day	0.0009 ng/kg bw/day	10		
toluene	DIY	acute neurotoxicity	27,000 µg/kg bw/event	220 µg/kg bw/event	99	9-29 µg/kg bw/day	n.a.
VOC	DIY	acute neurotoxicity	660 mg/m^3 white spirit (SB) with peak of 5880 mg/m^3 10 mg/m^3 (WB)	165 mg/m^3 white spirit (SB) with peak of 1420 mg/m^3 3 mg/m^3 (WB)	75	-	n.a.

n.a. not applicable
n.d. not determined
\- could not be calculated
[1] exposure assumed to be zero after the measure
* data given for children 0-6 months (for other age groups, see Appendix 6)
** data given for adults (for children, see Appendix 6)
*** data given for children 2-4 years of age
[2] in this case it concerns lamp oil intoxications, no exposure can be stated
[3] in this case, calculations are performed using incidence numbers (see Table 4), no exposure can be stated

Table 8. Overview of the decrease in incidence of effect in all investigated case studies.
Values (in number of persons) of the effected population are given if possible before and after the measure.

Compound	Product	Toxicology	Data used for RA	Effect	Incidence before	Incidence after
acrylamide	cosmetics	carcinogenicity neurotoxicity	rat study	cancer (thyroid, adrenals, testis) (animals)	2880	32
azo dyes	textiles	carcinogenicity	human	cancer (bladder)	35,000	0 / 21,000
	tattoos				-	-
dichloromethane	DIY	acute neurotoxicity	human and rat	CNS depression	83,000	0
formaldehyde	chipboard	carcinogenicity	rat + PBPK	nasal tumours	0	0
	cosmetics	sensitization		contact dermatitis	-	-
	textile	sensitization			0	0
lamp oil	household	acute poisoning	human	vomiting, nausiness to chemical pneumonitis	254	87
nickel	jewellery	sensitization	human	newly sensitized persons prevention of complaints of contact dermatitis	24,000 200,000	17,100 140,000
nitrosamines	teats/soothers	carcinogenicity	rat and human	liver and nasal tumours in animals, stomach/colorectal cancer in humans	0.03 - 100	0.003 - 10
	cosmetics				2.2 - 7900	0.4 - 1600
	balloons				negligible	negligible
toluene	DIY	acute neurotoxicity	human	headache/dizziness	5000	0
VOC*	DIY	acute neurotoxicity	human	irritation/headache/dizziness	1,200,000	0 / 240,000

n.a. not applicable
- could not be calculated
* for white spirit only

Table 9. Overview of the calculated health gain of all investigated case studies.
Calculation of the DALY is explained for the 'DALY lost' (by exposure before the measure) values, values in DALYs gained per year are roughly rounded

Compound	Product	Toxicology	Calculation of DALYs lost (before the measure) OR					DALYs lost	DALYs gained
				x factor x time		x cancer case			
			incidence before	weighing factor	time	DALY/cancer case	per year		
acrylamide	cosmetics	carcinogenicity	2880			8	/75	300	300
azo dyes	textiles	carcinogenicity	35000			8	/75	3700	1500-3700
	tattoos		-			-	-	-	-
dichloromethane	DIY	acute neurotoxicity	83,000	0.08-0.83[1]	1 hr to 2 days [1]		/75	100	100
formaldehyde	chipboard	carcinogenicity	0					0	0
	cosmetics	sensitization	-						-
	textile	sensitization	0						0
lamp oil	household	acute poisoning	254	0.33 and 0.67 [2]	1 day and 14 days [2]		/75	1	1
nickel	jewellery	sensitization elicitation	24,000 200,000	(60x0.1x)0.07 0.07	year year			10,000 14,000	3000 4200
nitrosamines	teats/soothers	carcinogenicity	0.03-100			8	/75	0.2 - 800	0.2 - 800
	cosmetics		2.2-7900					20 - 65000	14-55000
	balloons		negligible					negligible	negligible
toluene	DIY	reprotoxicity							0
		acute neurotoxicity	5000	0.1 [3]	4 hours [3]		/75	12	12
VOC	DIY	acute neurotoxicity	1,200,000	0.,08, 0.17 and 0.58 [4]	2, 4 en 24 hours [4]		/75	90	90

n.a. not applicable
\- could not be calculated

[1] different weighing factors and time periods established with Euroqol correlating with 3 used AEGL values.
[2] for acute effects 0.33 and 1 day and for chemical pneumonitis 0.67 and 14 days
[3] weighing factor for visual impairment
[4] numbers are spreaded over different effects

Table 10. Overview of the reliability of the different components in the calculation of health gain in all investigated case studies.

Compound	Product	Reliability in exposure estimate	Reliability in assessment of health effects	Reliability in DALY calculation*	Overall reliability
acrylamide	cosmetics	low	middle	middle	low
azo dyes	textiles	low	low	middle	low
	tattoos	-	-	-	-
dichloromethane	DIY	middle	middle	high	middle
formaldehyde	chipboard	high	middle	n.a.	
	cosmetics	low	high	n.c.	
	textile	middle	high	n.a.	
lamp oil	household	middle	high	high	high
Nickel	jewellery	middle	high	middle	middle
nitrosamines	teats/soothers	middle	low	middle	low
	cosmetics	middle	low	middle	low
	balloons	middle	low	middle	low
Toluene	DIY	low	high	middle	middle
VOC	DIY	low	low	middle	low

The reliability is given in qualifications of low, middle or high.
Low = not very reliable, range of 1000, middle = reasonably reliable, range of 100, high = reliable, range of 10.
n.a. not applicable (no health effects expected before measure)
n.c. not calculated (missing exposure data before measure)
* reliability in the DALY calculation includes uncertainty in the choice or derivation of the weighing factors, YLL with cancer, and estimates of the target population

6. General discussion

In this report, the impact of risk reduction measures on chemicals in non-food consumer products was investigated. For policy makers, there are several reasons to implement measures to reduce exposure of consumers to hazardous substances (see Introduction).

Two different lines of investigations were used. The first approach was making an inventory of existing studies in order to explore the possibility of extrapolation of study results to the field of consumer products. This was accomplished by looking at health impact assessments from several areas and for example REACH impact studies. Results of this investigation are discussed in section 6.1.
The second approach consisted of performing a quantitative estimate of potential health gain of individual case studies. This approach resulted in an estimated exposure reduction (of 0 -99% depending on substance and measure), and the associated estimated potential health impact (ranging from 0-55,000 DALYs), depending on substance and measure. Results and reliability of these nine case studies are discussed in section 6.2.

6.1 Quantification of overall health gain

In the introduction, it was mentioned that probably the largest contribution to reduce adverse health effects has already been achieved in the past. Fortunately, historic examples as arsenic compounds in wallpaper paste and benzene in glues that lead to significant health problems are not common nowadays. Current legislation already results in a condition that provides protection for consumers.

Classification of substances under Directive 67/548/EC (Annex I) with a C, M or R label has consequences which are dependent on the application of the substance and the corresponding legislation. In the Limitations Directive 76/769/EC (verbodsrichtlijn in Dutch) CMR substances category 1 and 2 are not allowed in preparations used by consumers above the general concentration limit of 0.1 mass%. For consumer articles, however, restrictions for a specific substance (such as nitrosamines in teats and soothers) need to be taken specifically when necessary. The Biocidal Products Directive (98/8/EC) prohibits the approval of biocides that contain CMR category 1 and 2 substances. The Cosmetics Directive prohibits the use of CMR category 1 and 2 substances as ingredients of cosmetic products. CMR category 3 substances are allowed in cosmetics only after a risk assessment and a subsequent risk management decision.
Classification of a substance (category 1 or 2) might therefore – indirectly – lead to a substantial potential health gain, if the substance is present in a large range of products and exposure is prevented as a result of classification. However, with the investigations up till now, and the knowledge we obtained, it is not possible to calculate the total health gain for all chemical substances (category 1 and 2) on Annex I after implementation of risk reduction

measures, because information such as the presence and the weight fraction of compounds in products, the weight fraction of a chemical in products, and the contribution to exposure is in many cases not available. Also, regarding carcinogenic compounds, one simply cannot add up all carcinogenic compounds without regarding differences in potencies. In addition, in a previous project on exposure to chemicals at the workplace, it was demonstrated that it is difficult if not impossible to translate effects into a DALY calculation for reprotoxic endpoints (see Baars et al., 2005).

As was done in the REACH impact studies, a health impact assessment might be done using *assumptions* on percentages of decrease in exposure, a percentage of presence in consumer products or a percentage of contribution of diseases caused by chemicals related to exposure to consumer products. However, there is not enough data to estimate these percentages; uncertainty in the outcome would be too large to justify the result. The approach chosen for the assessment of the health effects due to occupational exposure to chemicals (Baars et al., 2005), used the actual occurrence of a certain disease as a starting point. It was then tried – based on literature data from various sources – to estimate the contribution of workplace exposure to chemicals for that disease. For exposure to chemicals from consumer products, such an approach is not feasible. The reason again, is that there are not enough data to estimate the contribution of the total exposure from consumer products for a single chemical or group of chemicals. Data on the exposure to chemicals from consumer products are – in general – lacking.

Thus, a health impact assessment on the total field of legislation on chemicals in consumer products is not (yet) possible. Probably the largest health gain caused by policy interventions is resulting from the preventive character of current legislation and the risk assessment procedures associated with them. However, this potential 'gain' is difficult to quantify.

6.2 Health impact assessment for chemicals and consumer exposure - case studies

Although with rather large uncertainties, in several case studies it was possible to estimate in a quantitative way the potential effect of an implemented measure. In some other cases, the outcome of the exercise is not more than an effort to estimate its order of magnitude. As shown by the case studies, it is not possible to design a single 'blue print' for assessing the health consequences of a measure. In every case study, different information was available and as a consequence different approaches were followed for the analysis. Nevertheless, the case studies show valuable information that can be used in various ways. In the next sections, the different aspects will be discussed.

As a start, the consequences of a measure were demonstrated by analysing the decrease in level of exposure. In the nitrosamine case, for example, the decrease in exposure of young children to nitrosamines from the use of teats and soothers was 99%. Calculation of this difference in exposure already shows in a quantitative way the effectiveness of this measure.

In several case studies, the calculation could be extended to the quantification of an increase in the margin of safety (MOS), a decrease in incidence of effect and finally in the decrease of health loss, expressed in DALYs. Using the concept of DALYs, a tool for comparing the various potential effects of certain measures is available. Even if no gain in health effects can be calculated, a policy measure to resulting in lower or zero exposure to a (CMRS) compound is desirable for other reasons.

From the case studies, it could be learned that it is not easy to predict the potential health gain of a measure (expressed in number of DALYs). Many factors influence the outcome of such calculations. For some cases, the general feeling beforehand was that a measure would have a rather large impact; the expected impact was sometimes only based on hazard aspects, instead of actual risk. Although a measure need not be able to reduce risk or burden of disease, it can still be very valuable to reduce exposure and possible secondary consequences (see for example the case study on lamp oil intoxication). Possibly the expression in a DALY, which compares different diseases/ health effects with each other, may not the most relevant or most appropriate way to demonstrate the value of policy measures. A decrease of exposure to a substance with CMRS properties, can also be a very illustrative indicator. A discrepancy between the number of DALYs and the decrease in incidence after a policy measure was also shown for lamp oil. In the case of the lamp oil investigations, the quantitative impact of the measure expressed in DALYs was only 1 DALY. The number of intoxications by lamp oil however was clearly reduced after implementation of the policy measure, which was not reflected in the DALY outcome. In addition, the DALY methodology does not take into account secondary aspects of adverse outcomes. Subjective feelings of parents and the child on the actual intoxication, a visit to the hospital and other socio-economic aspects are all important consequences of such an intoxication but are not taken into account in the DALY calculation. These aspects, however, may still be important for policy makers to initiate measures.

Though the number of case studies is limited, they show some interesting tendencies (see Table 8).

- Measures implemented for compounds in products which are only used incidentally, resulting in more acute exposures, did not result in a high number of DALYs. This is seen in the case studies of lamp oil, toluene or dichloromethane. Another common aspect in these three case studies was that a small target population was involved. Because the health effects are of a short duration and apply to a small target population, the total number of DALYs is limited.
- Measures on compounds used in products with a more chronic exposure scenario and a large target population, did result in a higher burden of disease (when expressed in DALYs), as seen for example with nickel and azo dyes. It is not possible to draw a firm conclusion on this, because in the presented case studies only two endpoints (sensitization and carcinogenicity) are included for chronic exposure scenario's. Nevertheless, in the presented case studies, the measures taken on products which are used during a prolonged period of time (or daily), such as clothes, jewellery or cosmetics result in a higher number of DALYs. In the case study involving sensitization, it seems that measures taken for this

endpoint result a great health gain i.e. large numbers of DALYs. However, it should be realised that for the estimated case of nickel, a relatively common allergy was chosen (1 out of 10 persons is said to have a nickel allergy) which involves a large target population. Interestingly, allergy-like effects also contributed significantly in the burden of disease due to exposure to chemicals at the workplace (Baars et al., 2005). However, large potential health impact of measures directed on allergenic compounds is not surprising since the number of atopic and allergic people has been shown to have increased significantly during the past decades and amount nowadays several tens of the general population (Anderson et al., 2007; Health Council, 2003; Schnuch et al., 2004; Strachan, 1989).

Once again, it should be noted that the number of case studies is too limited to draw general conclusions. Also, caution should be taken because results are only very approximate estimates at best. Further analyses of case studies may result in a further substantiation of these indicative conclusions.

6.2.1 Comparison of the results from case studies with other investigations

The health impact of measures in terms of DALYs ranged in our study form 0 to several (ten) thousands. Since similar estimates have not been made for non-food consumer products, results will be compared with data related to other subjects.

The National Public Health Compass (www.nationaalkompas.nl) gives figures on mortality, prevalence or incidence and burden of disease in DALYs for 56 selected diseases in the Netherlands in 2003 (dated 19 June 2006). In the paragraphs below some illustrations are given.

For stomach and colorectal cancer, a total burden of disease is given of around 90,000 DALY. In the case study on **nitrosamines**, which are assumed to cause stomach and colorectal cancer in humans, the contribution via exposure to nitrosamines in consumer products resulted in about 500 (based on animal data) to 65,000 (based on human data) DALY. This implies that either about 0.55% (animal data) or 72% (human data) of all stomach and colorectal cancer cases would be caused by nitrosamine exposure via non-food consumer products. It cannot be concluded which of these two estimations is most accurate (if one is at all). When taking estimated background exposure into account (i.e. exposure to nitrosamines via other routes, and to other chemicals causing these types of tumours), the (point) estimate based on epidemiological data seems to give an overestimation (also note that part of these tumours may stem from other etiological factors, e.g. genetic, microbial, viral factors). Nevertheless, it indicates very clearly the wide range in the final outcome (more than a factor of 100) depending on the data used or available.

The Health Council report (2007) reports prevalences of 1-3%, 3-5% and 1.5-3% for food allergy, asthma and hay fever, respectively. The National Public Health Compass reports a number of people suffering of contact eczema of 3.7-5.3 % of the dutch population. However, this is based on registration by house docters. For contact eczema, the total burden of disease in the Netherlands (in 2003) is almost 30,000 DALY. In the case report on **nickel**, it is stated that nickel allergy would comprise about 12.5% of all contact allergies in the Netherlands, resulting in a total of about 3750 DALYs. The estimated health gain as a result of the implementation of the Nickel Directive was calculated to be 3000 DALYs for prevention of newly sensitized persons and 4000 DALYs for preventing complaints of persons already having a nickel allergy. Given the uncertainties established in the case report, this appears to correlate very well and provides some confidence in these results.

For the other case studies, the health effects involved were not reported in the National Public Health Compass.

In 'Our food, our health' (Van Kreijl et al., 2004/2006) an estimate of the possible health gain (in DALYs) was calculated for acrylamide found in food if exposure was avoided: based on estimated exposure rates it was calculated (for the Dutch situation) that the presence of **acrylamide** in food products may lead to between 75 and 130 additional cases of cancer per year. Assuming that each case will result in premature death and an average loss of five life-years, the health loss can be calculated as 375-650 DALYs per year in the Netherlands.
In the present study, it was estimated that the (former) use of acrylamide in cosmetics resulted in an estimated number of around 180 DALYs for cancer. The implemented measure resulted in around 300 DALYs health gain assuming that each case will result in premature death and an average loss of 8 life-years (see above). Based on these two investigations (with all uncertainties in it) it seems that both exposure sources (food products and cosmetics) contribute(d) equally to the overall health effects of acrylamide. The estimates relating to acrylamide are only approximate and may be too high, since they have both been extrapolated from the results of animal experiments based on conservative hypotheses (i.e. linear extrapolation from a high dose response observation).

For **nitrosamines** in food, based on conservative estimates, combined exposure to vegetables rich in nitrates and fish can result in tens to approximately one hundred additional cancer cases per year. Assuming premature death with an average loss of 5 life-years (as done in "Our food, our health"), the resulting health loss is approximately 100 to 500 DALYs.
In the present report, the exposure to nitrosamine from teats and soothers, or from cosmetics, using 8 life-years, resulted in about 30 DALYs per year in the Netherlands. The contribution of food to the total nitrosamine exposure is higher compared to the exposures resulting from cosmetics, as calculated for adults. However, in the case of nitrosamines in teats and soothers, the target population consists only of young children. For children in the age of 0-6 months, the contribution of the exposure of nitrosamines by food is much smaller compared to that for adults. The measure on teats and soothers resulted in an overall decrease in exposure of about 95%. The relative contribution of exposure from non-food consumer products is therefore higher for children than for adults.

The REACH impact studies (EC, 2003; Pickvance et al., 2005) mostly looked at skin diseases, cancers, and respiratory disorders. Looking at the endpoints in our case studies, it is interesting to see that the diseases resulting in the highest health gain are contact eczema and cancers. However, the approach by which the health impact is estimated is very different. In our case studies, we specifically try to estimate a (realistic) person-based exposure estimate as a start, with a comparison before and after the measure. This exposure estimate is then used further to assess the health impact on the population level. In the REACH impact study, the effectiveness of REACH was assumed very roughly to be a 1/3 decrease (lower bound) to 2/3 decrease (upper bound) of health effects caused by unknown chemicals. This estimation was determined without performing an analysis of possible changes in exposure, and without any endpoint-specification.

Comparison of the results from our case studies with the study on 'Health effects and burden of disease due to exposure to chemicals at the workplace – an exploratory study' (Baars et al., 2005) can not yield relevant insights. The starting point in that study was specific disease, for which it was tried to establish the contribution of occupational exposure to a chemical. Results showed the contribution of workplace exposure in a total burden of disease in the Netherlands, which is another approach compared to the methodology used in this report.

6.2.2 Reliability of the health impact assessment in the case studies

In the health impact assessment of the case studies, as summarized in section 5.4, information was given on the reliability of the different steps in the assessment. Some factors influencing this reliability are discussed further, and illustrated in Figure 3.

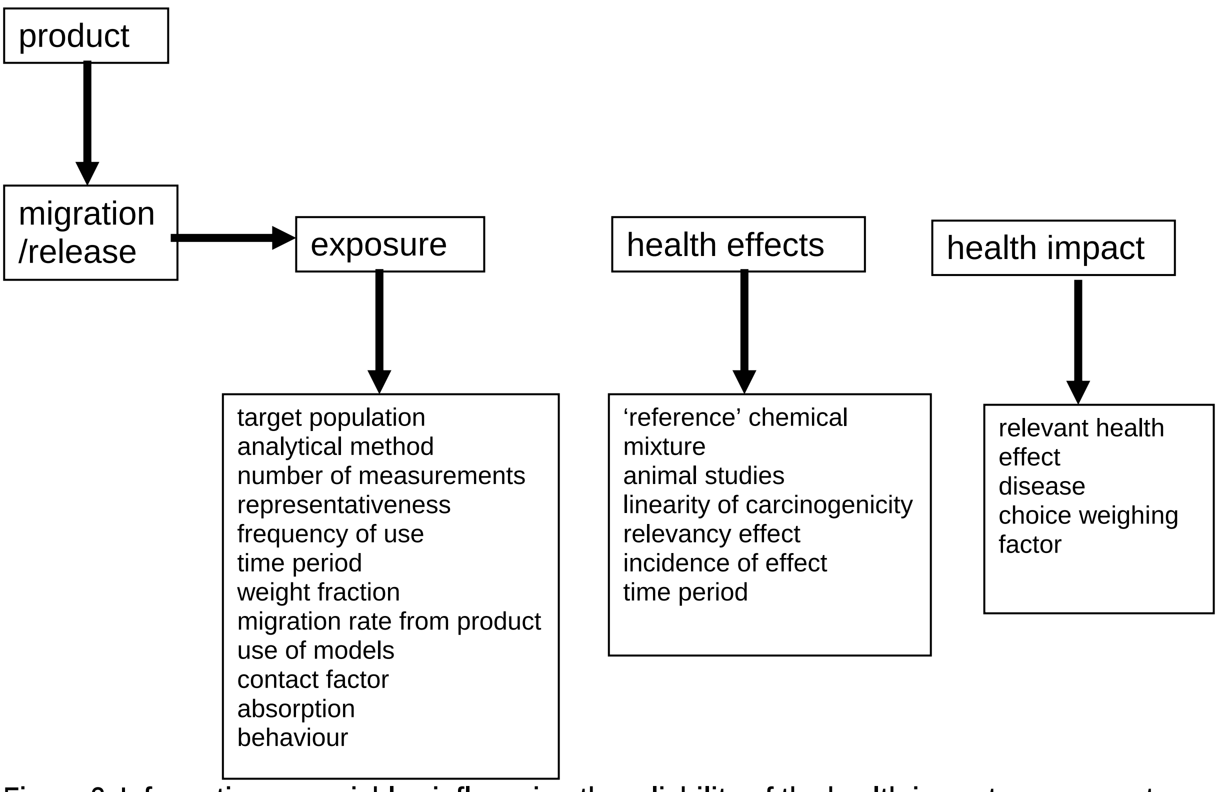

Figure 3. Information on variables influencing the reliability of the health impact assessment.

6.2.2.1 Exposure

For risk assessment procedures, which are meant to be protective, a worst case point estimate of exposure is often used, certainly as a first approach. In the case of a predictive health impact assessment, the exposure estimate should reflect the actual exposure situation as much as possible. For the studied cases, exposure data required for HIA differ according to the health effect and dose-response curve.

1. For most carcinogenic effects, although disputable, a linear, non-threshold dose-response curve is assumed in Risk Assessment. In these cases, for calculation of HIA it is sufficient to have information on the change in population average exposure related to a measure. The absolute value of exposure does theoretically not affect the HIA outcome.
2. For other health effects, related to more chronic exposure, associated with a clear threshold value, it is important to know the exposure distribution over the population In addition, the background exposure should be taken into account since this may determine to a large extent whether exposure is above the threshold or not. This is for example true for formaldehyde and nasal tumours. Data are generally lacking on actual consumer exposure distributions. For background exposure, all other sources of exposure should be quantified as much as possible, preferably at an individual level. This includes other food and non food consumer products, and environmental as well as occupational exposure. Clearly, this information was often not available or could not be retrieved within the scope of the study. This provides substantial uncertainty in the exposure estimations. The resulting error in HIA can vary from 0 to very large.
3. For effects related to short term peak exposures with assumed threshold level, such as effects on the central nervous system due to solvents, information on temporal exposure variation should be known. As for the situations described under 2, concurrent background exposure information and population exposure distributions should be taken into account. Again the absence of this type of information provides substantial uncertainty in the exposure estimations.

Besides incomplete data on exposure distribution and background exposure, there were some other aspects leading to uncertainties in exposure assessment in the studied cases. In general, overestimation of exposure leads to overestimation of health effects. In analogy, overestimation of exposure *reduction* leads to overestimation of health impact of a measure. Since the sources of exposure information and the magnitude of error in the exposure estimations may differ before and after the reduction measure, no general conclusions can be drawn on the direction of potential error in the estimated heath impact.

Measured exposure or product data

For most of the studied cases and measures, some measured exposure or analytical product data were available. The analysis and methodology to generate the exposure data before and after implementation of the measure were not always similar or information on methodology was lacking. This could have led to under as well as overestimation of the exposure reduction due to a measure.

In cases on exposure to mixtures of compounds (nitrosamines, VOCs and azo dyes), used exposure data were not or not necessarily representative for the mixture of compounds as found in the evaluated consumer product. Since there is potentially a large difference in toxicity between compounds in a mixture, this will have resulted in more uncertainty in exposure reduction and the HIA.

Modelling exposure
In most cases actual and representative exposure information of humans was lacking. In some cases exposure data were available but their representativeness for the Dutch situation was not always clear. On the other hand, in some cases actual human data on the health effects were available which makes exposure estimation unnecessary. Because of this lack of direct exposure data, exposure modelling is the only option to estimate the exposure.
The inhalation, dermal and oral exposure are modelled based on product information and other input data on use (frequency and amount) and exposure circumstances. Although for example the exposure modules from ConsExpo have been validated experimentally, these models provide an estimation of the exposure in reality, thereby introducing uncertainty. The data most lacking, also hindering the accurateness of exposure modelling, are data associated with product use and its variation (amounts, frequency, distribution in the population).
A special issue is the extrapolation form external (dermal, oral or inhalation) to internal exposure (taken into account absorption rates). This is sometimes necessary to be able to combine exposure from various routes or to use specific toxicological data for estimation of health impact. In most of these cases, assumptions were made on absorption rate because compound specific information was not available. This may have led to considerable errors of the estimation of the internal dose and hence of health effect.

Representativeness of data
Often, limited data had to be used to estimate population average exposure. This is true for analytical data as well as input data for modeling exposure. If data were available, representativeness of these data for the total target population was usually not known. Besides, the presentation of the data was generally insufficient to derive the average of these data. This may have led to additional misclassification.
Monitoring data supplied by VWA and similar organizations, their task being enforcement of legislation, could lead to over sampling consumer products suspected to contain higher concentrations. With the same dose-response information, this leads to overestimation of the health effect.
If data were not available for the Netherlands, foreign data were used. In some case the use of these data for the Dutch situation was reasonable (e.g. skin sensitization due to nickel (Danish data)), although representativeness for the Dutch situation was not always clear.

Because of lacking data, a practical approach, or because the measure has not been implemented yet, in several cases exposure after the measure was assumed to be zero or practically zero (e.g. acrylamide and dichloromethane). In reality, exposure to the substance will almost never be completely abolished. In these cases, the health impact of a measure will mostly be overestimated.

Exposure during specific time windows
In some case studies, relevant exposure occurred only for a certain period of life (for example children). In the case of carcinogenic effects, this relatively ‘high’ exposure is averaged over 75 years because it should be compared to a lifetime cancer risk. This may provide a substantial underestimation of the potential effects because high exposures early in life possibly contribute substantially more to the overall cancer risk than low exposure levels distributed over a lifetime (Bos et al., 2004). However, at present no methodology is available for a better estimation of cancer risk.

Target population
Several measures were directed on products which are not used by the total population or specific (age) group with known size. For these, mostly DIY products, no reliable data were available on number of actual users. Numbers can be under as well as overestimated, resulting in potential bias of unknown direction.

Overall effect on HIA
Depending on the availability and validity of the exposure information, the reliability of the exposure estimate ranges between high, with at maximum several factors between true and estimated exposure for formaldehyde in chipboard, and low, with the error being potentially several orders of magnitude, for about half of the measures. The absolute and relative effects on estimated health impact for the Dutch population are not per definition equally large. Sensitivity analyses may be used to estimate the potential size of these effects.

6.2.2.2 Health effects
In the present case studies, the starting point was decided to be compounds that had CMRS properties, thus carcinogenic, reproduction-toxic or sensitising. For some compounds, due to the exposure scenario chosen, the relevant effects were however more acute, concerning airway irritation, or acute neurotoxic effects such as dizziness and headaches. These effects were sometimes more relevant to use in the case studies than the CMRS endpoints associated with the selected substances.

The experience with the case studies in general clearly indicated one of the most essential aspects of this kind of health impact assessment: while the DALY-approach is designed from the clinical point of view using defined human diseases (allowing the comparison of their impact and severity), the current approach starts often with toxicological or physiological effects. A DALY-approach then requires the translation of such effects into ‘disease’. In some cases, this appears to be evident: the formation of tumours in animals translates into cancer for humans (see below for details). For other effects, this translation provides problems. Effects on liver weights or liver enzyme activities might be used to establish a No Adverse Effect Level (NOAEL) in risk assessment, but linking these effects to a related human disease is not directly evident (of course depending on the nature of the effect). Especially for reproduction toxicity, it is expected beforehand that it would be very difficult (see also Baars et al., 2005) to translate toxicity effects into ‘human disease’ allowing expression in DALYs. For example, when infertility or foetal loss is found in an animal experiment, it is difficult if not impossible to extrapolate this to actual human health effects, and even more difficult to weight this into DALYs. In the following sections these aspects are further discussed.

Extrapolation from animal toxicity data to human health effects
For the performance of a HIA, human epidemiological data are preferred, in spite of the fact that they are subject to potential biases. In reality, however, most effects of chemicals are only studied in animals. Therefore, extrapolations from animal to the human are necessary for a HIA. The 'traditional' risk assessment is completely designed to assess the 'safety' of a chemical: i.e. they have been developed from the view of public health protection. Therefore, no-effect levels in animal species are extrapolated to humans using so called assessment (or safety) factors for inter- and intraspecies variation (in general 10x10=100). The basis for this philosophy is that in most cases we do not know whether humans are actually more or less sensitive for the effects of the chemical under investigation, but we assume humans are 10 times more sensitive than the average animal, or whether certain humans are more sensitive than others, again assuming a factor of 10. For obvious reasons, such extrapolations are always on the safe (conservative) side. In this way, the total system 'ensures' the protection of public health.
For a HIA, however, we need to determine the true exposure and health effects as much as possible. The default extrapolation factor of 100 used in risk assessment is in this case probably not realistic. Because in reality these factors may be highly variable and even be smaller than one (in cases where humans are less sensitive than animals). However, it is at present unknown how to extrapolate the animal effects to humans as realistic as possible. This problem is illustrated in Table 11.

Table 11. Illustration of difference in risk assessment (RA) and health impact assessment (HIA).

	Risk Assessment	**Health Impact Assessment**
Exposure	Worst case estimate	Realistic estimate
	person based	population based
Toxicity	Define a No-Observed-Adverse-Effect-Level for the critical effect	Derive exposure-response associations based on actual occurring effects
	Focus on parameters indicative for toxicity	Focus on manifest effects
	Extrapolation to a safe level (protection for any adverse effect)	Extrapolation of effects in animals to effects in humans
	Assessment factors accepted in consumer protection paradigm	Assessment factors do not provide a realistic extrapolation
	PROTECTIVE	PREDICTIVE

Carcinogenicity
In the calculations concerning cancer as an endpoint, uncertainty is introduced because the relevance and difference in sensitivity for humans of tumours found in animals is not always clear. In the case of formaldehyde, the type of cancer induced in both humans and animals is similar. In contrast, in the case of nitrosamine, the information on the type of cancer from animal experiments and human epidemiological studies do not correspond. So, it is not certain whether a particular type of tumours observed in animals will actually also occur in humans. In addition, it is mostly not known whether humans are equally sensitive to the tumour inducing effects of a chemical. This introduces much uncertainty.
Furthermore, calculations were performed assuming a linear relation for dose and the occurrence of carcinogenicity. This assumption of a non-threshold approach using a linear relation is originating from the risk assessment paradigm where this non-threshold linearity is thought to be a conservative (i.e. safe) approach. Thus, in risk assessment it is tried to *protect* the population from cancer development. In the present case, however, we try to estimate the health outcome on a realistic base as much as possible. However, at present no other accepted ways of extrapolating tumour rates from animals to humans are available. The linear relation therefore seems the most practical approach available at this time.
In the report ‘Our food, our health’, the consequences of carcinogenic effects were estimated using a rounded factor of 5 years of life lost for each cancer case. No distinction was made between the various types of cancers and related survival periods. This was because the authors of the report stated that this would fall within the boundaries of the uncertainty in these calculations. In the present project we used 8 years of life lost per cancer case, taking into account premature death but also years lived with disease. This assumption might have a scientifically better base compared to 5 years, it is still only based on information of 65% of all cancers (see section 4.1.3.3).
Another difficulty is the evaluation of short-term exposures in relation to the endpoint of carcinogenicity. First, the example with nitrosamine, where children experience a (relative) ‘peak’-exposure for 0-6 months. Although it is known that even short-term exposure might contribute to tumour development, it was decided to average the exposure over life-time. This may provide a substantial underestimation of the potential effects because ‘peak’ exposures early in life may possibly contribute substantially more to the overall cancer risk than low exposure levels distributed over a lifetime (Bos et al., 2004). However, at present no methodology is available for a better estimation of cancer risk. Secondly, potential health gains were calculated per year. In the case of the endpoint cancer, it should be mentioned that the effect of a measure will be delayed because of a latency period in cancer formation: a stop or reduction in exposure does not directly result in a stop or reduction in cancer occurence.

Sensitization
In case of sensitization, the problem of avoiding behaviour was encountered. People having an allergy to a certain compound might never have complaints in real life because they avoid exposure to the allergy inducing agent. For example, people with a known allergy to nickel avoid wearing nickel containing jewellery. A weighing factor for constitutional eczema is available, and used for contact eczema, which might be somewhat high for contact eczema. In the nickel case, it was decided to further take into account that people do not have

complaints all the time, and not all people have similar complaints. Arbitrarily, a factor of 10% was used to include this avoiding behaviour.
For sensitization, especially regarding nickel, many epidemiological studies are performed. Data on prevalence only provides an indication of the part or percentage of the population that has not been sensitized in regard to a similar age group a few years ago. It does not directly display the decrease of incidence (number of new sensitized subject per year) of an allergy. To derive the incidence of newly sensitized subjects to a substance, birth and mortality rates are used in combination with the prevalence numbers before and after the measure. Since newborns are not sensitized by birth a fraction would become sensitized in coming years. The important assumption made, was that the prevalence would remain the same over time in an unchanged situation (no measure taken). Using life-tables would be a more refined approach to assess health impact over a few decades (Miller and Hurley, 2003).
The cause of the global rise in the prevalence of asthma of the 1990s remains the subject of debate. Part of the explanation is certain to be increased awareness of asthma within the medical community and the general public. However, the rise is in all probability also due partly to lifestyle changes associated with greater prosperity, such as changed dietary patterns, changed domestic environments and exposure to fewer infections (Matricardi, 2001; Nowak et al., 1996; Health Council of the Netherlands, 2007). It is assumed that such prosperity-related factors are particularly influential in the perinatal phase of life. This would explain why the rise (and the present decline) mainly involved children. This explanation is sometimes referred to as the hygiene hypothesis.

Reproduction toxicity
For reproduction toxicity, no case was included in this study. For toluene, a selected case for this endpoint, measures were implemented on products associated with short term exposures, leading to low long term average exposure. For these type of exposures the endpoint of reproduction toxicity was not relevant.
However, it would be a challenge to investigate the measure on a reprotoxic substance. Reproduction toxicity encloses a lot of different causes and disorders. A disorder can be present before fertilization (such as reduced fertility), during pregnancy (such as a higher chance on miscarriage) or after birth (decreased birth weight, congenital defects, developmental effects). Some of these disorders are relevant for women as well as for men. Different from other diseases and disorders, reproduction disorders are only manifest in people in the fertile years desiring to have children.
The extrapolation to a human disease will be a problem. A weighing factor might possibly be assigned to a miscarriage, depending on the age of the foetus. However, the question would be if a burden of disease should also be attributed to the foetus itself (similarly dependent of age), in terms of lost life-years. Would this situation amount to zero DALYs because no healthy years were lost or should it amount to a whole lifespan since the foetus was unable to develop into a born child?
How should loss of health be calculated for parents in the case of fertility? The parent may have no health complaints at all beside the fact that they cannot obtain children in a normal way. Or should it be calculated for the (unborn) child as well? In the case of children born with a congenital defect, should only health loss of the child be taken into account of also the effect of this on the parents?

As was already stated by Baars et al. (2005) the burden of disease due to exposure of reproductive toxicants is very difficult to assess and requires a) a very thorough investigation on the relation between exposure and effects and b) an expert discussion on the 'weighing' of such effects in order to calculate DALYs. Such further discussions for substances on the workplace are now included in a new project.

6.2.3 Possible health loss by alternatives

In the present case studies, only the reduction in exposure to a specific chemical (or group of chemicals) was taken into account. However, these chemicals are often present in a product for a certain reason. Reducing or banning the use of one chemical will often mean replacement by another. For example, when dichloromethane is banned from glue- or paint remover, this will be replaced by another compound. The policy strategy is directed towards less harmful substitutions. In the present case studies adverse health effects caused by possible alternatives (substitution) are not taken into account.
There may be some examples of adverse health effects introduced after the implementation of the measure, caused by replacement substances. In the case of reducing VOCs in paint, more water-based paints were introduced on the market. From the use of water-based paint containing acrylates, it is known that they might result in skin sensitization. Another example is the legislation on lamp oil. This measure was meant to ban coloured and scented lamp oils from the market. However, non-coloured oil was sold together with some colouring fluid allowing consumers to make their own coloured oil. In another, non-coloured oil was sold in coloured glasses. The impact of remaining exposure to non-coloured oil was not taken into account in the respective case study.

In conclusion, in several cases the total health gain resulting from an implemented measure could be lower than estimated because of the possible health effects of substitutes. Quantification of the net effect would require an additional full HIA. This was beyond the scope of our study. Besides, information on substitutes will often not be available. Furthermore, new legislation and/or administrative regulations are often subject to socio-economic analysis (SEA) in order to help determine whether a proposed regulation is necessary or burdensome. (OECD, 2000). In addition to requiring more rigorous analysis of costs and benefits, such initiatives call for better representation of, and consultation with, different stakeholders affected by the legislation. In many cases, the risks posed by a chemical will be uncertain and decision makers may favour adopting a precautionary approach. In general, the aim should be to strike a balance between the costs involved in reducing risks, the known benefits of the chemical in the use(s) of concern, and the benefits stemming from risk reduction.

7. Conclusions

For the first time the potential health impact of an implemented policy measure on a chemical in a consumer product is quantitatively determined. To what extent this is possible is dependent on the availability of data and existing knowledge.

- The impact of measures on chemicals in consumer products can be evaluated on different endpoints: i.e. reduction of exposure, reduction of incidence of health effects and, in some cases reduction in burden of disease.
- The evaluation of health impact of measures on chemicals in consumer products with the currently used approach is only useful and feasible when considering orders of magnitude; i.e. it only allows a to make a distinction between measures that have potentially (very) high health impact from those that have (very) low health impact.
- At present it is not possible to quantify the total health gain of all policy measures on chemicals in consumer products together; but it will undoubtedly be higher than the sum of health impacts of the (only nine) selected examples presented in this report.

The experience and extensive knowledge on the risk assessment of chemicals cannot be used directly for the prediction of the health impact of current exposures and exposure reduction measures.

- Performing a protective risk assessment using worst case exposure estimates and assessment factors in assessing health effects is principally different from assessing a health impact with a predictive character. Although both make use of the same type of data, the concept of the two approaches is quite different.

The reliability of a health impact assessment is affected by uncertainties in the three basic underlying steps, i.e. in the exposure assessment, the effect and risk assessment and in assigning the DALY values.

- In the exposure assessment, uncertainties may be due to lack or limited validity of:
  a. available (measured) data;
  b. inhalation and dermal exposure models;

c. insight in size of target population;
d. assumptions made for exposure models (frequency of exposure, amounts used et cetera);
e. information on background exposure;
f. population exposure distributions.

- In the effect and risk assessment, uncertainties may be due to lack of accuracy and specificity of the response data, i.e.:
  g. whether the single *observed* no-adverse-effect dose descriptor from animal data is in fact the *true* no-adverse-effect dose descriptor;
  h. whether effects observed in animals have relevance to humans;
  i. whether assessment factors for extrapolation from observations in animals to humans, within humans accurately describe the true differences.

- In assigning DALY values, uncertainties might be introduced due to:
  j. limited information on incidence and duration – or, alternatively, prevalence – of disease or health effect;
  k. assessment of weighting factors for severity of disease or health status;
  l. projection of retrospective incidence and mortality data on evolution of incidence and mortality in the future.

Next to the DALY-concept, parameters such as the decrease in exposure and decrease in incidence of effect may as well provide valuable insight on the impact assessment of implemented measures on chemicals used in consumer products.

- It should be realized that the use of DALYs for policy evaluations in the chemical risk area has substantial limitations and uncertainties as well: the extrapolation of an adverse effect in animals to a clinical health effect (disease) in humans is encountered as a problem in which there is not much experience and knowledge. This is a crucial step for calculating DALYs. Further methodological development is necessary.
- The outcome of a health impact assessment based on experimental data (i.e. obtained in animal studies) may be very different from the outcome based on epidemiological data. This may illustrate the extent of the uncertainty associated with the presently available methodology and the dependence on the quality of data.
- Health impact assessments are not the only relevant information for the decision making or evaluation of policy measures on chemicals. Other types of information may be equally or more important. This involves both scientific (i.e. exposure reduction) or other aspects (socio-economical or political aspects, secondary consequences et cetera).

Assessments for single substances entail potentially more reliability than assessments for mixtures i.e. groups of substances (such as nitrosamines, VOCs and azo dyes).

Not only because exposure, toxicological and epidemiological information and the associated uncertainties are restricted to one substance only, but also because the toxicity of a mixture on which the measure is directed in many instances is extrapolated from the experimentally derived toxicity of a single substance that is selected as model substance for the mixture.

8. Recommendations

> Health Impact Assessments based on presently applied methodology should only be used to support policy decisions for situations where for a single measure a (very) high health impact is estimated, or, where to prioritize among possible measures, those that show large absolute differences in health impact.

- The currently available methodology is not appropriate to draw conclusions on measures with estimated small health impact or between measures with small differences in health impact.
- To enhance useful application of HIA, methods should be developed that better quantify reliability (i.e. methods addressing uncertainty distributions for exposure as well as for effects). Alternatively, a tiered approach could be developed that allows a selection of those measures for which HIA is to be performed with sufficient reliability.
- In order to improve the knowledge on health effects of chemicals in consumer products, information on the occurrence of chemicals in products and on the use patterns of these products is highly essential.
- In order to improve the applicability of health impact assessments for policy making, it is useful to obtain insight in the extent of the differences between estimated health impacts based on toxicological data or on epidemiological data, in the factors underlying these differences, and in developing methods for weighing evidence from both types of data, including their uncertainties.
- Guidance on more predictive realistic exposure assessments and use of assessment factors in extrapolating health effects from animal studies to humans is necessary.
- In the present study, rather rough health impact assessments were performed. These assessments might be refined by, for example:
    - including an exposure assessment with variation analysis, in contrast to use an average exposure estimate.
    - introduction of life tables for health effects, For now, the quantification in DALYs was performed for one year, not taking into account other factors influencing the specific endpoint/disease over years, and not taking into account change in populations and delay time (for cancer). By using life tables, these two aspects are taken into account.

Suggestions for other related research:

- The performance of an additional case study regarding reproduction toxic properties. This could be performed because the extrapolation from an effect in an animal experiment to a corresponding disease in humans requires methodology not covered by the studied cases.

- Application of a totally different methodology of calculating the health impact to aim at a possible (rough) estimation of the total health impact of measures taken for non-food consumer products. For example, the exposure estimates could be calculated using intake fractions, poundage method, and/or total tonnage levels.
- Impact assessments of physiological and toxicological effects may require the development of a more adapted framework. Such a framework may provide a better tailored approach than the – clinically oriented – DALY concept.

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Abbreviations

COPD	chronic obstructive pulmonary disease
CMR	Carcinogenic, Mutagenic, Reproduction toxic
CMRS	Carcinogenic, Mutagenic, Reproduction toxic, Sensitizing
DALE	Disability-Adjusted Life Expectancy
DALY	Disability Adjusted Life Years
GHS	Global Harmonization System
HALE	Health-Adjusted Life Expectancy
HIA	Health Impact Assessment
HLE	Healthy Life Expectancy
HYE	Healthy Year Equivalent
MOS	Margin of Safety
NOAEL	No Observed Adverse Effect Level
QALY	Quality Adjusted Life Years)
RA	Risk Assessment
REACH	**R**egistration **E**valuation **A**uthorisation and Restrictions of **CH**emical substances
RIVM	National Institute for Public Health and the Environment
SAVE	Saved Young Life Equivalent
TNO	TNO Institute for Quality of Life
VOC	Volatile Organic Compounds
VWA	Food and Consumer Product Safety Authority
VWS	Ministry of Health, Welfare and Sport
WMS	Wet Milieugevaarlijke Stoffen
WTP	Willingness to Pay (WTP)
YLD	years lived with disability (YLD)
YLL	years of life lost (YLD)

Appendix 1 Assessing human health response in life cycle assessment using ED10's and DALYs: Cancer and non-cancer effects

Two interesting papers by Jolliet and co-workers need some attention (Crettaz et al., 2002; Pennington et al., 2002). Their approach will be discussed in some detail because of its potential to provide generic health effects estimates like for example *'number of years lost/mg intake'* of a specific chemical. The application of what they call screening-level estimates of the potential consequences associated with an exposure to a given chemical for use in life cycle assessment (LCA) may be also applicable for some first/rough estimates related to consumer products, although the approach is not undisputed as will be explained hereafter.

Life cycle assessment is a framework for comparing products according to their total estimated environmental impact, summed over all chemical emissions and activities associated with a product at all stages in its life cycle (from raw material acquisition, manufacturing, use, to final disposal). For each chemical involved, the exposure associated with the mass released into the environment, integrated over time and space, is multiplied by a toxicological measure to estimate the likelihood of effects and their potential consequences. Life cycle impact assessment and comparative risk assessment use the same building blocks for analyzing fate and potential effects of toxic substances.

In the above mentioned papers, the authors explore the use of quantitative methods drawn from conventional single-chemical regulatory risk assessment to create a procedure of the estimation of effect measure in the impact phase of LCA. They evaluated their approach for both cancer effects as well as non-cancer effects.

For cancer risk assessment the benchmark dose BMD10 (or LED10-lower bound effect dose) is increasingly advocated and applied (US EPA, 1996, 2001; Slob, 2001). This dose is defined as the 95% lower confidence limit on the dose producing a 10% response over background.

In their papers Jolliet and co-workers introduced in a similar way an effect dose ED10 as the maximum likelihood estimate of the dose corresponding to a 10% response over background. This ED10 dose is subsequently used as point of departure or reference point for linear extrapolation toward low doses resulting in slope factors (βED10's) representing the likelihood of the cancer effect. Calculations were performed for 44 chemicals from the IRIS database from US EPA and resulted roughly in values corresponding to about 50% of EPA own slope factors. In numbers this corresponds to roughly a twofold decrease in the value of the βED10's compared to the $q1^*$ values (= cancer potency values based on 10^{-6} risk). In addition, based on Murray and Lopez (1996), it was concluded that the contribution of the years lived with disability (YLDp) to the DALYp (DALY person) is usually small and that the range of DALYp is relatively small. They compared the DALYp values as originally published by Murray and Lopez in 1996 (DALYp prostate cancer = 2.1 and DALYp leukemia = 14.6) and suggest to use an average DALYp of 6.7 as a default value in order to derive severity-based effect factors for carcinogenic compounds.

For non-cancer effects they essentially applied the same principle as for the carcinogenic compounds by estimating a benchmark dose (ED10) and linearly extrapolate this to lower doses applying a slope factor (βED10). They noted that this is in marked contrast to many traditional procedures for non-cancer risk assessments and that it is only a first proposition but that it would facilitate estimations involved with low level exposures as is generally the case with LCA.
Next they modified a simple classification scheme developed by an ILSI expert panel (Burke, 1996) by applying weight factors to three different categories of non-cancer effects. All CMR substances supposed to have irreversible effects are placed in Category I, immunotoxicity, heart disease, liver damage and other probable reversible effects are placed in Category II and irritation and sensitization considered to cause reversible effects are placed in Category III. This translates into DALY's ranging from 6.7DALYp for Category I, 0.67DALYp for Category II and 0.067 DALYp for Category III.
The potential consequences of the effects are taken into account in a preliminary approach by combining the slope factor βED10 with the severity measure DALY, providing a screening-level estimate of the potential consequences associated with exposures, integrated over time and space, to a given mass of chemical released into the environment for use in LCA.

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Appendix 2 Overview table with possible substances for case studies and information on several criteria

Case	Domain: Toys	Cosmetics	Do-it-yourself products	Biocides	Textile	Packaging	Other	Acute	Chronic	C	M	R	S	Past	Future	Exposure data	Human data	Worker related	Legislation	Arguments for	Arguments against
Dichloromethane in DIY products			X					X	X	X					X	yes	little	yes	Guideline 76/769/EC	Acute and chronic, in near future	very incidental use and exposure; acute poisoning; less known on chronic effects (cancer)
Nickel in jewellery							X		X				X	X		yes	yes	yes (gold/silver smith, dentist, Euro coins)	Guideline 76/769/EC	No problem with extrapolation, 10 years duration	sensitization probably not many DALYs ?
Arsenic compounds in wall paper glue				X				X	X	X				X		?/yes	?/yes	yes	?	Extrapolation from occupational; old case; a lot of literature; mine-or steel industry	Old case; health effect at higher concentration than general population; consumers only incidental exposure
Formaldehyde in consumer products		X	X	X	X	X	X		X	X					X	?/yes	only acute?/ yes	yes	Chipboard resolution and cosmetics resolution	Large population; cleaning products indoor	Authorized exposure
AZO colour agents in fabrics					X				X	X	?			X		yes	no/ yes exposure; little on cancer	yes	Food and drug act resolution Azo-dyes (1998)	often exposure; scenarios are already known; can be done relatively fast	
Phthalates in toys	X				X				X			X			X	yes (migration etc.)	little	no	Disposition 1999/815/EC en 2004	Some calculations already performed; political subject	Probably minimal DALY contribution; reprotox effects difficult to extrapolate to children; phthalates also in packaging, cosmetics and food
Organotin compounds in clothing		X			X				X							limited /no	no (especially animal experiments)	no		Immunotoxicity	Incidental
(Poly)-Acryl amide in cosmetics and packaging		X				X			X	X				X	X	no	no (esp. rats)	Laboratory personnel, tunnel constructors	76/768/EC	Before policy measure possible high exposure; potential high exposed population; comparison with exposure from occupational and food (3 perspectives)	low consumer exposure (RAR ES); hot topic; also neurological effects; other groups involved; assumption for uptake through skin

Case	Domain																				
	Toys	Cosmetics	Do-it-yourself products	Biocides	Textile	Packaging	Other	Acute	Chronic	C	M	R	S	Past	Future	Exposure data	Human data	Worker related	Legislation	Arguments for	Arguments against
Nitrosamines in consumer products	X					X	X		X	X	X			X	X	yes	yes (cancer in rubber workers)	Yes	Regulation Packaging and consumer articles (Food and drug act; Directive 93/11/EC)	possible high contribution; existing calculations; earlier TNO project; comparison natural and synthetic rubber?; dermal exposure important in occupational setting	Integrated or cumulative exposure; several exposure scenarios
Pentachloro-phenol in sail/tent canvas				X					X					X		Yes on PCP; not so much on sail / canvas	yes	Yes	"Warenwetbesluit" Pentachlorophenol 1997 (EU 1992)	IARC monograph (1991)	Little amount DALYs
Coloured lamp oil							X	X						X		yes/no	yes	no	Food and drug act; resolution general chemical product safety (Limitation Directive 76/769/EC)	quick to investigate	incidental use and exposure; acute poisoning
Benzene in rubber solution / paint products/air freshener…..			X					X		X					X	yes?/yes	yes	yes		Scenarios for painting, car filling + interior (ES RAR), AEGL substance	probable low amount of DALY's?
gasoline																yes	yes	yes		many literature; exposure with filling gasoline; measure to evaluate	
AZO-dyes in tattoos [taken together with AZO-dyes in garments combination with fabrics							X		X	X					X	limited	no	no	Food and drug act resolution Tattoo dyes(Oct. 2003)		see AZO dyes textile
bisphenol A in drinking bottles							X					X				?; not so much drinking bottles	no (information on cell lines)	no	Food and drug act, Regulation Packaging and - en consumer articles resolution	exposure low, conclusion ii (enormous MOS) (BS RAR)	translation occupational to children not possible
fragrance/ perfume		X			X		X		X				X		X	no	no	no	Food and drug act resolution cosmetic products (European Guideline 76/768/EC)	Aromatic substances are on agenda, sensitization	Sensitization; availability data development in V/320105; not specific enough
enzymes in detergents							X		X				X			yes	yes	yes		already investigated; many literature available	Sensitization resulting in low amount of DALYs?
vinyl chloride in plastics							X		X	X						yes	yes	yes (industrial chemicals)		Substantial contribution carcinogenicity; not impossible; not much literature; IARC monograph	carcinogenic; low amount of exposure data; occupational only effects at high levels
trichloroethylene in cleaning products			X					X	X	X	X					yes	oa review in 1981	yes (dry cleaning)		1 product, 99.9% cons exposure (RAR ES)	Outdated; not much, some information on exposure; relevancy for general population?

Case	Domain: Toys	Cosmetics	Do-it-yourself products	Biocides	Textile	Packaging	Other	Acute	Chronic	C	M	R	S	Past	Future	Exposure data	Human data	Worker related	Legislation	Arguments for	Arguments against
2-ethoxyethanol in paint/ varnish/ cleaning products							X		X			X			X	yes	yes	yes	Preparation guidelines (99/45/EG).		of current interest; review 2003
cadmium in plastics	X						X		X	X		X ?		X		?; not so much plastic	yes?	yes	Features of certain preparations (99/45/EC); prohibition guideline	jewels and brazing sticks (scenario in ES RAR), vibrators	Small amount of DALYs?; Cd is prohibited
toluene in carpet glue/ spray paint/ car products			X					X	X			X			X	yes	yes	yes	Preparation guideline (99/45/EC).	conclusion iii for repro/acute tox/eye irritation for scenario spray painting and carpet laying (ES RAR)	high exposure of population to benzene?
a flame retardant in computers / car interiors / indoor							X		X			X ?				?/ yes	no	yes			Think of risk-benefit instaed of only risk; literature on effects in humans
new ideas for 2006																					
cadmium in plastics	X																		yes, Limitations Directive		
Preservatives																					
Methyldibromoglutaronitril (brand name Euxyl K400) = preservatives in cosmetics		X											X								
VOC (Volatile organic compounds)			X															yes			
cyclohexane (see above)			X													ES RAR				conclusion iii for carpet laying (consumers)	
lead (in paint on wooden toys)	X															Yes, report VWA, ES RAR (2005)	yes		yes (Toy guidelines ?)		
Aromatic substance (e.g. musk ambrette)		X												X		Used until ±1990, vgl. met nitromusken wel	yes	no	no, IND quitted use		
a biocide																					
chromates (use of treated wood; colouring pigment,)										X	X		(X)			ES RAR					
propan-2-ol or turpentine oil in shoe care products																					

	Domain																				
Case	Toys	Cosmetics	Do-it-yourself products	Biocides	Textile	Packaging	Other	Acute	Chronic	C	M	R	S	Past	Future	Exposure data	Human data	Worker related	Legislation	Arguments for	Arguments against
1,4 dichlorobenzene (moth repellent, air freshener, toilet block)							X	X	X							ES RAR (acute tox, liver tox)					
1,2,4-trichloorbenzene (spray paint, car/bicycle polish)			X						X							ES RAR (liver tox)			Proposal for Limitations Directive		

This table was made to facilitate the discussion on choosing the case studies, dated April 2005. An update was made in December 2005.

Abbreviations:
DIY = Do-It-Yourself
ES = Existing Substances
RAR = Risk Assessment Report

Appendix 3 Case study acrylamide

Elleny Balder, Susan Peters, Liesbeth Preller, Winfried Leeman, Dinant Kroese
(TNO)

1. Introduction

The policy of the Ministry of Health, Welfare and Sport aims at excluding products that involve chemical, microbiological or radiation risk. Insight in the nature and magnitude of the risk that is associated with carcinogenic, mutagenic, reprotoxic and sensibilizing (CMRS) agents in consumer products is limited and gives insufficient handle for policy and surveillance. This report intends to give more insight in the presence of and the risk of CMRS substances in consumer products and aims to identify the most important risks. This report addresses the influence of legislation on exposure to acrylamide from consumer products in the Dutch general population.

2. Background information

2.1 C, M. R, or S legislation

Acrylamide has been shown to be neurotoxic. Furthermore, it may cause cancer, may cause heritable genetic damage and there is a possible risk of impaired fertility. Acrylamide has been shown to cause cancer in animals in studies where they were exposed to the chemical at very high doses. Acrylamide has also been shown to cause nerve damage in people who have been exposed to very high levels at work. The main effects of acrylamide in animal experiments are neurotoxicity, genotoxicity to both somatic and germ cells, carcinogenicity and reproductive toxicity.
Human poisonings from acrylamide have been limited to factory and construction workers exposed to high doses.
Acrylamide has been classified according to the 28th ATP of Directive 67/548/EEC4 as:
Carc.Cat. 2; R45 May cause cancer
Muta.Cat. 2; R46 May cause heritable genetic damage
Repr.Cat. 3; R62 Possible risk of impaired fertility
T; R25-48/23/24/25 Also toxic: danger of serious damages to health by prolonged exposure through inhalation, in contact with skin and if swallowed
Xn; R20/21 Also harmful by inhalation and in contact with skin
Xi; R36/38 Also irritating to eyes and skin
R43 May cause sensitisation by skin contac

In 2002, restrictions have been set to the concentration of acrylamide in cosmetics (cosmetics directive 76/786/EEC and 2002/34/EC). Since then, the use of polyacrylamides are permitted in cosmetics if the concentration of acrylamide monomer is less than 0.1 mg/kg product for non-rinse body care products, and 0.5 mg/kg product in other cosmetics.

2.2 General information

2.2.1 Substance information

Acrylamide (C_3H_5NO; CAS nr: 79-06-1) is formed in food during the heating process by the reaction between asparagine and reducing sugars (fructose, glucose, etcetera) or reactive carbonyls. Acrylamide is a white odorless crystalline solid, soluble in water, ethanol, ether and chloroform. It is used to make polyacrylamide, which is used, for example, in some cosmetics and in some food packaging materials (e.g., paperboard and paperboard products subject to FDA food additive regulations), in paper and glues, in soil conditioning agents, and in the formation of plastics and specialized grouting agents. Polyacrylamide is also used to treat sewage and wastewater and to purify drinking water. Polyacrylamide is not toxic; however, in each of these uses, some of the original monomer remains in the end product in very small quantities. In addition, acrylamide is known to be a component of cigarette smoke. Recently, acrylamide has been detected in a wide range of food products, especially in high-carbohydrate foods prepared at high temperatures. The levels of acrylamide found in some foods are much higher than the levels recommended for drinking water or levels expected to occur as a result of contact between food and food packaging (from paper) or use of cosmetics.
The amount of monomer that is used directly (in contrast to the polymer) in consumer products is so small that it is not relevant for consumer exposure. Degradation of the polymer to produce acrylamide monomer is very unlikely. The only point of concern is therefore the level of the free monomer present in the product. The residual level of monomer in the polyacrylamide should be below 0.1% w/w in the EU and most values are much lower than this.

2.2.2 Exposure sources and routes

Table A3.1 gives an overview of sources of exposure. In this case, the effect of legislation related to cosmetics is evaluated. Other sources will be regarded as background exposure. Exposure to acrylamide can be relatively high in certain occupational circumstances but evaluation is beyond the scope of this study.
Polyacrylamides have also been used in coatings. However, as analysis has indicated that the residual monomer is present in a concentration below the detection limit of 0.01% (Wright, 1995 in: European Union, 2002), this route of exposure is also considered negligible.

Table A3.1. Potential sources of exposure to acrylamide for consumers

	Route of exposure		
	Inhalation	**Dermal**	**Oral**
Drinking water			X
Cosmetics		X	
Paper products		X	
Soil conditioners		X	
Textiles		X	
Food consumption			X
Cigarette smoke	X		

3. Description of exposure

3.1 General

Exposure to acrylamide has been evaluated thoroughly in several risk assessments. Mostly the main focus is on acrylamide exposure resulting from food consumption; only few reports also address exposure resulting from non-food consumer products. As information on acrylamide levels in non-food consumer products is sparse, the relevant data reported in the Risk Assessment Report, RAR (European Union, 2002) was used and where applicable completed with additional published data and/or adapted to the Dutch consumer situation.

3.1.1 Cosmetics

Polyacrylamide is reported to be used in several cosmetic formulations, at concentrations ranging from 0.05% to 2.8%. Residual levels of acrylamide in polyacrylamide can range from <0.01% to 0.1%, although representative levels were reported at 0.02% to 0.03%. In the Risk Assessment Report (European Union, 2002) it was reported that a survey among the members of the Cosmetic, Toiletry & Perfumery Association of the United Kingdom reported the use of polyacrylamide in cosmetic preparations (rinse-off and non rinse-off skin products including suntan lotions) at a level of up to 2%. Based on a maximum monomer level in the polymer of 0.01%, and the assumption that the dermal route is the only route that needs to be addressed, the exposure was calculated using levels suggested by the TGD (1996). Total daily exposure to polyacrylamide monomer from non-rinse skin products was thus calculated to be 65 µg, resulting from a half skin cover with general purpose creams two times a day or daily use of body lotion, plus the daily use of setting product and the use of nail products. Rinse-off skin products containing polyacrylamide could include shampoo (2.4 µg), assuming that only 10% of the products is left on the skin. Totalling up these potential daily exposure results in 67 µg of the acrylamide monomer from non-rinse off and rinse off cosmetics. This figure represents a reasonable worst-case scenario for daily deposition of acrylamide on the skin of a frequent user of cosmetics. The above exposure estimates are based on maximum monomer level in the polymer of 0.01%. Considering 67 µg per day as a reasonable worst case, 50% from this, 34 µg, is assumed to be the average dose for the general population.

The Scientific Committee on Cosmetic products and Non-Food Products intended for Consumers (SCCNFP) recommended revised levels of acrylamide in cosmetics (European Union, 2002). The recommended tolerable level is <0.1ppm for non-rinse products and <0.5ppm for rinse-off products. These levels will result in exposures which are 1,000 and 200 fold lower, respectively, than those calculated above for non-rinse and rinse-off products. These recommended levels are now the allowable levels. In Table A3.2 an overview is given of exposure values based on the RAR 2002 values, and the new allowable levels.

In the Risk Assessment Report, the absorption by the dermal route was assumed to be 75%. With a mean bodyweight of 70 kg, the body burden arising from skin exposure was calculated to be 34 µg * 0.75/ 70 kg bw = 0.36 µg/kg bw/day. The population exposed is the whole Dutch population of 16 million people. The given data does not allow making distinctions between different subgroups.

Table A3.2.Exposure to acrylamide through (dermal) use of cosmetics.

Exposure values	RAR 2002, before 2002	After 2002*	unit
non-rinse cosmetics	65	0.065	µg/day
rinse cosmetics	2	0.01	µg/day
total worst case exposure	67	0.075	µg/day
average total exposure (50%)	34	0.038	µg/day
internal exposure (75% skin absorption)	25	0.028	µg/day
internal exposure per kg bodyweight (person 70 kg)	0.36	0.0040	µg/kg bw/day

* Based on allowable concentrations of 0.1 and 0.5 mg/kg acrylamide in non-rinse and rinse products; calculated with exposures being a factor 1000 and 200 lower, respectively.

An additional route of exposure that may need to be considered is the use of polyacrylamides in tissue augmentation (Patrick, 2004). Polyacrylamide gels are injected in the human body for facial and body corrections in cosmetic and reconstructive medicine and surgery. AQUAMID, which is reported to be similar to other fillers, consists of 2.5% polyacrylamide visco-elastic gel (PAAG) and 97.5% water. The residual monomer concentration is 1-2 ppm. No long-term effect studies have been published for adverse effects of this specific application. Most (relatively short-term) frequently reported complications are infection, granuloma and migration. The authors estimated that the concentration of monomer acrylamide in AQUAMID is 2 µg per syringe of 1 ml and that a treatment of 10 ml injected into a 30 year old male of 70 kg, would result in an exposure of 0.00002 µg/kg bw/day. No information was gathered yet on the incidence of these cosmetic procedures in the Netherlands, what the usual injected volume is and how often these treatments are repeated.

3.1.2 Background exposure

Drinking water

In the Risk Assessment Report (European Union, 2002), the daily dose through intake of drinking water was calculated from the maximum expected concentration of acrylamide in drinking water (0.125 µg/l), a daily intake of drinking water of 2 l/day and the average bodyweight of humans (70 kg).
The European Union legal limit for drinking water is 0.1 µg/l of water. The exposure of acrylamide via drinking water at this legal limit would be:
0.10 µg/l * 2 l/day * 1/(70 kg bw) = 0.003 µg/kg bw per day.
The exposed population will be the whole Dutch population of 16 million people.
In documents on contamination of drinking water in The Netherlands, no indication was found that exposure levels exceeded this legal limit of 0.1 µg/l. No information is given on actual exposure levels of acrylamide. It is therefore assumed that the calculation is a worst case scenario, and that the average exposure will be 50% of that level, being 0.001 µg/kg bw per day.

The exposure by dermal contact with water was assumed to be negligible, compared to the amount through consumption of drinking water.

Paper

Polyacrylamide is used in the pulp and paper production industry as a binder and as a retention aid for fibres. In the Netherlands the use of polyacrylamides for indirect food additives as components of paper and paperboard is approved. No measurements are available on the levels of residual acrylamide left on the paper, but in the Risk Assessment Report the maximum levels were calculated.
In the paper industry typically a 0.2% polymer working solution is used and typical values for the polyacrylamide/dry paper ratio are 1.5 kg/tonne. As the maximum free acrylamide in the polyacrylamide is 0.1% w/w this means that there is a maximum of 1.5 g/tonne (1.5 ppm) of acrylamide in the dry paper. However, as polyacrylamide is added at the wet end of the paper making where solid pulp is present in water at about 1% w/w and acrylamide is extremely water-soluble, the acrylamide is most likely to remain in the aqueous phase that is for the largest part removed (moisture content of paper is approximately 10%). This is a 100-fold dilution of any free acrylamide so that the absolute maximum level of acrylamide in paper is assumed to be 15 mg/tonne (15 ppb) - below the limit of detection. Hence in the RAR it is concluded that there appears to be a negligible exposure to consumers from this application.

Textile

Polyacrylamides have been used in the past as sizing agents for wool as well as to bind textile fibres and as water repellents. A survey carried out by The International Wool Secretariat has disclosed that polyacrylamide is not used anymore as a sizing agent anywhere within the EU (European Union, 2002). Hence there is no known consumer exposure for these applications.

Food

In 2002, the World Health Organization (FAO/WHO, 2002) estimated that total dietary acrylamide intake ranged between 0.3-0.8 µg/kg bw/day. Konings et al. (2003) estimated, based on the Dutch National Food Consumption Survey in 1998, the mean acrylamide intake to be 0.48 µg/kg bw/day (P95 = 0.6 µg/kg bw/day) in a representative sample (aged 1-97 years) of the Dutch population. Bioavailability from food matrices is not known, although biomarker studies show that acrylamide is at least partially absorbed. The exposed population will be the whole Dutch population of 16 million people.

Tobacco smoke

The exposure to acrylamide from tobacco smoke was determined by the following parameters: the percentage of persons that smoke, the average number of cigarettes smoked per day and the acrylamide content per cigarette. We assumed a 100% uptake in the body for the inhalation exposure route. Filtered cigarette mainstream smoke has been reported to contain acrylamide, ranging from 1.1 to 2.34 µg per cigarette (Smith et al., 2002). For this calculation we used the average of these values: 1.72 µg/cigarette. The percentage of persons that smoked was calculated from the CBS Statline database, as was the average number of cigarettes smoked per day by smokers. On average 40% of the adult men and 30% of the adult women smoke cigarettes, resulting in 35% of the whole population. The number of

cigarettes smoked per day by smokers is on average 16 cigarettes. Exposure to acrylamide for smokers would be:
16 cigarettes * 1.72 µg/cig * 100% = 28 µg.
For a person of 70 kg, this would mean 0.4 µg/kg bw/day for smokers, and averaged over the total population of 16 million people 0.35*0.4=0.1-0.15 µg/kg bw/day .

No information is available on acrylamide in side stream smoke. Assuming that the total amount is equal to 1.72 and will all be emitted to the room, and a person of 70 kg is 1hours per day present in a fully mixed standard room of 58 m^3 with the equivalent side stream smoke of 1 cigarette, and a respiration rate of 20 m^3 per 24 hours, exposure would be
1.72 µg/58 m^3 * 16hr/24hr * 20 m^3 / 70 kg =0.006 µg/kg bw per day.

Soil conditioning agents
Polyacrylamide gels are used in soil conditioners for consumer use. These packs, varying from 10 g to 150 g, contain 33% polyacrylamide gel and the instructions on the pack suggest a vigorous mixing of the pack contents with the soil or compost (European Union, 2002). The recommended dilution for use are 1 to 1.75 g per litre of compost or 100 g per m^2 of soil. As there are no measured data on dermal exposure to acrylamide monomer in these soil conditioning procedures a calculation was made to obtain this information. If the residual acrylamide monomer level is 0.1% then, when a consumer mixes together 17.5 g of conditioner with 10 litres of compost, they are handling a maximum of 5.8 mg (17.5*0.33*0.001) of acrylamide monomer. Once wet this compost will contain a concentration of 5.8 mg/litre of acrylamide in the water (assuming that 10% of the compost is water, that it is perfectly mixed and that all of the monomer has dissolved in the water). Assuming a surface area of 820 cm^2 (area of the hands) and a liquid film thickness of 0.01 cm (EPA default) in contact with the hands, the RAR calculation concluded that there will be an exposure to about 0.8 ml of solution which will contain about 5 µg of acrylamide.

Assuming 75% absorption and 70 kg bodyweight this represents a body burden of 5/70.0.75 = 0.05 µg/kg bw/day when conditioner is used. If conditioner is used three times a year, the exposure averaged over one year will be 0.05 * 3/365 = 0.002 µg/kg bw/day. Potential airborne exposure resulting from the mixing procedure was not taken into account.

Table A3.3. Background exposure to acrylamide, averaged over the total population of 16 million people.

Source	Exposure (µg/kg bw per day)
Drinking water	0.001
Paper	-
Textile	-
Food	0.48
Tobacco smoke (active)	0.1-0.15
Tobacco smoke (side stream)	0.006
Soil conditioning agents	0.002
Total	≈ 0.6

Table A3.3 shows that exposure through food intake contributes most to background exposure and is the same order of magnitude as exposure through cosmetics prior to the new legislative measures, and about a factor 100 higher than exposure through cosmetics after the 2002 legislative measures.

4. Description of toxicity

4.1 Introduction

The toxicology of acrylamide has been evaluated extensively by several authorities. The present evaluation is based on the evaluations of the Joined FAO/WHO Expert Committee on Food Additives (JECFA) published in 2005 (JECFA, 2005), the EU risk assessment report of acrylamide (European Union, 2002) and the evaluation of the Dutch Expert Committee on Occupational Standards, a committee of the Health Council of the Netherlands, published in 2006 (Gezondheidsraad, 2006). In case relevant or additional information is available from other evaluations, or remarks are made with respect to the evaluations used, these are specified as such.

4.1.1 Acute toxicity data

Upon single exposure, acrylamide is toxic or harmful by all routes of administration. The principal effects prior to death relate to neurotoxicity, although severe effects on spermatid development were also noted.
Acrylamide is a skin irritant, with skin peeling being a particular problem, and is considered as an eye irritant although data are limited. Furthermore, acrylamide induces skin sensitization, whereas no data are available regarding respiratory sensitization.

4.1.2 Chronic toxicity data

The principal effect observed as a result of repeated exposure, by all routes, is peripheral neuropathy. Histopathology has indicated peripheral nerve lesions at 2 mg/kg bw/day, whereas no effects were observed at 0.5 mg/kg bw/day in a 2-year rat study. Additionally, degeneration of spermatids and spermatocytes was observed amongst animals receiving approximately 36 mg/kg bw/day for 8 weeks, although this study was not designed to identify a NOAEL.
Acrylamide is a direct-acting mutagen *in vitro* and *in vivo* to both somatic cells and germ cells (inducing heritable mutations).
In animals, impaired fertility was demonstrated in male rats exposed to 15 mg/kg bw/day or more for 5 days. The impaired fertility may have been associated with effects on sperm count and sperm motility, or on impaired copulatory ability as a secondary result of neurotoxic effects (such as impaired hind limb function). No effects on fertility were observed in a 2-generation reproduction study in which male and female rats of each generation received 5 mg/kg bw/day for 10-11 weeks.
There was no evidence of selective developmental toxicity at exposure levels in rats or mice that were not associated with maternal toxicity.

Acrylamide is carcinogenic in animals producing increased incidences of a number of benign and malignant tumours in a variety of organs (e.g. thyroid, adrenals, testicular mesothelioma). There is also a suggestion of acrylamide-induced tumours in brain and spinal cord. The tumour types observed show a possible relationship with disturbed endocrine function and raise the possibility of a hormonal mechanism. In this respect it is noted that a possible genotoxic mechanism of tumor formation is not considered compatible with hormonal dysregulation since other factors beyond DNA damage are probably required for the observed target tissue specificity of tumorigenesis (JECFA, 2005).
The potential carcinogenicity of acrylamide has not been thoroughly investigated in humans. Two human cohort mortality studies did not show any clear increase in cause-specific mortality as a result of acrylamide exposure although there were clear inadequacies in one of the two studies available. No firm conclusions can be drawn from these studies.
Acrylamide has been evaluated by the International Agency for Research on Cancer in 1994 (IARC Monograph Vol 60; 1994) and classified as probably carcinogenic to humans (Group 2A) based on sufficient evidence of carcinogenicity in animals and based on its mutagenic properties.

At present there is no information to indicate significant differences between rodents and humans in sensitivity to cancer formation from acrylamine. The most sensitive carcinogenicity estimate using the 95% lower confidence limit for the benchmark dose (for 10% extra risk of tumors), is 0.30 mg/kg body weight per day and is based on animal studies (JECFA, 2005).

5. Current Risk Assessment

For acrylamide, two types of effect, pheripheric neuropathy and cancer, are considered of relevance. Repeated administration of acrylamide to experimental animals resulted in damage to peripheral nerves (peripheric neuropathy) as the most critical effect, while at higher dosages in addition muscular and testicular atrophy and decreased erythrocyt-parameters have been observed. Peripheral neuropathy and hemoglobin adduct formation have also been seen in occupationally exposed humans. In 1985 WHO derived a TDI of 12 μg/kg bw/day based on neurotoxicity in subchronically exposed rats. With the same data US-EPA concluded to a RfD of 0.2 μg/kg bw/day (US-EPA, 2001). In a chronic toxicity and carcinogenicity study with rats peripheric neuropathy was observed with a LOAEL of 2 and a NOAEL of 0.5 mg/kg bw/day (Konings et al., 2003). This NOAEL will be used for the evaluation of the DALY for peripheric neuropathy.

Apart from the health based limit values based on the non cancer risk, cancer risk figures at life long intake were calculated by the FAO/WHO (2002), US-EPA (2001), NFCA (2002) and the Dutch Health Council (Gezondheidsraad, 2006) in which carcinogenicity (malignant thyroid, adrenal, and testicular tumours) following a genotoxic mode of action is considered. In this respect it is noted that tumour formation might be related to disturbed endocrine function. Although the mode of action inducing tumour formation is not clear, a linear dose response is considered.

An overview of cancer risk estimates is reported by Konings et al. (2003). The WHO (1996) elaborated an additional carcinogenic risk of a lifelong daily intake of 1 µg per person amounts to 1 case per 100,000 exposed people (equivalent with a unit life time cancer risk at 1 µg/kg bw/day of 0.7 per 1000, or an additional carcinogenic risk of 1 per 10,000 exposed people at a lifelong intake of 0.14 µg/kg bw/day). The US-EPA (2001) conservatively estimated the carcinogenic risk as a unit lifetime cancer risk at 1 µg/kg bw/day of 4.5 per 1000 (equivalent with an additional carcinogenic risk of 1 per 10,000 exposed people at a lifelong intake of 0.02 µg/kg bw/day). The Scientific Committee of the Norwegian Food Control Authority (NFCA, 2002), estimated a unit lifetime cancer risk at 1 µg/kg bw/day of 1.3 per 1000. This is equivalent with an additional carcinogenic risk of 1 per 10,000 exposed people at a lifelong intake of 0.08 µg/kg bw/day (Konings et al., 2003).
Recently, the Dutch Health Council estimated the additional lifetime risk of cancer in humans, using the linear method. Under lifespan conditions, the estimated tumor incidence is 0.5 per 1000 at 1 µg/kg bw/day, which was based on the calculated incidence of tumor-bearing animals in a carcinogenicity study in rats published by Johnson et al. in 1986 (Gezondheidsraad, 2006).
As the evaluation of acrylamide by the Dutch Health Council is the most recent evaluation which is considered to cover the latest scientific aspects of risk assessment, the lifetime cancer risk estimation in human performed by the Dutch Health Council will be used for the risk evaluation.

6. Calculation of Public Health Gain

6.1 Decrease of exposure

Exposure through use of cosmetics will be decreased from 0.36 µg/kg bw/day before to 0.0040 µg/kg bw/day after legislative measures for a person of 70 kg. This reduction will only be achieved if exposure in all products is below the allowable levels. No information on true exposure after the measure was available.
Due to lacking exposure information, no calculation could be made for sub groups of the population.

Decrease in exposure is of the same order of magnitude as the background exposure as calculated based on the RAR 2002 and Dutch food intake information: Background exposure is about 0.6 µg/kg bw/day averaged over the total population, but will be higher in smokers than in non-smokers.

6.2 Increase Margin of Safety

The margin of safety (MOS) approach is another method to describe the effect of the decrease in exposure. Generally, a reference MOS describes the margin which is allowed between human exposure and the dose at which no adverse affects are observed in animals or humans. When the MOS is too low, efforts should be made to reduce the exposure until the desired MOS is reached.

For consumers, dermal exposure as a result of acrylamide in cosmetics is considered of relevance. A NOAEL of 0.5 mg/kg bw/day is used as starting point for the evaluation of peripheric neuropathy. MOS values exceeding 100 (10 x 10, for interspecies and intraspecies differences) are considered not to be of concern.

For the tumor incidence related to acrylamide exposure via cosmetics, a MOS calculation is not applicable, i.e. for carcinogens, acting via a mutagenic mechanism, no safe level can be given.

In Table A3.4, the MOS approach using the exposure levels of acrylamide exposure before and after the reduction measures are presented.

Table A3.4. Margin of Safety before and after reduction in exposure levels

Exposure scenario	**Exposure (µg/kg bw/day)**		**MOS**		**Concern**	
	Before	**after**	**before**	**after**	**before**	**after**
Dermal exposure via cosmetics; peripheric neuropathy	0.36	0.004	1390	125000	no	no

Using the MOS approach, no concern for peripheric neuropathy is calculated after dermal exposure although a clear reduction in exposure is found.

6.3 Decrease of incidence of effect

For the exposure scenario dermal exposure via cosmetics, a clear decrease in exposure is calculated. For peripheric neuropathy, the exposure before and after measures taken are both at a level which are not of concern. As the MOS calculations are performed using average exposure levels, a decrease in effect might be assumed for high exposure groups. However, as no exposure data are available for these groups, this assumed decrease cannot be calculated.

For the tumor incidence related to acrylamide exposure via cosmetics, a tumor incidence of 0.5 per 1000 at 1 µg/kg bw/day (Gezondheidsraad, 2006) is used as starting point. It is assumed that a linear extrapolation of tumor induction can be used.

An exposure to acrylamide of 0.36 µg/kg bw/day, as calculated before measures were taken, indicate an additional tumor incidence of 180 persons per 10^6, whereas an exposure of 0.004 µg/kg bw/day, as calculated after measures were taken, indicate an additional tumor incidence of 2 persons per 10^6. For induction of tumors, a decrease in additional tumor incidence as a result of acrylamide exposure via cosmetics is calculated to be 178 cases per 10^6 persons.

It should be noted that for the full reduction in tumor induction derived at above a latency period has to be taken into account.

6.4 Derivation of DALYs

The average exposure to acrylamide via cosmetics has been estimated at 0.36 µg/kg bw/day and 0.004 µg/kg bw/day, before and after measures has become effective, respectively. As a result of the intervention, the mean exposure via cosmetics is decreased with 0.356 µg/kg bw/day.

For peripheric neuropathy, both average exposure levels to acrylamide are well below a level considered to induce effects. Therefore, no DALY can be calculated for peripheric neuropathy induced by acrylamide.

For induction of tumors, a decrease in additional tumor incidence as a result of acrylamide exposure via cosmetics is calculated to be 180 per 10^6 persons before and 2 per 10^6 persons after measures are taken. It should be noted that for a reduction in tumor induction a latency period has to be taken into account. For the calculation of the DALY, the latency period is however not taken into account. Comparison of the DALY before and after measures taken are therefore showing the maximal effect, which will become effective only after this latency period.
As the ratio for the development of tumors is unknown and the impact on illness is difficult to describe (eg. age at cancer diagnosis, length of illness period, medical treatment effects, and/or recovery or death ratio), a standardised DALY of 8 is used for each person developing tumors as a result of acrylamide exposure.

For the DALY calculation, it is assumed that:
- the full population of 16 million people in the Netherlands are exposed to cosmetics,
- 180 per 10^6 persons are developing tumors before measures were taken as a result of acrylamide exposure via cosmetics,
- 2 per 10^6 persons are developing tumors after measures were taken as a result of acrylamide exposure via cosmetics,
- for each person developing tumors a standardised DALY of 8 is considered.

Based on these data and assumptions the DALY is calculated to be:

incidence of tumor induction (per million) * population exposed * 8.

Before measures are effective: $(180/10^6) * (16*10^6) * 8 =$ 23040 DALY

After measures are effective: $(2/10^6) * (16*10^6) * 8 =$ 256 DALY

So the net gain in DALYs is rounded to 23000. However, if one considers that the induction of tumours is mostly associated with life-time exposure (or at least a substantial part of life), the calculated health-gain effect will effectively only be realized after about a similar life time period: i.e. one has to divide this net DALY number by this latency period to obtain the health-gain per year. Thus, for this acrylamide case the DALY gain per year from the policy measure will be 23000/75 , i.e. 300. Clearly, the degree of uncertainty in this number is high.

7. Discussion

7.1 Target population

In this case measures taken to reduce acrylamide in cosmetics have been evaluated. Nearly all people are at risk of being exposed to cosmetics. The total population can be estimated accurately.
Background exposure contributes for more than 50% to the total exposure, of which food is the primary source. The exposed population includes all people which is known accurately.

7.2 Exposure

Cosmetics
Most of the exposure information is retrieved from the RAR 2002. Exposure can be assessed accurately if is known which specific products are used, its precise contamination, the amount being used, all specified for different age sub groups. Since no measured data were available om acrylamide in cosmetics, exposure information as given in the RAR is based on calculations. No information is given on its validity and it is not known to which extent the information is valid and representative for the Dutch population.
Average exposure has been suggested to be half of the reasonable worst case scenario, which may deviate up to a few factors of 'real' exposure.
Exposure after the legislative measures has been based on the estimation that exposure of non-rinse and rinse products will be a factor 1000 and 200 lower. This is a crude estimation, based on the assumption that all products will apply to the new legislative measures. Also for this time period no exposure information is available to corroborate this assumption. Hence, the error in the exposure estimation before and after the measures is therefore potentially moderate. The estimated reduction in exposure should be regarded as maximum achievable with new legislation and not the real reduction in exposure.

For estimating toxicological effects also the absorption should be known. For this, a crude value has been used of 75% as given in the RAR, with unknown validity.

Overall, errors in exposure are most likely moderate (up to a factor 100).

Other exposures
Also for background exposure generally the same crude exposure information has been used, except for the contribution of food. That estimation has been made based on a large survey among the Dutch population considering all age groups. Food is on average estimated to be the major background exposure. The error in background exposure is therefore most likely relatively small. However, the contribution of smoking, on average about 25% of food, is

based on little information, of unknown validity, and can therefore contribute to more error in background exposure.
Since for the calculation of the public health gain the absolute reduction in exposure is relevant (because of the assumed linear exposure-response association for carcinogenic effects, being the only effect of potential concern), errors in background levels do not affect the estimate in absolute health gain but do affect the absolute value of potential health effects due to total acrylamide exposure in both periods separately.

7.3 Toxicology

For acrylamide, two types of effect, pheripheric neuropathy and cancer, are considered of relevance.

Repeated exposure to acrylamide in experimental animals resulted in damage to peripheral nerves (peripheric neuropathy) as the most critical effect, while at higher dosages in addition muscular and testicular atrophy and decreased erythrocyt-parameters have been observed.
A threshold level (lowest NOAEL found) of 0.5 mg/kg bw/day is considered for peripheric neuropathy.

Several evaluations of acrylamide showed evidence of carcinogenicity (malignant thyroid, adrenal, and testicular tumours) following a genotoxic mode of action, although tumour formation might also be related to disturbed endocrine function. The mode of action inducing tumour formation is considered to have a linear dose response. An additional lifetime risk of cancer of 0.5 per 1000 at 1 μg/kg bw/day in humans is considered for the DALY calculations based on the most recent evaluation of acrylamide by the Dutch Health Council.

7.4 DALY calculation

For peripheric neuropathy, the average exposure levels to acrylamide are well below a level considered to induce effects. Also, if major sources of background exposure are considered to occur simultaneously, it is unlikely that effects do occu in the general population. Therefore, no DALY can be calculated for peripheric neuropathy induced by acrylamide.

For the induction of tumors, a decrease in additional tumor incidence as a result of acrylamide exposure via cosmetics is calculated to be 180 per 10^6 persons before and 2 per 10^6 persons after measures are taken. This reduction in tumor incidence results in a decrease of about 23000 DALY (23040 DALY before measures are effective, 256 DALY after measures are effective), being about 300 DALYs per year.

It is noted that comparison of the DALY before and after measures taken are showing the maximal effect of the measures, which will become effective only after a latency period.

Overall, the health gain due to regulations on acrylamide in cosmetics be 300 DALYs per year. This is only due to potential carcinogenic effect. Exposure levels of consumers are too low to induce peripheric neuropathy. The validity of the DALY-estimates is restricted mostly because of the lack of representative exposure data for the Dutch population prior to measures and the complete lack of data for the period after the measures, and the relevance of the toxicological data for humans related to a lack of epidemiological data for acrylamide. Furthermore, it is noted that relative high exposure levels of acrylamide via food (eg via chips and crips) might be considered which are not included in the present evaluation.

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Appendix 4. Case report azo-dyes

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1. Introduction

Colour is an important aspect in every day life. Colours have a signal function in e.g. foods, clothes, cosmetics, and traffic. Products are therefore often provided with colours. These colours should attach itself to the product and last for a long time. One group of the colouring agents is the so-called azo dyes. These synthetically colorants are produced by the formation of azo bonds (-N=N-) or multiple azo bonds. Azo dyes are widely used in textiles, leather, cosmetics, plastics, ink, and to a lesser extent in tattoos. Under certain conditions reductive cleavage of the azo bonds may occur. As a result aromatic amines, primary aromatic amines used in the synthesis of the dye, are split off. A number of these aromatic amines, for example benzidine (category 1 carcinogen according to the classification of WHO/IARC) (Janssen and Meijerink, 1998), have been classified human or animal carcinogen. The azo dyes based on these amines are considered to be carcinogenic as well (Zeilmaker et al., 1999; 2000).
Consumers can be exposed to these azo colorants and therefore in 1994 Germany banned the use of these azo dyes in textile and leather and other products suspected of coming into contact with human skin for prolonged periods, such as clothes. The Netherlands, Austria and Norway were soon to follow and shortly thereafter the EU circulated a draft Directive that would apply the ban across its member states (OECD).
In addition, azo dyes were also used as colorants in tattoos. Tattoos are applied with thin needles into the dermis skin layer where a colour 'reservoir' is formed. Up until now it is unknown whether the azo dyes are reduced to aromatic amines in the subcutaneous area. Research was mainly focused on the reduction of aromatic amines when applied to the skin. A recent new development in the removal of tattoos has lead to an interest in what happens to the azo dyes *in* the skin during removal. Removal of tattoos with laser treatment has proven to be effective. The hypothesized mechanism of action is that the colours are degraded by the laser. Currently, there are concerns that this degradation will lead to the formation of carcinogenic aromatic amines.
This case is included because of daily prolonged dermal contact of azo dyes in certain textiles. Prohibition of the suspected carcinogenic azo dyes in these textiles is expected to have considerable beneficial effects on the population health. The possible beneficial effect of the measure to restrict suspected azo dye from tattoo colorant on population health is not discussed in this case report.

2. Background information on azo dyes and aromatic amines

2.1 Legislation

The use of azo dyes which may form one of the 22 aromatic amines listed on appendix A in textiles and leather (clothes) that come into prolonged contact with the skin is banned with the Commodities Act Regulation Azo Dyes (from: Staatscourant 143, 29 July 1996, (Zeilmaker et al., 1999)) according to the EU Council Directive 76/769/EEC which was later on expanded according to 2002/61/EC in regard to azo dyes present in textile or leather toys and bed linen. The use of certain azo dyes as colorants in (temporary) tattoos was prohibited January 1st 2004 according to the Commodities Act Regulation tattoo colorants 'Warenwetbesluit tatoeagekleurstoffen'. Tattoo colorants are not allowed to contain compounds that are able to form aromatic amines listed in Appendix 4.1

2.2 General information

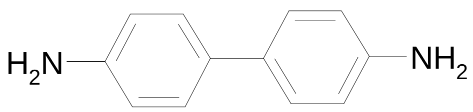
The main advantages of azo colorants are that they are very easy to produce and give a wide spectrum of colours. In the Colours Index, a list of colours available for the industry, a total of approximately 2000 azo dyes are registered. As a result, azo dyes are widely used in all kinds of products. Amongst other they are used in textiles (clothes, bed linen, toys, furniture), leather (clothes, toys, furniture, belts, wallets, watch straps), petroleum products (in the Netherlands mainly solvent red is added to petroleum to distinguish petroleum from other liquids), cosmetics (hair dyes), plastic, and inks. Consumers can be exposed to azo dyes from all these products. Because azo dyes are water soluble the aromatic amines are easily solved in saliva and sweat, and ultimately taken up by the body.
Azo dyes accounted for 65% of the dye industry in fiscal year 1991 (Collier et al., 1993) of which a large proportion is meant for the textile and leather market. In Japan about 60% of Direct Black 38, an azo dye based on benzidine, was used for dying fibres and 20% for dying leather (IARC, 1982). Approximately 70% of the azo dyes are used in the textile and leather market (think of clothes, toys, footwear, wigs etcetera) in 1997 (Mensink et al., 1997). Most likely this figure of 70% does not include a large proportion of suspected azo dyes, because the measure was already effective.
The high usage of azo dyes in textiles and the prolonged contact with carcinogenic aromatic amines from azo dyes, led to legislative measures that were taken. The measure was not based on quantitative data explaining the lack of data. For this reason it is unknown to what extend the textile and leather market contained the suspected carcinogenic azo dyes before the measure.

After the measure, the VWA (Dutch Food and Product Safety authority) monitored textile and leather products and still found suspected azo dyes in some products (Reus and Westerhoff, 2001; Bouma and Reus, 2004). Prove of presence of suspected azo dyes in consumer products is established when concentrations are higher than 30 ppm. Since the manufacture, production, and import are prohibited in Europe it is expected that these azo dyes are being imported in products from third countries. Consumer exposure to azo dyes may therefore still occur.

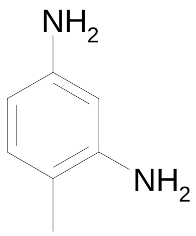
A research on the chemical and microbiological safety of tattoo colorants was conducted by the Dutch Food and Product Safety Authority (VWA). Among other constituents, one or more aromatic amines from azo dyes were found in 17% of the colour samples taken. The detection method of the aromatic amines was identical to the detection method of aromatic amines in textiles.

3. Description of Exposure

The measure only prohibited the use of the listed aromatic amines and azo dyes based on them present in textiles and leather (and later on toys, bed linen and tattoos). Textiles dyed with azo dyes that have infrequently contact with skin (such as household textiles and towels) were left out for consideration in the Council Directive and therefore other sources apart from textiles and leather are not taken into account.
Because much data on prevalence in products is lacking and it requires a lot of work to conduct an exposure assessment for all aromatic amines only two of 22 aromatic amines will be considered. Benzidine is selected because it is the most occurring aromatic amine in textiles. In addition, the toxicological profile of benzidine has been well described (see paragraph toxicology). The other aromatic amine is 2,4-toluenediamine (for chemical structure see Figure A4.1). For these two aromatic amines, exposure data are present (although limited).



Benzidine



2,4-toluenediamine

Figure A4.1. chemical structures of aromatic amines benzidine (top) and 2,4-toluenediamine (bottom).

It is unknown whether exposure to aromatic amines from tattoo colorants occurs. The fact that tattoos fade in time gives reason to believe that azo dyes disappear from the tattoo site. As mentioned before the tattoo colorant is applied in the dermis of the skin layer. Small blood vessels are present in this layer of the skin which may take up azo dyes and/or aromatic amines. Next to the exposure from tattoos itself, exposure from the removal of tattoos may occur. To make a rough estimation on the magnitude of exposure from tattoos certain information is required. However, specific data on exposure to azo dyes and aromatic amines from tattoos are lacking. A reliable exposure assessment could not be conducted for tattoos and thus exposure from tattoos will not be discussed in this report.
Therefore only consumer exposure from textiles and leather to the listed aromatic amines (and azo dyes) will be considered in this report.

3.1 Exposure from textiles

There are three possible routes of exposure concerning azo dyes present in textiles and leather. The first route of exposure is via the dermal route. Subjects are exposed to azo dyes when clothes or other garments that contain azo dyes are worn. This route of exposure includes both adults and children. The second possible route of exposure only includes infants. Oral exposure may occur when the very young mouth toys, clothes (e.g. string of sweater) or bed linen made of textile in which azo dyes are present (LGC 1998; Zeilmaker, Kroese et al. 1999; Zeilmaker, Kranen et al. 2000).
The third possible route of exposure is via the respiratory tract. This mainly occupational exposure occurs during the fabrication and production of azo dyes and/or products to which azo dyes are added. Inhaled air by the employees may contain concentrations of azo dyes. Air concentrations of benzidine were measured in a benzidine manufacturer plant and a range of 0.007 to 17.6 mg/m^3 was observed in an open system (NTP). This route of exposure is not considered relevant for consumers. Inhalatory exposure may also occur indoors (car interiors are covered with carpets which may be dyed with azo colorants; the time spent in cars is therefore also considered as indoors). Azo dyes may be present in the air (maybe in the form of dust) as a result of wastage. However, data on indoor air concentrations are not available.

3.2 Target population

Regarding exposure to azo dyes from textiles the entire Dutch population is the target population. A separation is made between adults and infants due to the oral exposure of infants during mouthing behaviour. Infants of average age of 10.5 months are considered here. The target population is estimated to be 16 million, resembling the Dutch population (Statistics Netherlands 2005). Because life time exposures are considered in this case, infants are not regarded as a separate group.

3.3 Results

The exposure to azo dyes and associated aromatic amines is calculated here for both the dermal and oral route. As mentioned in the introduction, it is aimed to assess the exposure before the measure was enabled and after. Data such as: market share of azo dyes in textile and the amount of azo dyes present in textile differ from the present situation. The input parameters required for the calculations are provided below.

3.3.1 Dermal exposure

The dermal exposure to azo dyes from clothes is calculated with ConsExpo 4 for both adults and infants. The formula and parameters required for the calculations are provided below.

$D_{cloth} = [(PA * S_{factor} * L / BW) * U * f / 365] * P_{azo} * P_{amine}$

D_{cloth}	Chronic dermal exposure from textiles (µg/kg/day)
PA	Product amount (g)
S_{factor}	Skin correction factor (fraction)

L	Leachable fraction (µg/g)
BW	Body weight (kg)
U	Absorption (fraction)
f	Frequency of use (/year)
P_{azo}	Prevalence of azo dyes in textile (fraction, not in ConsExpo)
P_{amine}	Prevalence of aromatic amine in azo dye (fraction, not in ConsExpo)

- *Body weight*

The body weights of adults and infants (10.5 month old) are 70 kg and 9.45 kg, respectively (Bremmer and Van Veen, 2000).

- *Skin factor and product amount*

To assess the exposure to aromatic amines from wearing clothes it is important to estimate the proportion of cloth that effectively comes into contact with the skin in order to be exposed (Zeilmaker et al., 1999). Some garments are worn directly to the skin, while other garments such as sweaters will only partly contact the skin. To correct for this a skin contact factor is used. For example, clothes directly worn to the skin will be assigned a contact factor of 1, but a sweater may be assigned a contact factor of 0.3.
For the present exercise, it is not desirable to determine the skin contact factor for all garments separately, but instead an average skin contact factor for all garments is desired. This provides an opportunity to assess the exposure from all textile clothes in one effort. However, the skin contact factor for all garments is dependent on seasonal changes, because outfits change as the seasons change. For all cloth worn together; a skin factor can be assigned describing the average contact factor. A skin contact factor of 0.4 was assumed.

How many clothes individuals wear is closely related to the weight of the clothes. Again, the product amount (weight of all clothes worn simultaneously) depends heavily on the individual and season. In a small experiment, individuals were asked to weigh their clothes separately, except shoes, and add the weights to obtain a total. It was observed that clothes worn simultaneously weigh 1382 g (N=6, winter garments). However clothes worn in the summer are generally thinner and less layers of clothes are worn. From separate weighing it came forward that sweaters weigh approximately 400 g. Assuming that a sweater is not worn during the summer period and lesser layers, the weight of clothes in the summer is calculated: 932 g (N=6, average of winter garment minus sweater). Averaging both figures for winter and summer provides a product amount of 1150 g. Clothes of an infant were weighed as well, 300 g (rounded from 284 g).

- *Leachable fraction*

The leachable fraction refers to the amount of compound (e.g. benzidine) that migrates from the textile to the skin (all clothes worn simultaneously). This migration is specific per azo dye or aromatic amine and per fabric and may change after clothes are washed
(Oomen et al., 2004).
From Zeilmaker et al. (1999) a leachable fraction for benzidine was determined. For four garments the leachable amount was measured, these figures ranged from 0.63 to 5.7 µg/g. On

average a leachable amount of 2.19 μg/g textile for benzidine was derived. This value is used to calculate the exposure to benzidine from textile clothes.
For 2,4-toluenediamine the leachable amount was derived from an experiment in the *in vitro* digestion model by Oomen et al. (2004). Three digestions of the same piece of textile containing 2,4-toluenediamine were performed in the *in vitro* digestion model. This procedure was followed for several exposure times. In total 66 digestions were carried out. This provided an average leachable amount of 34 μg/g textile for 2,4-toluenediamine with a range of 10 to 50 μg/g. However, the leachable amounts are determined in a sucking experiment designed to resemble the mouthing behaviour of children. It is unknown whether the same leachable amounts can be expected from wearing clothes. Leaching into saliva may be significantly different from leaching into sweat (dermal contact).
In contrast, from footwear (children's slipper) a leachable amount of 0.17 μg/g textile for 2,4-toluenediamine was found (Zeilmaker et al., 1999). This value is significantly lower than the values observed by Oomen et al., but was determined for dermal contact and not oral exposure. For 2,4-toluenediamine the leachable amount of 0.17 μg/g textile for 2,4-toluenediamine will be used, because this figure is based on dermal exposure instead of oral exposure.

It must be noted that the leachable fractions of benzidine and 2,4-toluenediamine was determined by measuring the 'free' amines and those bound to the azo dye. To measure the aromatic amines bound to the azo dye a reductive cleavage was performed by chemical reaction. It was observed that the amount of 'free' amines was very low compared to the amount amines coming from the azo dye (Zeilmaker et al., 1999). This led to the conclusion that bound aromatic amines are responsible for the larger part of the exposure. Further, this indicates that reductive cleavage of the azo dyes by the skin is an important factor for exposure (see also section absorption).

- *Absorption*

The dermal absorption for benzidine and benzidine derivates was tested by Shah and Guthrie (1983). Twenty-four hours after dermal application to rats approximately 40% was recovered in either faeces or urine. In total, almost 50% was dermally absorbed after 24 hours. For 2,4-toluenediamine, Germany prepared a risk assessment report for the Existing Substances program of the European Union (EC, 2005). For skin penetration a value of 24% is reported from male human volunteers in a study conducted by Marzulli et al. (1981)
(cited from EC, 2005).

The absorptions mentioned above were derived after exposure to the aromatic amines. However, the exposure results from aromatic amines bound to azo dyes for the larger part while 'free' amines only contribute for a small part. In a study by Collier et al. (1993) the absorption and reductive cleavage of three azo dyes, ANSC, Sudan I, and Solvent Yellow 7, was observed in a human skin *in vitro* assay. A similar exercise was performed in rodent skin *in vitro* assays where rat and guinea pig skin was used. Within 24 hours 5, 30, and 35% of respectively ANSC, Sudan I, and Solvent Yellow 7 was absorbed by the human skin. In contrast, the absorption in rodent skin ranged from 5% to over 60%. From the amount azo dyes

absorbed by human skin approximately 30% was reduced to aromatic amines (Collier et al., 1993).
These absorption figures are considered more relevant than the absorptions figures for the individual aromatic amines, because the exposure is more related to absorption of the azo dyes. The exposure from ‘free’ amines is considered negligible. Therefore, assuming that human skin can absorb 30% of azo dyes leaching from a fabric and 30% of that amount is reduced in the skin to aromatic amines, based on findings by Collier et al., provide an absorption of 9% (0.3 * 0.3 = 0.09). It is acknowledged that only three azo dyes were tested in the study by Collier, but at present, there are no additional studies that would either confirm or discard these findings. It is assumed that other azo dyes behave similarly. Therefore, absorption of 9% will be used for both aromatic amines in the present exposure assessment.

- *Frequency*

Clothes will be washed after being worn. As a result the leachable amount after washing may be significantly different. Exposure to aromatic amines is expected to be lower after washing, but to what extend is not known. In a report prepared by ETAD it was shown that after approximately 20 cycles of wash steps no aromatic amines would leach from the product (ETAD, 1997). The amount that leaches from the product will most likely decrease after every wash cycle, therefore an exposure frequency of 10 was assigned per product. For exposure assessment, therefore, it is assumed that exposure from a certain cloth will take place 10 times with a product cycle of 4 months (= average period in which a cloth is replaced or additional cloth is bought). In short, from one cloth a subject is exposed 10 times (due to washing of clothes) and a cloth is replaced three times per year. Thus multiplying exposure from one cloth (10) with renewal (3) provides the exposure frequency of 30/year.

- *Prevalence*

The above parameters are used as input data for ConsExpo 4.1 to calculate the dermal exposure to benzidine and 2,4-toluenediamine present in clothes. However not all clothes contain these aromatic amines. Therefore the outcome must be corrected for the prevalence of aromatic amines in textiles (when assuming that textiles in all usage categories contain similar amounts of azo dye) and for the part benzidine or 2,4-toluenediamine are present as constituents in azo dyes.

Before the measure

In a report by CREM two investigations were described concerning positive results of the presence of suspected azo dyes in leather and textile (Mensink et al., 1997). Research was conducted in Germany (by TÜV) and in the Netherlands (by TNO) to obtain the percentage of products per product category that contains suspected azo dyes or aromatic amines. The original research reports by TÜV and TNO concerning testing methodologies and results were not available. Detailed information on selection methods of articles and testing methodologies are therefore lacking. Only the results of both studies as shown in Mensink et al., (1997) are given.
Although the Regulation entered into force on August 1, 1996, textile and leather products containing azo-dyes were still allowed to be sold until September 1, 1997. For this reason, both studies are considered to describe the prevalence of azo dyes before the measure.

TÜV Rheinland Institute
The research by TÜV was conducted during two periods, from January 1994 to November 1995 (1) and from December 1995 to mid April 1997 (2).
The research was conducted including generally leather and textile products. In the first period, average percentages of 28.2% for leather and 15.3% for textile were found. In the second period, average percentages of 15.3% for leather and 6.8% for textile products were found (note that 15.3% is the average of the prevalence for articles, for instance 29.5% of the gloves tested contained a carcinogenic aromatic amine). Based on the results shown in Mensink et al., (1997) it was not evident at what concentration level a sample was determined to be positive.

TNO Delft
TNO found an average percentage of approximately 15% for clothing in the testing period March 1996 to March 1997 (Mensink et al., 1997). In general, clothing was analysed, but to a smaller extent also leather products and toys. In total 792 analyses were performed of which 125 tested positive. A sample was tested positive when the concentration of the aromatic amine exceeded 30 ppm.

VWA
In a study conducted by Dutch Food and Consumer Product Safety Authority (VWA) which was completed in 1995 (reported in 1997) showed lower percentages. In textiles 6% of the products was found to contain suspected azo dyes in concentrations above 30 ppm and 5% below 30 ppm (Keuringsdienst van Waren, 1997). In the report by Zeilmaker et al. (1999) prevalence numbers displayed were on average 8%, before the measure, while outside the Netherlands even higher prevalence numbers were observed (14% in Germany and up to 56% in Denmark).
Because prevalence data before the measure are limited and show disperse percentages, it is difficult to estimate the prevalence based on that information. Due to the fact that relatively high prevalence numbers were found outside the Netherlands and variation between articles was large; the prevalence is set at 25% for azo dyes as a rough estimation (Table A4.1; scenario 1).

After the measure
Prevalence numbers after the measure are scarcer. The VWA issued a monitory action for suspected azo dyes in leather. VWA found a prevalence of 15% which does not deviate much from prevalence numbers before the measure (Reus and Westerhoff, 2001). However, during monitory actions products are selected based on suspicion and hence the study is biased. On the other hand selection bias can also have occurred during monitory actions before the measure. Setting reliable prevalence numbers is therefore difficult.
It is decided to describe two situations for the exposure from azo dyes in textile after the measure. Situation one (in Table A4.1; scenario 2) describes the prevalence for azo dyes of 15% as observed by the VWA. In the second situation it is assumed that a total reduction of azo dyes in textile was achieved. The exposure to the azo dyes is consequently negligible (zero; scenario 3).

Prevalence of benzidine and 2,4 toluenediamine amongst aromatic amines
The prevalence of benzidine and 2,4-toluenediamine in azo dyes is unknown. Benzidine is the most occurring aromatic amine used as constituent for azo dyes and is expected to occur in 30% of the azo dyes. The prevalence of 2,4-toluenediamine is expected to be lower (10%) than benzidine. The prevalence numbers of benzidine and 2,4-toluenediamine are solely based on assumption and lack scientific basis.

Table A4.1. Overview of parameters used for calculation of dermal exposure to azo dyes and associated aromatic amines from textile.

Dermal exposure	*Adults*	*Infants*	*Remarks*
Product amount (g)	1150	300	See above
Skin correction factor (fraction)	0.6	0.6	Assumption
Leachable fraction benzidine (µg/g)	2.19	2.19	See above
Leachable fraction 2,4-toluenediamine (µg/g)	0.17	0.17	See above
Body weight (kg)	75	9.45	(Bremmer and Van Veen, 2000)
Absorption (fraction)	0.09	0.09	See above, (Collier et al.,1993; Zeilmaker et al.,1999)
Frequency (/year)	30	30	See above
Prevalence azo dye scen. 1, before (fraction)	0.25	0.25	See above
Prevalence azo dye scen. 2, after (fraction)	0.15	0.15	See above
Prevalence benzidine (fraction)	0.3	0.3	See above
Prevalence 2,4-toluenediamine (fraction)	0.1	0.1	See above

When above parameters were used as input in ConsExpo (model dermal exposure from migration) the dermal exposure could be calculated bearing the prevalence figures in mind. Dermal exposure to azo dyes from textiles was calculated for two scenarios for adults and infants (life time exposures). The exposure for infants, assumed duration 2 years, is spread out over 75 years of life leading to relatively low exposure levels.

Scenario 1 (before measure):

- Adults: 8.0 ng/kg/day benzidine
  0.21 ng/kg/day 2,4-toluenediamine

- Infants: 0.4 ng/kg/day benzidine
  0.011 ng/kg/day 2,4-toluenediamine

Scenario 2 (after measure):

- Adults: 4.8 ng/kg/day benzidine
  0.12 ng/kg/day 2,4-toluenediamine

- Infants: 0.25 ng/kg/day benzidine
  0.006 ng/kg/day 2,4-toluenediamine

Scenario 3 (after measure):
No exposure to azo dyes from textiles is assumed.

Oral exposure

Children can be orally exposed to azo dyes and associated aromatic amines when mouthing textile toys and/or to a lesser extend clothes (Garrigos et al., 2002; Bouma and Reus, 2004). Especially the very young up to the age of three will put textile toys and other textiles frequently in their mouth. Children often have a favourite toy which is kept close to them; therefore a reasonable assumption would be that children will only mouth a few toys. Furthermore, for this scenario it is assumed that a children's toy is bought for a life time and that children will not mouth toys longer than two years (in general, because children will grow out of this mouthing habit).

The oral exposure can be calculated by using the formula stated in Appendix B. Hereby, the migration rate of aromatic amines from the product is taken into account. The formula does not take fluctuations of the migration rate into account. Most likely, the migration rate will decline when the total amount of aromatic amine present has decreased. Therefore, due to suspected sustained contact with the textile toy and affection of an infant for a toy; the formula is not well suited. Because when a two year mouthing period is assumed, more aromatic amine would be taken up than originally was in the product.
Due to this sustained mouthing behaviour of children it is a reasonable assumption that all present azo dyes and associated aromatic amines will eventually leach from the product, even though the migration rate (see Appendix 4.2) is rather low. Using the total amount of aromatic amines present is considered a valid approach in this particular case.

In order to calculate the life time oral exposure to benzidine and 2,4-toluenediamine from mouthing toys the following parameters should be known: product amount, total concentration of aromatic amine ('free' and bound to azo dye), oral absorption, and the probability of a toy containing aromatic amines.

- *Product weight*

The product weight resembles the average weight of a textile toy or the part of a toy what is made of (coloured) textile. It was estimated that the average weight mounts up to 10 g.
In Zeilmaker et al. (2000) the amount of 2,4-toluenediamine in a textile toy was shown, which was measured by the Regional Inspectorate for Health Protection (at present Dutch Food and Product Safety authority). Seven toys were investigated for the presence of carcinogenic aromatic amines which provided a concentration range of 30 to 359 µg/g product. Mensink et al., (1997) reported a range of 50 to 480 µg/g. For the calculation of oral exposure a product concentration of 200 µg/g product will be used. Benzidine was not found in the textile toys investigated by the Inspectorate for Health Protection. Further, benzidine levels in textile may fluctuate significantly; therefore no concentration of benzidine was estimated.

- *Oral absorption*

Exposure to aromatic amines through the oral route is mainly determined by bound aromatic amines to azo dyes and for a small part by 'free' amines, as was mentioned above. Chung (1983) states that azo dyes can be reduced to aromatic amines by the intestinal bacteria. Thus, it is assumed that all azo dye will be reduced to their aromatic amines in the gastrointestinal (GI) tract, due to the large capacity of the present bacteria and the relative long duration in the GI tract.
Within a few days all orally administered 2,4-toluenediamine was already excreted in urine (EC, 2005). Therefore, the oral absorption of 2,4-toluenediamine is set at 100%.

- *Probability*

The probability of a toy containing aromatic amines is hard to assess. Many toys do not have textile or leather fabrics on it. Furthermore when toys do have textile or leather fabrics, it is unknown whether or not they contain aromatic amines. For that reason, it is assumed that the probability (= prevalence) is the same as for textile clothes. This probability was set for scenario one at 25% and for scenario two at 15% (see section dermal exposure; prevalence). Multiplying this probability with the part of toys which have textile fabrics (assumption 20%) will provide the probability of a toy containing aromatic amines of 0.05 (scenario 1) and 0.03 (scenario 2).
2,4-Toluenediamine is used in azo dyes for about 10% (see above). Multiplying 0.05 (scenario 1) with 10% will provide the probability a toy contain that certain aromatic amine (P_{toys}), leading to a probability of 0.005 for 2,4-toluenediamine. For scenario 2, 0.03 is multiplied with 10% leading to a probability of 0.003 for 2,4-toluenediamine.

To calculate the life time exposure from mouthing toys by infants (average age 10.5 months, weight 9.45 kg) first the total amount of 2,4-toluenediamine was calculated. Multiplying the product weight with product concentration provides 2000 µg (200 µg/g * 10 g). To obtain a life time exposure this amount will be spread out over 70 years: 2000 µg divided by 70 * 365 = 0.078 µg/day. Accounting for the body weight and for the probability provided 0.04 ng/kg/day (scenario 1) and 0.025 ng/kg/day (scenario 2).

Scenario 1 (before measure):

- - ng/kg/day benzidine
  0.04 ng/kg/day 2,4-toluenediamine

Scenario 2 (after measure):

- - ng/kg/day benzidine
  0.025 ng/kg/day 2,4-toluenediamine

Scenario 3 (after measure):
A negligible exposure was assumed in this scenario.

Total exposure

The total exposure is determined by adding up the dermal exposure and oral exposure to either benzidine or 2,4-toluenediamine (see Table A4.2).

Table A4.2. The exposure levels from different routes and for the two scenarios are provided in the table. The total life time exposure is the sum of the dermal and oral exposure. The values in the table are rounded numbers.

	Dermal life time exposure (ng/kg/day)		**Oral life time exposure (ng/kg/day)**	**Total life time exposure (ng/kg/day) (rounded)**
	Adult	Infant	Infant	
Scenario I				
Benzidine	8.0	0.4	-	8
2,4-toluenediamine	0.21	0.011	0.04	0.3
Scenario II				
Benzidine	4.8	0.25	-	5
2,4-toluenediamine	0.12	0.006	0.025	0.2
Scenario III				
Assumed no exposure	0	0	0	0

4. Description of toxicity

Research to aromatic amines as a result of cleavage of azo dyes has been conducted to study the carcinogenicity of azo dyes and showed that not all azo dyes lead to formation of carcinogenic aromatic amines. In a report by Zeilmaker et al. (2000) six aromatic amines were considered to assess the cancer risk from azo dye exposure. Of the six considered by Zeilmaker et al. (2000), benzidine and 2,4-toluenediamine were selected to estimate the health benefit from banning the carcinogenic aromatic amines.

- benzidine CAS# 92-87-5
- 2,4-toluenediamine CAS# 95-80-7

Benzidine is the best studied and documented aromatic amine (ATSDR, 1995). From animal studies with oral exposure to benzidine cardiovascular, haematological, renal, hepatic, and genotoxic effects were observed at relatively high dosages. Bladder cancer was also observed in animal studies after chronic oral exposure to benzidine in mice and rats. Human cases of allergic contact dermatitis were correlated with exposure to benzidine, but data on exposure levels on the skin were unavailable. Epidemiological studies where benzidine was inhaled by the workers, displayed a pronounced increase of the incidence of bladder tumours (ATSDR,

1995). For this reason bladder cancer was considered the critical effect for exposure to benzidine.
Its carcinogenicity was evaluated by the US EPA and a Negligible Risk Level (NRL) was established for life time exposure. This corresponds with an additional cancer risk of one in a million when exposed at 0.3 ng benzidine per person per day for a life time exposure (Zeilmaker et al., 2000).
The obtained NRL (by US EPA) was derived from two epidemiology studies (performed by Zavon et al. (1973) and Rinde and Troll (1975)). In the study conducted by Zavon, the incidence of bladder cancer in workers exposed to benzidine was observed and compared to the incidence of bladder cancer in the general public. Exposure levels of benzidine, however, were not directly measured in this study. Instead, the US EPA used the exposure levels that were estimated from benzidine levels in urine in an epidemiological study by Rinde and Troll in rhesus monkeys. In the study with rhesus monkeys a relation between oral benzidine exposure and urinary excretion was established. This relationship between exposure and excretion was used to calculate the exposure to benzidine in humans from their urinary benzidine levels (Zeilmaker et al., 1999; Zeilmaker et al., 2000). In order to combine the two epidemiological studies to derive a NRL, US EPA had to assume that both oral absorption and inhalation absorption were 100% since data on absorption of benzidine was lacking. This assumption is supported by the fact that the Risk Assessment Report on 2,4-toluendiamine uses an inhalation absorption of 100% by default for 2,4-toluenediamine. This assumption also indicates that the NRL (0.3 ng/person/day) of benzidine can be considered as an internal value in risk assessment.
An animal study was also available for benzidine to derive a NRL. When extrapolation steps from animal to human were performed a significantly higher NRL was obtained. Using the TD_{50} for benzidine from an animal study (described in Zeilmaker, Appendix 4.3 (Zeilmaker, et al., 2000)) an NRL was found at 238 ng/day life time exposure. Normally, extrapolation of carcinogenicity data from animal to human is conducted when suitable human data is lacking. Extrapolations are based on the assumption that dose-response characteristics of chemical carcinogens are the same in animal and human. Data above shows that this may not be the case for benzidine with possible explanation that humans are the more sensitive species.

For 2,4-toluenediamine a risk assessment report was prepared by Germany. Its main target organ from chronic exposure is the liver, but toxic effects were also observed in the kidney, lung and reproductive system in male rats after oral exposure. Carcinogenicity studies predominantly displayed tumours in the liver (EC, 2005).
For 2,4-toluenediamine no data on human epidemiology studies was available. Using the carcinogenicity data for 2,4-toluenediamine from animal studies an NRL was found at 420 ng/person/day life time exposure (Zeilmaker et al., 2000).
However, structural similarities between benzidine and 2,4-toluenediamine and TD_{50} values in the same order of magnitude (1.7 mg/kg/day vs. 2 to 4 mg/kg/day) have led to the assumption that humans may respond more sensitive to 2,4-toluenediamine than animals. Instead of using the traditional approach in deriving the NRL, potencies of the aromatic amines in experimental animals were used as scaling factor for the carcinogenic potency of aromatic amines in humans relative to benzidine. In this context a NRL could be derived for 2,4-toluendiamine (Zeilmaker et al., 2000). Aromatic amines that differ less than tenfold in animal carcinogenicity in comparison to benzidine, such as 2,4-toluenediamine, were assigned the same NRL (potency

scaling factor = 1). A NRL of 0.3 ng/person/day was obtained for 2,4-toluenediamine in the report by Zeilmaker and colleagues.

The uncertainty in the toxicology of both aromatic amines is large. Although a human study was available for deriving a NRL, the exposure assessment in that study was determined by the relationship between exposure and excretion in urine in rhesus monkeys. The underlying assumption was that benzidine behaves similarly in rhesus monkeys as in humans. This assumption may not be true, causing a large uncertainty in the derived NRL. On the other hand, extrapolations from animal studies to derive a NRL for benzidine provided a NRL almost three orders of magnitude higher (0.3 ng/day vs. 238 ng/day). Extrapolations from animal to human are based on the assumption that dose-response characteristics of chemical carcinogens are the same in animal and human. Again, this may not be the case, regarding the large differences in NRL which may indicate that humans are more sensitive than animals.
Logically, the decision for using the NRL based on human data or NRL based on animal data will have a major impact on the risk assessment. The NRL based on human data is more conservative and is therefore preferred in risk assessment. For this reason, the NRL based on human data will be regarded here.
A NRL of 0.3 ng/person/day for benzidine and 2,4-toluenediamine will be used to calculate the additional risk.

It is acknowledged that the choice of NRL has a major influence on the calculatezd risk. When the NRL based on animal data was regarded the risk would be much lower. Therefore, for illustration purpose the additional risk and DALYs are calculated in appendix C using animal data.

5. Current risk assessment

The NRL of 0.3 ng/person/day life time exposure corresponds to a one in a million additional cancer risk. The relation between exposure levels and risk for genotoxic carcinogens is assumed linear. Comparing exposure levels with the NRL which corresponds to a risk level will provide an additional risk at a certain exposure level. First, the NRLs of both compounds are recalculated so that the NRL has the same unit as the exposure (for example NRL benzidine is 0.3 ng/person/day divided by body weight of 75 kg results in 0.004 ng/kg/day).
The risk is characterized by combining the exposure from wearing clothes by adults and infants and mouthing toys by infants (total exposure) with the toxicology (NRL) of both compounds. The additional cancer risk was calculated for two scenarios. The first scenario regards the exposure before the measure was taken; the second scenario describes the exposure after the measure was taken.
A third scenario is regarded where it is assumed that there is no longer exposure to the aromatic amines, obviously without exposure there is no risk.

For scenario 1:

Benzidine: A total life time exposure of 8 ng/kg/day benzidine was calculated. Compared to the NRL of benzidine 0.004 ng/kg/day, provides an additional risk of 0.002. An additional risk of 1 * 10^{-6} is ‘accepted’.

2,4-toluenediamine: A total life time exposure of 0.35 ng/kg/day 2,4-toluenediamine was calculated. Compared to the NRL of 2,4-toluenediamine 0.004 ng/kg/day, provides an additional risk of 6.5 * 10^{-5}.

For scenario 2:
Benzidine: A total life time exposure of 7.1 ng/kg/day benzidine was calculated. Compared to the NRL of benzidine 0.004 ng/kg/day, provides an additional risk of 0.0013.

2,4-toluenediamine: A total life time exposure of 0.21 ng/kg/day 2,4-toluenediamine was calculated. Compared to the NRL of 2,4-toluenediamine 0.004 ng/kg/day, provides an additional risk of 3.9 * 10^{-5}.

6. Calculation of Public Health gain

6.1 Decrease in exposure

The decrease in exposure is determined by the decrease of the prevalence of the azo dyes in textiles. Scenario 1 describes the exposure before the measure where a prevalence of 0.25 was taken into account. In the second scenario the prevalence was set at 0.15. It was assumed that the occurrence of specific aromatic amines and their concentrations in textile, when azo dyes are present, would remain the same as before the measure. Hence, the exposure is decreased by a factor 1.7 (0.25/0.15 = 1.7).
In the third scenario it was assumed that no exposure to suspected azo dyes would occur from textiles after the measure. The decrease of exposure is thus maximal and the incidence would be zero. Obviously, this is not realistic, because exposure to suspected azo dyes may occur from other consumer products such as towels, hair dyes, and food consumption next to background air concentrations (SCCNFP, 2002; Federal institute for Risk Assessment (BfR) 2003; Platzek et al., 2005). Detailed information on these consumer products or air concentration levels, however, is insufficient to assess the exposure from these sources to suspected azo dyes.

6.2 Increase in Margin of Safety

No margin of safety was estimated.

6.3 Decrease in incidence effect

The number of additional cases is determined by the additional risk and the target population. The target population was set at 16,000,000 individuals, which resembles the total Dutch population. The number of additional cases per scenario and compound is shown in

Table A4.3 As the exposure was decreased by 1.7 fold, logically, the number of cases is decreased by the same factor (49,000 / 29,000 = 1.7).

Table A4.3. Calculated additional cancer risks and additional cases for both aromatic amines and both scenarios.

	Additional risk	Target population	Additional cases
Scenario I			
Benzidine	0.002	16,000,000	33,583
2,4-toluenediamine	$6.5 * 10^{-5}$	16,000,000	1,035
Total scenario 1 (rounded)			**35,000**
Scenario II			
Benzidine	0.0013	16,000,000	20,150
2,4-toluenediamine	$3.9 * 10^{-5}$	16,000,000	621
Total scenario 2 (rounded)			**21,000**
Scenario III	-	16,000,000	**-**

6.4 Derivation of DALY

The critical effects considered in the animals were bladder cancer and liver cancer for benzidine and 2,4-toluenediamine, respectively (as mentioned in paragraph toxicology). This does not necessarily mean that bladder cancer and liver cancer will be observed in humans after exposure to these chemicals. In this particular case, bladder cancer also was observed in an epidemiological study with workers after exposure to benzidine. However, it may be possible that benzidine can also elicit other forms of cancer. The NRLs therefore correspond to an additional risk of cancer in general, with the exception of certain chemicals which are known to cause specific tumour formation.
The number of additional cancer cases per scenario and an average DALY of 8 for each cancer case are used as input to calculate DALY values. This resulted in 280,000 DALYs in the first scenario, which is before the measure. After the measure 168,000 DALYs were calculated (scenario 2). The health benefit or health risk reduction mounts up to 112,000 DALYs (see Table A4.4). However, when the exposure is reduced to zero the reduction is maximal, i.e. 280,000 DALYs. Yearly the health benefit can be calculated by dividing the DALY by the life expectancy, i.e. 75 years. This mounts up to 1500 DALYs/year.

Table A4.4. Calculated additional cancer cases, DALYs, and health benefit.

	Additional cancer cases	DALYs
Scenario 1	35,000	280,000
Scenario 2	21,000	168,000
Health benefit (rounded) Per year		**112,000 → /75 = 1500**

Again, it must be noted that the choice of NRL has a large impact on the derived DALY. For comparison reasons the same exercise to calculate the additional risk, additional cancer cases, and DALY was performed when exposure was compared to the NRLs based on animal data. The reader is referred to Appendix 4.3.

7. Discussion

The DALY calculation resulted in high values. Before the measure 280,000 DALYs were calculated. After the measure 168,000 could be derived showing a health risk reduction of 112,000 DALYs due to the measure. It can be expected that the drop in prevalence of suspected aromatic amines in azo dyes will continue the longer the measure is effective. Ultimately, when exposure is non-existent from azo dyes the health risk reduction is maximal, i.e. 280,000 DALYs (rounded). However, the uncertainty in the derivation of the DALYs is large. This uncertainty can be found in both the exposure assessment and toxicology of the compounds.

7.1 Uncertainties and Assumptions

- *Prevalence of suspected azo dyes and aromatic amines*

The prevalence of suspected azo dyes in textile was based on measurements conducted by consumer protection agencies, such as the Dutch Food and Product Safety authority and the German TÜV (Technische Überwachungs Verein). The number of studies conducted before the measure showed a large variation in the prevalence ranging from 8% to 56%. Monitory actions after the measure showed prevalence figures around 15%. All monitory actions, before and after the measure, are prone to selection bias, because these actions are targeted to find suspected azo dyes in textiles and leather. The prevalence of suspected azo dyes used, both before and after the measure, may have overestimated the actual prevalence.
Toys made of textile or which contain textile garments were often not considered in these studies. For the exposure assessment it was assumed that the prevalence was the same in toys as was for textile, with an additional correction for toys that do not contain textile. The assumption that the probability is equal to that in textiles is reasonable, because textile toys are often manufactured from similar materials as textile clothes are, e.g. clothes meant for dolls.
The prevalence of the aromatic amines benzidine and 2,4-toluenediamine were assumed to be 0.3 and 0.1, respectively, but lack any scientific basis. Benzidine is one of the most prevalent aromatic amine present in azo dyes and was therefore assigned a higher prevalence value.

Another important assumption is that these two selected aromatic amines are representative for the 22 proven or suspected carcinogenic aromatic amines. Because there are no indications what the ratios between the prevalence of suspected aromatic amines might be, no additional corrections were made to account for basing the exposure on only two aromatic amines.
Due to the lack of information the assumptions are rather weak. Hence, the resulting uncertainty from prevalence numbers is large.

- *Leachable fraction and dermal absorption*

The leachable fractions were determined in experiments performed by the Inspectorate for Health Protection (at present Dutch Food and Product Safety authority) and provided by Zeilmaker et al. (1999). The method used, was first to determine what fraction 'free' amines could leach out and further the fraction of amines bound to azo dyes. It was observed that the amount of 'free' amines was very low compared to the fraction bound to azo dyes (Zeilmaker et al., 1999). Hence the exposure to aromatic amines heavily depends on the reductive cleavage potential in the human skin. In the study by Collier et al. (1993) absorption through *in vitro* human skin and reduction of three azo dyes was investigated. The author observed that approximately 30% was absorbed and consequently 30% was also reduced to its aromatic amines. This provides a dermal absorption of 0.09 (9%). These observations, furthermore, enabled us to use the leachable fraction derived from Zeilmaker et al. (1999), because the reductive cleavage potential is incorporated in the dermal absorption.

However, the leachable fraction may vary significantly when different textiles and/or azo dyes are considered (Oomen et al., 2004). Furthermore, the leachable fraction may differ over time due to washing steps. The use of a distribution to describe the variation and uncertainty is desirable, but information is insufficient. Therefore, it is unknown how uncertain the estimations of the leachable fractions are.
Furthermore, it was assumed that the absorption and cleavage percentage of the three azo dyes can be used for the present case. The assumption that other azo dyes will behave similarly is high unlikely given the fact the observed variation between the three tested azo dyes (Collier et al., 1993).

- *Oral exposure*

The oral exposure was based on the assumption that all present azo dye is eventually ingested by the infant. The underlying assumption is that an infant is often very attached to its toys. In addition, the oral exposure was calculated based on mouthing of one toy. Then, the exposure was spread out over a life time, which is basically erroneous. One must bear in mind that each individual will have a peak exposure in early life.
The oral exposure was based on 2,4-toluenediamine only, because for benzidine no concentrations were found in toys in literature. For this reason no oral exposure assessment was performed for benzidine, because making an assumption on the concentration of benzidine present in toys would place a large uncertainty on the oral exposure assessment.
The actual oral exposure to suspected aromatic amines from mouthing toys may therefore be an underestimation due to lack of information.

All assumptions are set in such a way that an average exposure scenario is approached by expert judgment. A deterministic approach was used, because information was lacking to obtain distributions on the selected parameters. Furthermore it was not possible to give an indication on the uncertainty or certain distributions of parameters. A point value was chosen instead. It must be noted that above assumptions have led to large uncertainties in exposure assessment. The outcome of exposure assessment must be regarded with extra caution.

- *Toxicological profile*

The choice of which NRL to use had a major impact on the risk characterisation and consequently the derivation of DALYs. NRL based on human data were four orders of magnitude lower than NRLs based on animal data and thus is more conservative. However, this might indicate that humans are more sensitive than experimental animals.
As mentioned before, the NRL for benzidine based on human data, determined by US EPA, is subject to uncertainty. The relation between exposure to benzidine and urinary levels of benzidine was established in rhesus monkeys (Zeilmaker et al., 1999; Zeilmaker et al., 2000). Whether this relation is the same in humans is unknown. The NRL for 2,4-toluenediamine was obtained by first comparing its carcinogenic potency in animals to benzidine and then apply a correction factor (for difference in potency) on the NRL of benzidine. Hence, the NRL of 2,4-toluenediamine is subject to an even larger uncertainty, because of an additional extrapolation step from carcinogenic potency in animals to carcinogenic potency in humans.
Currently the Dutch Health Council (NL: gezondheidsraad) is revising the NRL for benzidine thoroughly, although no information is published thus far (personal communication Gerlienke Schuur/Paul Janssen).
For comparative reasons the same exercise was also performed using the NRL based on animal data in appendix C. This clearly shows that the choice in NRL makes the difference in reducing the health risk with 98,000 DALYs or with 130 DALYs. In both cases one could argue that the measure was effective from the health benefit point of view.

The uncertainty observed in exposure assessment and toxicology was reflected in the derivation of the DALY. In view of the fact that exposure and NRLs are used to derive the additional risk for cancer, their uncertainties are taken along in further calculations. The DALYs calculated for consumer exposure to azo dyes and its constituents cannot be considered as solid values, because of the large uncertainties. In this case report the uncertainty is mainly determined by the choice of which NRL to use in risk characterisation.

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Appendix 4.1

List of 22 carcinogenic aromatic amines:

	CAS number	Chemical
1.	60-09-3	4-amino azobenzene
2.	90-04-0	o-ansidine
3.	91-59-8	2-naphtylamine
4.	91-94-1	3,3'-dichlorobenzidine
5.	92-67-1	Biphenyl-4-ylamine
6.	**92-87-5**	**Benzidine**
7.	95-53-4	o-toluidine
8.	95-69-2	4-chloro-o-toluidine
9.	**95-80-7**	**2,4-toluenediamine**
10.	97-56-3	o-amino azotoluene
11.	99-55-8	5-nitro-o-toluidine
12.	101-14-4	2,2'-dichloro-4,4'-methylenedianiline
13.	101-77-9	4,4'-methylenedianiline
14.	101-80-4	4,4'-oxydianiline
15.	106-47-8	4-chloroaniline
16.	119-90-4	o-dianisidine
17.	119-93-7	3,3'-dimethylbenzidine
18.	120-71-8	p-cresidine
19.	137-17-7	2,4,5- trimethylaniline
20.	139-65-1	4,4'-thiodianiline
21.	615-05-4	4-methoxy-m-phenylenediamine
22.	838-88-0	4,4'-methylenedi-o-toluidine

Appendix 4.2

For illustration purpose the formula for oral exposure from mouthing toys is described here. Additional parameters needed are provided in main text.

The oral exposure due to mouthing of toys and textiles can also be calculated via the following formula (adapted from Bosgra et al. (2005):

$Oral_{toys} = PW * A * P_{toys} * F * T_{mouth} * M / BW$

$Oral_{toys}$	Chronic oral exposure from mouthing toys and textiles (µg/kg/day)
PW	Product weight (g)
A	Oral absorption (fraction)
P_{toys}	Probability of a toy containing aromatic amine/azo dye (fraction)
F	Correction factor for deviating concentration in respect to concentration of aromatic amine/azo dye from product at determined migration rate (dimensionless)
T_{mouth}	Total exposure time (min/day)
M	Migration rate (µg/min)
BW	Body weight (kg)

- *Mouthing time*

The exposure time resembles the time an infants mouths his or her toy per day. As a default in risk assessment a mouthing time of three hours is used, which is considered to be worst case (Schuur and Baars, 2004).
From a study conducted by Könemann (1998) to assess the phthalate release into saliva, an observational study was conducted to determine the mouthing habits of infants. In this study infants were handed a toy and observed for several hours. The data from Könemann (1998) was used by Bosgra et al. (2005) where the variability between individuals was separated from the variability within the individuals. This provided a lognormal mouthing distribution with a geometric mean of 9.7 minutes (SD = 6.95 minutes). The distribution contained mouthing times ranging from zero to approximately four hours.
Here, we consider the mouthing times of toys (containing textile) and clothes, while the mouthing time distribution only considers the mouthing of toys and not clothes. For this reason it was decided to use the 75th percentile of the mouthing time distribution as a realistic scenario. This provided a mouthing time of 36 minutes.

- *Migration rate*

Migration from clothes and/or toys is reliant on some aspects. The sort of fabric may influence the migration rate. Woollen fibres are more easily released than cotton for instance. Repeated sucking of textile toys can be seen as a form of wash-step. This may influence the migration rate since the concentration in the fabric is lower than before. Next to the fabric, also the azo dye and associated aromatic amine has also influence on the migration rate.

Oomen et al. (2003) and Oomen et al., (2004) determined the leachable amounts of several fabrics, among which was a textile fabric containing 2,4-toluenediamine, by exposing the fabrics to digestion fluids. The fraction of aromatic amines that migrates from the product into the digestion fluid (= migration rate) can be used to assess the oral exposure from mouthing fabrics. The migration rate was not addressed in the report by Oomen et al. (2004) for 2,4-toluenediamine (benzidine was not regarded in the report), but a migration rate could be derived by dividing the leachable amount 34 µg/g by the time of the experiment (30 minutes), assuming no saturation occurred. This provides a migration rate of 1.13 µg/min per g product for 2,4-toluenediamine. For benzidine no such information is available. Therefore the same migration rate as for 2,4-toluenediamine will be used for benzidine.

- *Correction factor*

The migration rate for 2,4-toluenediamine was determined from a cloth that contained 499 µg/g 2,4-toluenediamine. For benzidine it was calculated that on average 1030 µg/g benzidine is present. A much higher concentration of benzidine at start leads to a higher amount of benzidine able to migrate from the cloth onto the skin. Therefore a correction factor is introduced into the formula above (F). When assuming a linear relation between start amount and amount able to migrate from the cloth a correction factor of 1030 µg/g divided by 499 µg/g equals to 2.06 is derived (concentration at which the migration rate was determined assuming 2,4-toluenediamine has the same migration rate as benzidine). Logically for 2,4-toluenediamine the correction factor is 1.

Table A4.5. Overview of parameters used to calculate oral exposure to aromatic amines from mouthing toys.

Oral exposure	*Infants*	*Remarks*
Product weight (g)	10	Assumption
Oral absorption both compounds (fraction)	1	
Probability toys scenario 1 (fraction) 2,4-toluendiamine	 0.015 0.005	Probability adjusted for non textile containing toys
Probability toys scenario 2 (fraction) Benzidine 2,4-toluendiamine	 0.009 0.003	Probability adjusted for non textile containing toys
Mouthing time (min)	36	75^{th} percentile
Migration rate (µg/min/g product)	1.13	
Correction factor (dimensionless) Benzidine 2,4-toluenediamine	 2.06 1	
Body weight (kg)	9.45	Bremmer and Van Veen, 2000

Appendix 4.3

In the main text it was decided to use the NRL based on human data. Furthermore it was stated that this is a conservative approach in comparison to the NRL based on animal data. Here, the same exercise in deriving the additional risk and consequently the deriving of the DALYs will be conducted with the NRL based on animal data.

NRL benzidine: 238 ng/day = 3.2 ng/kg/day (body weight = 70 kg)
NRL 2,4-toluenediamine: 420 ng/day = 5.6 ng/kg/day (body weight = 70 kg)

First, the additional risk is determined per scenario per compound.
For scenario 1:
Benzidine: A total life time exposure of 8 ng/kg/day benzidine was calculated. Compared to the NRL of benzidine 3.2 ng/kg/day, provides an additional risk of $2.7 * 10^{-6}$.
2,4-toluenediamine: A total life time exposure of 0.26 ng/kg/day 2,4-toluenediamine was calculated. Compared to the NRL of 2,4-toluenediamine 5.6 ng/kg/day, provides an additional risk of $4.6 * 10^{-8}$.

For scenario 2:
Benzidine: A total life time exposure of 5.1 ng/kg/day benzidine was calculated. Compared to the NRL of benzidine 3.2 ng/kg/day, provides an additional risk of $1.6 * 10^{-6}$.
2,4-toluenediamine: A total life time exposure of 0.15 ng/kg/day 2,4-toluenediamine was calculated. Compared to the NRL of 2,4-toluenediamine 5.6 ng/kg/day, provides an additional risk of $2.8 * 10^{-8}$.

Secondly, the number of additional cases must be calculated by multiplying the additional cancer risk with the target population.

Table A4.6. Calculated additional cancer risks and additional cases for both aromatic amines and scenarios. Note: NRLs based on animal data was considered.

	Additional risk	**Target population**	**Additional cases**
Scenario I			
Benzidine	2.7 * 10^-6	16,000,000	42
2,4-toluenediamine	4.6 * 10^-8	16,000,000	1
Total scenario 1			**43**
Scenario II			
Benzidine	1.6 * 10^-6	16,000,000	25
2,4-toluenediamine	2.8 * 10^-8	16,000,000	0
Total scenario 1			**25**

For each cancer case an average DALY of 5 was assigned by agreement.
Scenario 1: 43 [additional cases] * 8 [DALYs per cancer case] = 344
Scenario 2: 25 [additional cases] * 8 [DALYs per cancer case] = 200

From the measure 130 healthy life years can be gained (344-200 = 144) and maximally 344 DALYs when the NRL based on animal data is used.

Appendix 5 Case report dichloromethane

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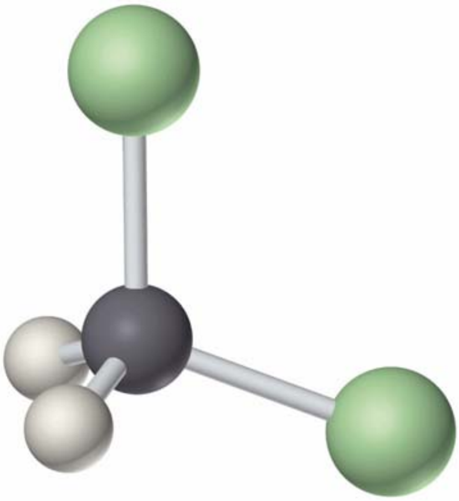
November 2006

1. Introduction

In the do-it-yourself (DIY) sector individuals can be exposed to chemicals that are present in all kinds of products, such as paints, glues, oils et cetera. During DIY activities chemicals can be released from their container or other surfaces which may result in health effects in humans. Methylene chloride is such a chemical, which is released during DIY activities. As a result the operator is exposed and may suffer from health effects. Methylene chloride (CAS No. 75-09-2, Einecs No. 200-838-9), also known as dichloromethane (DCM), is a well described volatile organic solvent known to cause central nervous system (CNS) effects in humans. Currently, DCM is under revision of the European Commission in the framework of council directive 76/769/EEC on the marketing and use of DCM (for chemical structure see Figure A5.1). For these reasons methylene chloride makes an interesting case and was selected.



Methylene chloride

Figure A5.1. Chemical structure of methylene chloride. Black is carbon-atom, green is chlorine-atom, and grey is hydrogen-atom (CH_2Cl_2).

2. Background information on dichloromethane

2.1 Legislation

Because a proposal for restrictions on the marketing and use of DCM based paint strippers for Directive 76/765/EEC is considered, DCM is an interesting case. A ban for DCM from the market for consumer usage is proposed. This is still under discussion in the Limitation Working Group, while industry is putting forward other options to reduce the risks for consumers (ETVAREAD, 2004).

In this case study, the present situation and banning of DCM from consumer market will be regarded as the exposure before and after the measure.
DCM is found on the Annex I list (according Directive 67/548/EEC) and classified as Xn (harmful) and R40 (carcinogen category 3). A childproof lock must be present when DCM concentration exceeds 1%. Painting cans which require tools to open are also considered to be childproof locked (VWA, 2005). There is however no limit on concentration levels of DCM in consumer products.

2.2 General information

DCM is commercially produced mainly by two methods: the direct chlorination of methane and catalytical hydrochlorination of methanol in vapour or liquid phase. Characteristics of DCM are a low molecular weight (84.9 g/mol) and a high vapour pressure (350 mm Hg), explaining its volatility.
The main use of DCM is in industries as a metal degreaser and chemical solvent. The use amongst consumers is, as mentioned above, mainly in the DIY sector as paint/glue remover, adhesive, and as aerosol in spray cans. The percentage of DCM varies from 70-90% for the paint/glue removers, 65% for adhesives, and maximal 35% for aerosols.
This report focuses on consumers that are exposed to DCM. DCM main usage is in paint strippers and far less in household products. Therefore the adult population (among which: hobbyists) is considered the target population. The sensitive population during acute exposure consists of individuals with heart arrhythmia or ischemic heart disease and possibly children in case of acute exposure. In case of chronic exposure the sensitive population consists of individuals who metabolise DCM in large amounts to formaldehyde via the gluthation-S-transferase pathway (see chapter 4 on toxicology). Since DCM has a high vapour density (2.93 in comparison to air = 1; IPCS, 1996), DCM concentrations might be higher closer to the ground. The air that children breathe, since children breathe at lower altitudes, thus may contain higher concentrations of DCM. Although children do not execute the job themselves, they may play around. Furthermore, the use of DCM in household products in the Netherlands is regulated.
There are alternatives for methylene chloride usage in paint strippers. The chemical substitutes, however, are not as potent as DCM and require higher levels of application and longer duration time to obtain the same effectiveness, in most cases. One of the possible substitutes for DCM is the use of dibasic esters (DBE). DBE is a water based paint remover. DBE is regarded as the most important substitute for DCM, because it is almost equally effective. Other alternatives are heating and scraping the paint from the surface or sandblasting.

3 Description of exposure

Consumer exposure to DCM occurs mainly during two DIY activities; paint stripping and glue removing. Data is available on acute exposure to DCM from stripping paint in literature, but due to experimental settings do not completely reflect a realistic scenario. Exposure data on removing glue was not available at this moment. Therefore, it was decided to model the exposure to DCM, which has the main advantage of describing a realistic scenario. Measured exposure levels from literature could then be used for comparison purposes. DCM consumer exposure from paint stripping and removing glue was calculated with the program ConsExpo 4.0 (developed by RIVM). ConsExpo 4.0 models the exposure, from input data, during the activity and during the day of activity. Thereby ConsExpo 4.0 estimates the acute exposure and chronic exposure as a result of the DIY activities.

Very high peak exposures may occur during DIY-activities (use of paint strippers and adhesives) when safety precautions are not taken in account. The EPA estimated levels of exposure to DCM from 10 ppm to 5940 ppm (conversion factor 1 ppm = 3.53 mg/m^3) in a target population of paint strippers while working on furniture and woodwork (IPCS, 1996). Even with high ventilation, exposures in the breathing zone can be relatively high (Riley et al., 2000). The long-term or chronic exposure is most probably due to the same DIY-activities.

Background exposure via ambient air and open drinking water is present. Exhaustions from factories that utilize or produce DCM may contain DCM. The concentrations found in literature for ambient air concentrations in the Netherlands are quite low. Values between 1.4 (suburban) and 43 µg/m^3 (waste site) with a mean concentration of 9 µg/m^3 were observed by Guicherit and Schulting (1985) as mentioned in Environmental Health Criteria (IPCS, 1996). These exposure levels are much lower than short-term exposure levels or the long-term exposure from DIY activities. It depends heavily whether an industrial site is nearby or whether or not one lives in an urban environment. Concentrations in the air are generally higher in urban environments and even higher near sources of DCM emission. Oral exposure may also occur through food and drinks (decaffeination of coffee beans and extraction of certain spices), but concentrations are not known.

3.1 Target Population

As mentioned before, the target population in this study consists of people in the DIY sector. From a report of the Statistics Netherlands (CBS), it appeared that 25% of the population spends one to four hours on DIY activities per week. This would result in a population of approximately 3 million individuals. However, only a small part of the individuals will use a paint stripper or glue remover during their DIY activities. The information on the number of individuals using DCM containing products in the DIY sector is not known. If one assumes that 5% uses a paint stripper or glue remover based on DCM, it would result in a target population of approximately 150,000 individuals. This method of assessing the target population is rather rough.
A second option is to use sa les/production numbers as point of departure. In a TNO report by Tukker and Simons (1999), a paint stripper production containing DCM of 2,400 tons per year was noted. Thirty per cent of that is prescribed to the DIY market leading to an annual tonnage of 720. It is uncertain what amount is expected to stay on the Dutch market. Comparing export of paint, approximately 50% is exported. Assigning the same percentage

would lead to 360 tons. Assuming an average can of 1.5 l (weight: approximately 1.5 kg) leads to a consumer number of 240,000 individuals.
A third option, which probably will show the most reliable estimation, is conducting a field research. One could question painters for their sales of paint strippers in comparison to paint (for instance 1 can paint stripper on 100 painting cans). This number can then be compared to the annual sold paint cans (reliable number) to obtain estimation for the number of paint stripper cans. Two sales representatives of a DIY market and a paint shop were questioned but were not able to estimate the comparative sales number. This option remains inconclusive.
The first option was chosen over option two and three, because it was based on recent data from CBS. In contrast, the second and third option was either based on data from 1995 or inconclusive. Therefore, for further calculations a target population of 150,000 will be used as a best estimate.

3.2 Exposure to paint stripper

The exposure to paint stripper is modeled using ConsExpo 4.0., using the evaporation mode for inhalation exposure and the diffusion mode for dermal exposure.
The exposure to paint strippers is mainly via inhalation of the product. Paint stripper is available in normal cans from small to large and consists normally of 75% to 90% DCM (only considering the paint strippers based on DCM) (VWA, 2004). Recently, the Dutch Food and Consumer Product Safety Authority (VWA) issued a report on the safety directions that should be present on paint stripper products. The VWA, measured the concentrations of DCM and methanol in various paint strippers present on the Dutch market. (Average outcome was: concentrations DCM 83%, with a range 49-90% and methanol concentrations not higher than 10%) (VWA 2004). It is known that paint strippers may also contain other components, but they are present in small amounts. DCM is the effective compound and is solved in methanol. Vapor retardants and propellants may also be present, of which the first may affect the evaporation. For exposure assessment, it is assumed that other components than DCM or methanol will not affect evaporation. The range of 75 to 90% DCM is taken into account for exposure assessment.
According to two paint stripper producers 300 to 500 ml paint stripper is needed to treat 1 m^2. It was assumed that an average paint stripping job has a surface of 1 m^2. The amount and application time are related to the surface, thereby bearing in mind the variability of the DIY workers. There are individuals who work slower and more precise than others and will therefore use less paint stripper. The exposure time is always larger than the application time. After having stripped the paint, other activities like scratching of the old paint, repainting, and cleaning up must be executed. For stripping an area of 1 m^2 an application time of 10 to 20 minutes and a total exposure time of 100 minutes were taken into account. The amount needed to treat the surface is as mentioned above: 300 to 500 ml (that comes down to approximately 300 to 500 grams).
Since individuals work in different areas, it was decided to take the average volume per room in a house. In a report by RIVM, data from 15,000 dwellings were used to obtain average room values and ventilation rates (Bremmer and Van Veen, 2000a). The room volumes were averaged to 30 m^3 with a standard deviation of 4.89 m^3 where a normal distribution was

assumed. Ventilation rates are not indefinitely linked to room size and may depend on many aspects, such as whether individuals open or close doors and windows, use ventilation shafts or devices. Those aspects can make a difference in the exposure to DCM. In addition, the age of the house is linked to the ventilation rate, because old houses are often not well isolated. A uniform distribution was assumed, ranging from 1.5 to 4 per hour. The lower limit of 1.5 for ventilation rate was assumed, because when working with paint strippers it is expected individuals to read the safety directions. In addition, DCM may become sensitive to the skin and eyes. As a result, individuals will open windows and/or doors if possible. In this report the range of the ventilation rate is not linked to a specific room and are therefore regarded valid for any room (Bremmer and Van Veen, 2000).
The average weight of a DIY worker was assumed the same for the general public. According to fact sheet General (Bremmer and Van Veen, 2000) the average weight for an adult is 75 kg (standard deviation 13.9 kg). Inhalation rates are needed to estimate the concentration of DCM that can enter the airways, during the activity or for even longer periods. From the ICRP (1994) a lognormal distribution was obtained with a geometric mean of 17.6 m^3/day and geometric standard deviation of 1.34 m^3/day during moderate activity for adults. From Tukker and Simons (1999) came forward that the uptake fraction of DCM via inhalation was 70-75% based on pulmonary uptake when human subjects were exposed to 180-710 mg/m^3 DCM (IPCS, 1996; Tukker and Simons, 1999). A bioavailability of 75% was chosen, because the absorption is increased with a heavier state of exercise and increasing body fat.
During the activity it is expected that individuals will spill some of the paint stripper and a part will end up on their skin. Dermal exposure through air is considered negligible. DCM would evaporate immediately from skin surface into air. Dermal exposure from spills can be significant, based on skin exposure from stain, which has similar characteristics as paint strippers. Their viscosity and high amounts of organic solvents make it easy to spill (Bremmer and Van Veen, 2000). Therefore, exposure through skin was also included in the calculations with ConsExpo 4.0. Skin surface on which can be spilled, i.e. head, hands, and arms, is estimated to be 191 cm^2. The amount spilled is related to the total amount used. Approximately 0.27% of the total amount is spilled according to fact sheet paint (Bremmer and Van Veen, 2000; Bremmer and Van Veen, 2000) (paint stripper is compared with stain as both having low viscosity and high amount of solvent). The amount spilled is set constant at 8 gram paint stripper, because individuals are expected to clean their hands since irritations can occur. Skin permeability according to Tukker and Simons (1999) was 6.58 mg/h/cm^2 derived from animal studies (see Table A5.1).
No extrapolation factors are suggested by Tukker and Simons (1999).
Most individuals will use paint strippers only for small surfaces. However, larger surfaces might be treated as well (such as doors or wooden furniture) that require more time to treat and larger amounts of paint stripper. To obtain an exposure distribution from paint stripping to DCM another exposure scenario, beside the average paint stripping job, was used as input for ConsExpo 4.0. The input data was set at such a manner that it would result in a 99^{th} percentile exposure/case. Although input data is based on assumption, a 99^{th} percentile can be assessed with reasonable plausibility. A release area of 4 m^2 (surface area of a wooden door) was chosen as point of departure. Product amount, time spent applying the paint stripper, room volume (20 m^3 as 25^{th} percentile from Bremmer and Van Veen (2000)), and ventilation rate were set most unfavorable (see Table A5.1). Both scenarios (average and

worst case) were used to determine the exposure distribution. The average exposure was set at 50th percentile and the worst-case estimation at 99th percentile and resulted in 660 ppm and 3808 ppm, respectively. These values were used as starting point in PROAST to make a lognormal consumer exposure distribution (see Figure A5.2).

3.3 Exposure to glue remover

Exposure to glue removers is somewhat similar to paint strippers. Glue removing in this case consists of removing of glue that was used to keep carpets and vinyl floors in their place. It is believed that the frequency of removing glue is lower than stripping paint. Spills of glue remover are not so evident during this activity, because one is working mainly on the floor. Therefore only the inhalation exposure route is considered here. A default scenario for removing glue is described below. Because glue removing activities will not differ much from each other, setting up two default scenarios to obtain an exposure distribution is not necessary.
The exposure time is set at 4 hours. After having removed the glue from the surface, one has to clean-up and perform other activities to redecorate the room. The application time is set at 60 minutes taking a release area of 5 m^2 into account. The product amount is related to the surface area according to the information from the product data sheet. The fraction of DCM in glue removers is not known, but is expected to be in the same range as paint stripper. From a VWA report an average weight fraction of 0.70 (range 49-90%) could be derived. Further, the same input data as for stripping paint are used for assessing the exposure for removing glue (see Table A5.1).

Table A5.1. Overview of input data for ConsExpos 4.0 for both DIY activities.

	Paint stripper		**Glue remover**		**Reference**
Parameter	**Code** [a]	**Values** [b]	**Code**	**Values**	
General DCM					
Molecular weight CH_2Cl_2 (g/mol)	C	84.9	C	84.9	Chemfinder
K_{ow} (10log)	C	1.25	C	1.25	Chemfinder
Vapour pressure (mmHg)	C	350	C	350	Chemfinder
Body weight (kg)	N	75 (13.9)	N	75 (13.9)	Factsheet General (Bremmer and Van Veen, 2000)
Frequency (1/yr)	C	1; 5	C	1	Assumption
Inhalation					
Exposure duration (min)	C	100 / 240	C	240	Assumption
Product amount (g)	U / C	300-500 / 2000	U	2500-5000	www.alabastine.nl and www.sikkens.nl
Application time (min)	U / C	10-20 / 80	C	60	www.alabastine.nl and www.sikkens.nl
Weight fraction (%)	U	75-90	C	70	IPCS (1996), ATSDR (2000); Assumption
Release area (m^2)	C	1 / 4	C	5	Assumption
Room volume (m^3)	N / C	30.1 (4.89) / 20	N	30.1 (4.89)	Factsheet general (Bremmer and Van Veen, 2000)
Ventilation rate (1/hr)	U	1.5-4 / 4	U	1.5-4	Factsheet general (Bremmer and Van Veen, 2000)
Molecular weight matrix (g/mol)	C	32	C	32	Chemfinder
Mass transfer rate (m/min)	D	0.298	D	0.298	ConsExpo 4.0
Uptake fraction (%)	C	75	C	75	IPCS (1996) and Tukker and Simons (1999)
Inhalation rate (m^3/day)	L	17.6 (0.076)	L	17.6 (0.076)	ICRP (1994)
Dermal					
Exposed area (cm^2)	C	191	-	-	Factsheet general (Bremmer and Van Veen, 2000)
Amount spilled (g)	C	8	-	-	Factsheet paint (Bremmer and Van Veen, 2000b)
Skin permeability (mg/h/cm^2)	C	6.58	-	-	Tukker and Simons (1999)

[a)] Codes for values and distributions: C, constant value; N, a normal distribution with between brackets the standard deviation; U, uniform distribution with lower bound and upper bound; D, default value for the mass transfer rate approximated by the Thibodeaux's method; L, lognormal distribution with between brackets the coefficient of variation.
[b)] For stripping paint two scenarios were taken into account. The values represent the average / worst case scenarios.

3.4 Results

After assessing the exposure with ConsExpo 4.0, the results showed that the acute and chronic systemic dose constitutes of 90% inhalatory exposure and 10% dermal exposure. This shows that dermal exposure can play a significant role. However in determining the risks of DCM during DIY activities only the inhalation data are used, because toxicity levels are based on inhalation studies and do not include dermal exposure. It should be considered that the dermal exposure contributes to the toxicity (for chronic as acute systemic exposure) and risks can be slightly underestimated.

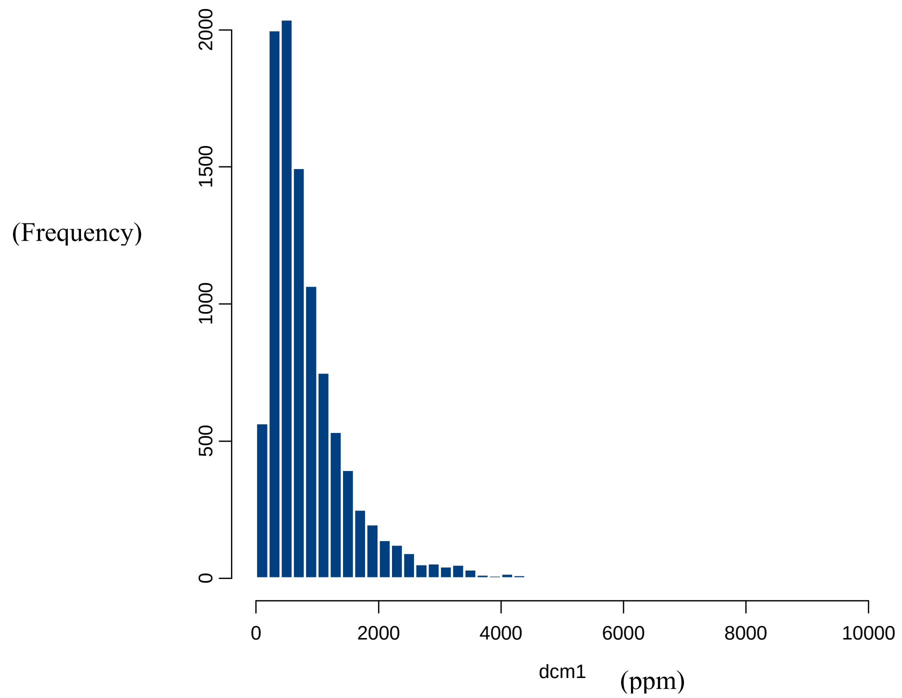


Figure A5.2. Exposure distribution obtained from PROAST mediated with input data from ConsExpo 4.0. A log-normal distribution was assumed. On the X-axis the air concentration in ppm is shown. On the Y-axis the frequency is shown from a total runs of 10,000.

3.4.1 Acute exposure

Air concentrations estimated for paint stripping with ConsExpo 4.0 resulted in air concentrations ranging from 50 ppm to approximately 5000 ppm. The average (50^{th} percentile) concentration per event paint stripping was 660 ppm. Figure A5.2 shows the log-normal distribution for paint stripping in which it is obvious that only a small part of the population is exposed to levels higher than 2000 ppm.
Somewhat similar results were found in experimental settings to determine the consumer exposure to DCM from paint stripping. In the report by ETVAREAD (2004) lower concentrations were found for paint stripping products from across Europe. Concentrations

between 400 to 1700 ppm for 10 paint stripper products were found. The paint strippers were tested by application of 375 ml on 1 m^2 of clipboard in a 15 m^3 room with an air exchange rate of 4. A total exposure time of 25 minutes (5 min application, 10 min affecting, and 10 min removing) was taken into account. Ruehl et al. (2004) summarized measurements from simulation of stripping work using DCM containing paint strippers. Air concentrations measured varied between 352 and 1881 ppm by an application of 375 ml and an air exchange rate of 4 per hour with room volume set at 15 m^3. The air concentrations measured are 8 hour shift averages and do not reflect the entire job. IARC (1999) displays the results of an investigation of the use of household products containing DCM in the United States. The estimated levels ranged from 9.8 ppm to a short term exposure of 5936 ppm although the majority was below 496 ppm. The EPA estimated levels of exposure to DCM from 10 ppm to 5940 ppm in a target population of paint strippers while working on furniture and woodwork (IPCS 1996). Van Veen et al. (2002) conducted a study to validate his model (a predecessor of ConsExpo 4.0) with experimental data. The experiment consisted of a treated surface area of 1.28 m^2 to which approximately 400 grams paint stripper was applied by volunteers in their own pace. Afterwards the subjects were instructed to walk around for 60 minutes. During that time air concentrations were measured every minute by infrared spectrometry at 1.60 cm height. The ventilation rate was determined at 0.25-0.3 per hour, but later increased to 0.5-0.75 per hour. The experimenters observed air concentration levels ranging from 168 to 448 ppm.

The average concentration per event glue removing was about two-fold higher in comparison to consumer exposure from stripping paint (estimated with ConsExpo 4.0): 2220 ppm. The range of the consumer exposure distribution, in comparison to stripping paint, was shifted slightly to the right indicating higher exposures as a result of removing glue. The 90^{th} percentile was 3640 ppm. Figure A5.3 below shows the distribution of exposure for glue removing. There were no concentrations found below the lowest category. This means that there is no zero exposure during this activity. People who do not perform the task are not considered. The exposure distributions describe the consumer exposure to DCM from a DIY activity for a certain individual who performs the task.

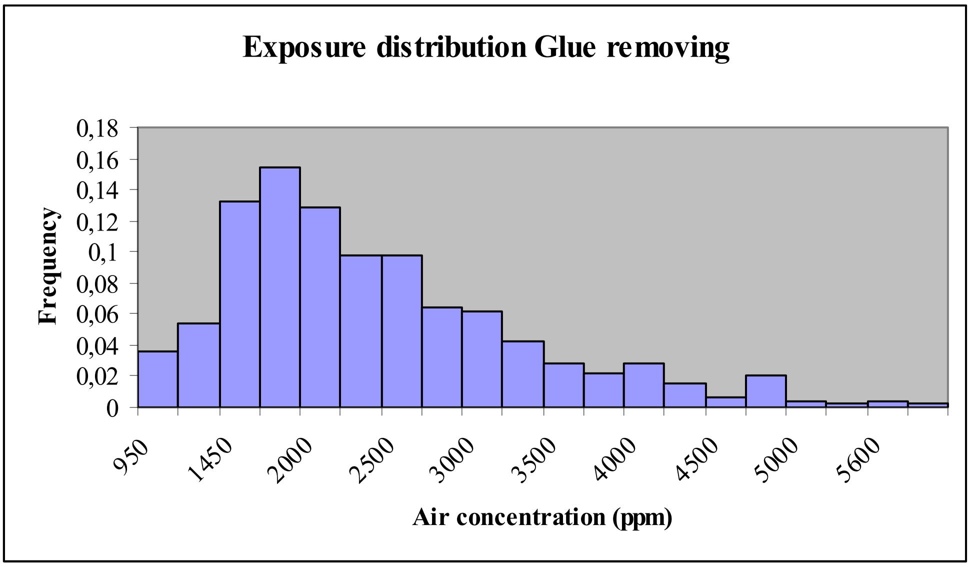


Figure A5.3. Exposure distribution as obtained from ConsExpo 4.0. The figure shows the exposure distribution due to exposure to glue remover containing DCM. The concentration is shown in ppm. The Y-axis shows the frequency of possible scenarios (considered as a separate individual) as a fraction of 1. The exposure is divided in categories.

3.4.2 Chronic exposure

For assessing the chronic exposure to DCM from DIY activities, the average inhalation concentration on day of exposure was determined. This is a 24 hour average; levels were 370 ppm for removing glue vs. 46 ppm for stripping paint. With these values an extrapolation was made to an inhalation exposure per year and eventually per 50 years (average concentration on day of exposure divided by 365 and multiplied by the frequency, to obtain a life long exposure one has to multiply with a factor of 50/70, because life long exposure takes 70 years into account and only 50 years of one's life are considered for exposure). The chronic exposure ranged from 0.09 ppm (average, 1x frequency) to 0.45 ppm (average, 5x frequency) for paint strippers. Glue removers are not as much used as paint strippers, therefore only a 1x frequency was assessed. The average exposure was 0.72 ppm (average, 1x frequency). The chronic exposure to glue removing is higher than for paint stripping. This is logical since it was estimated that the consumer exposure on day of exposure was higher for removing glue

For risk characterization and further calculations for acute exposure both exposure distributions (for paint stripping and glue removing) will be used. For chronic exposure a range of 0.09 ppm to 0.45 ppm for paint strippers and 0.72 ppm for glue removers will be considered in risk characterization.

4 Description of toxicity

4.1 Acute health effects of DCM

A clear distinction must be made between short term exposures and long term exposures to DCM, because health effects as a consequence from short term exposure are different from health effects due to chronic exposure.
Acute exposure to DCM can lead to central nervous system (CNS) depression, elevated carboxyhaemoglobin (COHb) levels, eye sensitization, and skin irritation and burns. Simultaneously heating (due to a stove or sun radiation) and DCM exposure one may also suffer from phosgene poisoning, which can have severe consequences on human health. Exposure to DCM leads to internal exposure to the brain which can cause CNS depression. This can result in light-headedness, difficulties in enunciation, nausea, tingling or numbness of the extremities. Very high vapour concentrations may result in unconsciousness (narcosis), coma, and eventually death. Elevated COHb levels can lead to early exhaustion, decreased oxygen consumption, diminution of visual perception, diminishing learning abilities, headaches, confusion, unconsciousness and eventually death. The effects of elevated COHb are almost similar to that of CNS depression, but are mainly caused by hypoxia. Individuals with ischemic heart disease are at extra risk due to additional loss of oxygen. Heart failure is therefore also considered as a health effect from acute exposure.
Human voluntarily exposure to DCM has been conducted to study the metabolism of humans. The range of exposure is obviously low, but decreased vigilance was noted. Human health effects are best described by accidents that have occurred over the years. ATSDR and forensic institutes have recorded occupational accidents and fatalities that occurred after being exposed to DCM (Leikin et al., 1990; Mahmud and Kales, 1999; ATSDR, 2000; Fechner et al., 2001). In most cases, the victims suffered from CNS depression and elevated COHb levels. In one case (Stewart et al., 1976) fatality as a consequence of myocardial infarction was registered, probably the subject had previous heart problems.
It must be noted that there is extra danger for individuals who use DCM for DIY activities, because the odour threshold is higher (800 ppm) than the no observed effect level (NOEL) for humans (although the NOEL is not set, it is definitely lower than 800 ppm). For assessing acute health effects only CNS-depression will be considered. CNS depression was chosen over COHb formation, because external exposure correlates well with internal brain concentrations, while COHb formation is confounded by personal habits (for instance smoking) (Andersen et al., 1987; NAC/AEGL, 2005).
In a report by NAC/AEGL guideline levels for acute exposure to DCM were derived from human and animal data. The AEGLs are exposure levels, which represent threshold limits for the general public, including infants, children and individuals that may be more sensitive. Levels are derived for 10 and 30 minutes, and 1, 4, and 8 hours of exposure periods. Besides, AEGLs were derived for different kinds of severity.

- AEGL1: airborne concentration of a substance above which it is predicted that the general population could experience notable discomfort, irritation or certain asymptomatic, non sensory effects. The effects are not disabling and are transient and reversible upon cessation of exposure.

- AEGL2: airborne concentration of a substance above which it is predicted that the general population could experience irreversible or other serious long-lasting adverse health effects or an impaired ability to escape.
- AEGL3: airborne concentration of a substance above which it is predicted that the general population could experience life-threatening health effects or death.

In Figure 4 below, the 8 hour exposure period was left out, because the exposure time for paint stripping and glue removing activities are much shorter. The AEGL1 and AEGL2 values were derived by using brain concentrations that were obtained from human data. From Stewart et al. (1972*)* absence of CNS effects was noted at air concentration of 514 ppm in human volunteers. This air concentration was considered to be an AEGL1. From this concentration a brain concentration of 0.063 mM was calculated via physiologically based pharmacokinetics (PBPK) modelling as a point of departure to calculate brain or air concentrations of DCM for various time points which are correspondent to 0.063 mM DCM in the brain. A similar strategy was followed for AEGL2 were an air concentration was found of 751 ppm by Reitz et al. (1997) where CNS effects were clearly present; which corresponds with 0.137 mM DCM in the brain. Derivation of AEGL3 was somewhat problematic. Human data were considered not adequate for derivation of AEGL3. Therefore animal data was used. A study conducted by Haskell Laboratory in 1982 led to an air concentration of 11,000 ppm after 4 hours exposure to which no deaths occurred. A brain concentration of 3.01 mM DCM was calculated for the rat. Applying an overall uncertainty factor of 3 (intraspecies of 3 for human variability, no interspecies factor) leads to 1.0 mM for humans as point of departure (NAC/AEGL, 2005). In summary, the point of departures for CNS depression were the maximum DCM concentration in the brain of 0.063 mM, 0.137 mM, and 1.0 mM for derivation of AEGL1, AEGL2, and AEGL3, leading to 200, 740, and 4900 ppm, respectively. (NAC/AEGL, 2005).
In animal studies research was conducted to several endpoints, whether they are systemic, (cardio, neurological, developmental and hepatic) or death. The Agency for Toxic Substances and Disease Registry (ATSDR) summarized numerous studies in which it was obvious that neurological and cardio effects occurred at low exposure levels. Mice seem to be more sensitive to DCM than other species tested (ATSDR, 2000).

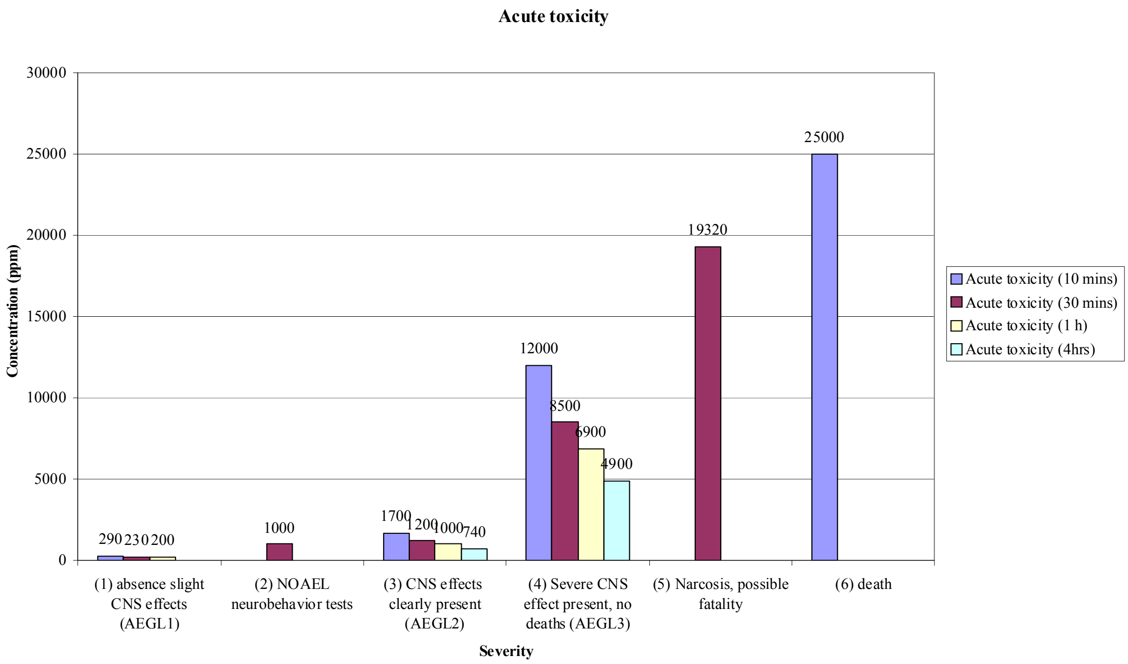


Figure A5.4. The AEGL levels and other (no)effect levels for different exposure times are set in categories to obtain a global dose-response relationship for acute exposure to DCM. For risk assessment the AEGLs for four hour exposure is used.

4.2 Chronic health effects of DCM

In a drinking-water study by Serota (Serota et al., 1986a/b) in mice and rats, tumours and neoplasms were observed in the liver and lungs after exposure to DCM. Although in rats mainly benign tumours were found, an excess of tumours in lung (alveolar/bronchiolar neoplasms) and liver (hepatocellular neoplasms) were observed in B6C3F1 mice. Previous studies also made clear that DCM could induce tumour formation in rodents. However, it seems that mice are specifically sensitive to DCM in comparison to rats and hamsters. Therefore DCM was registered as a suspected human carcinogen by the US EPA (ATSDR, 2000; ENVIRON, 2005).
The mechanism of action of methylene chloride is through the mixed function oxidase (MFO) system. Cytochrome P450 2E1 enzymes convert DCM to methyl chloride and subsequently CO and COHb. This metabolic pathway has a high affinity for DCM, but is saturated at low air concentrations (in mice at approximately 200 ppm). When saturated, another metabolic pathway takes place by glutathione S-Transferase (GST). Through this secondary pathway formaldehyde and CO are formed (see Figure A5.5). Formaldehyde is a known carcinogen and is most likely the tumour inducer and not DCM itself (Andersen and Krishnan, 1994; Schlosser et al., 2003). Casanova et al.(1996) reported DNA-protein-cross links after DCM exposure in rats due to formaldehyde formation. At concentrations above which the shift from MFO pathway to GST pathway as primary pathway occurs, tumors were observed in laboratory animals. It has been proven that this shift also occurs in humans (Slikker et al., 2004). There is GST (T1) polymorphism, which means that there are

individuals who do not metabolize DCM via the GST pathway: the so-called non-conjugators (Jonsson and Johanson, 2001).
The EPA calculated the inhalation unit risk based on the data from a NTP (NTP, 1986) study concerning female mice. Endpoints considered were combined adenomas and carcinomas. By using a PBPK model developed by Andersen et al. (1987) a unit risk of $4.7 * 10^{-7}$ per µg/m^3 was derived over a 70 year life-time period (NAC/AEGL, 2005).

CH_2Cl_2 → $CHOHCl_2$ → ***HCOCl (formyl chloride)*** → CO → CO_2

CH_2Cl_2 → ***$GSCH_2Cl$ (chloromethylglutathione)***→ $GSCH_2OH$ →
1)→ HCHO
2)→ GSCHO → HCOOH → CO_2

Figure A5.5. Both metabolic pathways. Top: the MFO pathway which results in formyl chloride and CO formation. An important product of the pathway is the formation of COHb. Bottom: the GST pathway with the lower affinity, but higher capacity. It is expected that this pathway plays a role in the carcinogenicity of DCM by the formation of formaldehyde (HCHO).

However, current understanding on the carcinogenicity of DCM is that the compound is a mouse specific carcinogen (Graves et al., 1995; Casanova et al., 1997; Green, 1997; Sherratt et al., 2002). David et al. (2006) obtained a 500 times lower unit risk for DCM when taking human data and an improved PBPK model into account. Elucidation of the metabolism of DCM in humans showed that the mouse gene (GST T1) is more efficient in catalyzing the conjugation of DCM than the orthologous human enzyme does. In addition, mice exhibit higher levels of converting enzymes in bile and liver. These arguments indicate that it is unlikely that DCM represents a carcinogenic risk for humans (Sherratt et al., 2002). In epidemiology studies on the relation between cancer and exposure to DCM show no clear evidence for a positive correlation (Dell et al., 1999). An updated evaluation of IARC in 1999 (IARC, 1999) was stated: “There is inadequate evidence in humans for the carcinogenicity of dichloromethane”.
For these reasons carcinogenicity was not taken into account as critical endpoint. It is assumed that there will be no health gain on prohibiting long term exposure.

5 Current risk assessment

The risk is characterized by the exposure to a certain chemical and the toxicity of the chemical. The normal procedure would include determining a margin of safety for DCM. However, the point of departure in this study is not a NOAEL or a benchmark dose or any other solid value, but three differently based limits. The AEGL limits are all based on CNS depression, but at different stages of severity.
For risk characterization exposure data obtained from ConsExpo 4.0 were compared with the AEGL levels. This is a crude approach, because in this approach one is not able to quantify the risk. Instead one can only give estimation on how the dose-response relationship would look like and base its risk estimations on that. For example, an exposure level between AEGL1 and AEGL2 can only mean that symptoms are expected to be worse than observed

for AEGL1 level, but less bad than observed for AEGL2 level; hence a comparative risk characterization.
From the consumer exposure distribution of stripping paint a log-normal distribution was found. A small part of that distribution lay below the AEGL1 level; 6%, who will not really be affected by exposure to DCM. A large part of the distribution is situated between the AEGL1 and AEGL2 levels (50%) and another large part between AEGL level 2 and three (43.6%). A very small part even crosses the AEGL3 level (0.4%) that may suffer from very severe CNS depression or may even die from the high exposure.
The exposure to DCM as a result of removing glue when treating a surface of 5 m^2 far exceeds the AEGL1 level and lowest exposures are even higher than the AEGL2 level. Almost 99% of the exposure distribution (read population) is exposed to levels between 740 ppm (AEGL2) and 4900 ppm (AEGL3) and just a small part exceeding the AEGL3 level (1.2%). Overall it is obvious that removing glue in most cases poses a higher risk than stripping paint.

6 Calculation of Public Health gain

6.1 Decrease in exposure

The health risk reduction can be determined at three separate levels (exposure, effect and DALY). In this report it was assumed that the use of DCM in DIY products will be banned. There is a proposal for restrictions on the marketing and use of DCM based paint strippers for directive 76/765/EEC. When this proposal will be implemented, it is clear that the exposure will drop to a negligible level (ideally) from DIY activities and the remaining consumer exposure would be that of ambient air and possible food and drinking water contamination. A reduction of approximately 100% should already indicate a significant health risk reduction from the supposed measure.

6.2 Increase in Margin of Safety

The margin of safety (MOS) approach is another method to describe the effect of the decrease in exposure. Generally, a desired MOS describes the margin which is allowed between human exposure and the dose at which no adverse affects are observed in animals or humans. When the MOS is too low efforts should be made to reduce the exposure until the desired MOS is reached. For this present case it was assumed that the exposure to DCM after the measure would be negligible. Thus, determining a MOS after the measure is not possible. Because the reduction of the exposure was approximately 100% the MOS would be very high.

6.3 Decrease of incidence of effect

When the proposed measure will be implemented, one can be sure that acute exposure no longer occurs for consumers. Hence, the related health effects for acute exposure will disappear. The chronic exposure from the ambient air, food, and drinking water may still occur. It can be assumed however that these levels will drop, because the production of DCM and hence the emission will be lower.

6.4 Derivation of DALYs

To derive an approximation of DALYs for DCM usage in the DIY sector one requires data on the number of individuals that use DCM and the health effects as a consequence of exposure to DCM. The DALY calculations can be performed in a simplified manner or in a more advanced manner. The latter requires more information about age on onset of disease or fatality and takes discounting and age-weighting into account. In the past there has been a lot of criticism on the latter method (see general introduction – to be written in main document) in regard to equity. In this report the simplified method will be used, since there is not sufficient information to execute the advanced method and moreover not to include socio-economic parameters like stage in life.

6.4.1 Derivation of DALYs for acute health effects

For the acute endpoints the symptoms accompanying the AEGL levels were used as markers. It was assumed that exposure levels found between the limits exhibited the symptoms that were set for the lower AEGL. Secondly, the next step would be to assess the number of individuals that will exhibit the symptoms. This can be estimated from the exposure distributions. The exposure distributions do not represent individuals, but possible exposure scenarios leading to an exposure of one individual. The same individual may be at the other end of the distribution when another job is executed. For purpose of this exercise it is assumed that the distribution does represent individuals. The percentage between two AEGLs of the distribution multiplied by the total consumers equals the individuals with a certain symptom. Furthermore, the symptoms were assigned a disability weighing factor and an average duration of the disability. The population between AEGL 2 and AEGL 3 was divided in half because the symptoms are so diverse (ranging from moderate CNS depression to narcosis) so that a single disability weight would not be proper. A simple calculation will then result in a DALY per symptom. These DALYs added up together will result in a DALY for acute health effects of DCM (see Appendix 5.1 and Appendix 5.2).
The disability weights that were set for AEGL1, AEGL2, and AEGL3 were based on the EuroQol method. The symptoms that belong to the AEGL levels were determined by their score in EuroQol (see Appendix 5.1). The disability weights and the durations are listed in Table A5.2. The duration of the disabilities are based on expert judgment.
For stripping paint the major parts of the distribution lie between AEGL1 and AEGL2 and between AEGL2 and AEGL3. The DALY is calculated by multiplying the disability weight with the duration of the disability and the part of the population. For acute exposure due to paint stripping the total amount resulted in 63 (60) DALYs (based on population of 150,000 individuals). No fatality was included. Although in the period of 1960-1990 one death was recorded in the Netherlands (Gerritsen and Buschmann, 1960).
The exposure to glue remover was estimated to be somewhat higher. Therefore the distribution shifted slightly to the right in comparison to paint stripper activities. Approximately 99% of the distribution lies between the AEGL2 and AEGL3 levels. The rest

lies above the AEGL3 level. Calculations resulted in a total of 143 (140) DALYs (based on a population of 150,000 individuals).

Table A5.2. The health effects and related disability weights and assumed duration of the disabilities.

Health effect	Disability weight	Duration of disability (years)	EuroQol score
Dizziness, irritation (AEGL1)	0.08	0.04/365	111211 [a]
Light CNS effect (AEGL2)	0.17	0.5/365	212111 [a]
Heavy CNS effect (AEGL2)	0.58	1/365	213322 [a]
Life threat (AEGL3)	0.83	2/365	323323 [a]
Death (AEGL3)	1	NA	

[a] EuroQol scores were determined according six dimensions (Van der Maas and Kramers, 1997)

7 Discussion

7.1 Exposure to DCM from DIY activities

Exposure to DCM during DIY activities can reach high peak exposures. Air concentrations may even reach levels which are life threatening to humans. Fatalities have been reported in the United States and across Europe, but were attributed to non-compliance with safety directions. Sometimes safety directions are willingly pushed aside, while in other situations it is not possible to follow safety directions. A fatality case has also occurred in the Netherlands. During paint stripping in a basement while heating with a kerosene stove; high DCM concentrations and formation of phosgene gas were pointed out as cause of death (Gerritsen and Buschmann, 1960). Since then, no other fatality cases have been reported in the Netherlands.

The use of DCM containing products in the consumer market is hard to assess, because sales numbers are not available. It may well be that individuals never use DCM containing products and other (for instance hobbyists) several times a year. The estimation of 150,000 individuals who use DCM containing paint stripper (data on DCM containing glue removers were not available) is not a reliable estimation. The assumption of 5% ever using a paint stripper containing DCM is purely based on expert judgment. This option was chosen over option two and three (section 2.2.1), because it was based on recent data from CBS. In contrast, the second and third options in paragraph 3.2.1 were based on data from 1995 or proven to be inconclusive. Furthermore, the market of DCM containing products has changed, because of health concerns that were linked to exposure to DCM containing products (Tukker and Simons, 1999). As a result the production of DCM has decreased in the past years making the production number not useful for assessing the population number. Issuing a questionnaire on the use of paint strippers may be helpful to obtain a better estimation of the target population.

Risk assessment was based on an adult population (15-70 years old). Infants and children might also be exposed to DCM from DIY activities. DCM has a higher vapor density than air which may lead to higher concentrations close to the floor where children breath and play

(Riley et al., 2000; SCHER, 2005). However, children were left out for assessment, because it is expected that the operator will have the highest exposure. It must be noted, however, that children and infants may be at risk when exposed.

The level of exposure due to stripping paint and removing glue depends heavily on the job at hand and the person in question. Use directions from product information underline this. The application amount depends on the treated surface (smooth, rough, corners and edges) and the number of paint layers. Obviously the application time will also vary for the DIY activity. Not only the application time will vary with the job, but also with the individuals. It can be expected that more experienced individuals will complete the job faster. On the other hand, the more experienced individuals are most likely to use DCM containing products more often.

The exposures calculated by ConsExpo 4.0 are based on a one compartment exposure model. The inhalation model incorporates the exposure to a vapor from a release area which increases over time. For dermal exposure the instant application (spills) model was chosen and assumed that diffusion through the skin takes place. Riley et al. (2000) adapted a predecessor of ConsExpo to develop a two compartment model. With the two compartments air concentrations can be calculated for near the source and in the entire room space. The author aimed at obtaining a more relevant external peak exposure. On the other hand DCM has such a high vapor pressure that DCM would diffuse so fast that air concentration in the room would also represent the near source concentration although DCM concentrations may be higher closer to the ground, because it is heavier than air. It was concluded that the ConsExpo 4.0 program would suffice for exposure calculation purposes.

Output data from ConsExpo 4.0 (for paint stripper) was used as input data for PROAST to obtain an exposure distribution. The two scenarios (average and 99th percentile) were needed, because it is not possible to assess the exposure for the two scenarios simultaneously in ConsExpo. ConsExpo 4.0 is not able to relate distributions of certain parameters which are dependent on each other. This leads to illogical links between certain parameters. For instance: stripping a surface of 4 m^2 can not be performed with 350 grams in only 10 minutes. Therefore two scenarios were needed to obtain a consumer exposure distribution. Both scenarios and everything in between are not unrealistic, but it is obvious that small tasks with lower exposures are more often performed as is shown in the exposure distribution (see figure A5.2). This problem did not exist for removing glue and an average case was selected.

Calculating the exposure with a program is easy and costs are low, but real measurements during DIY activities are still preferred. Artificial measurements of DCM exposure may serve as a tool to validate exposure calculations by ConsExpo 4.0 (average exposure was 660 ppm with a range of 50-5000 ppm). Measurements by the EPA proved to be in the same range (IPCS, 1996). In the report by ETVAREAD on vapor retardants exposure levels of DCM were measure in laboratory circumstances. Air concentration levels (TWA 25 mins) ranged from 400 to 1700 ppm for 10 paint stripper products from across Europe. Seven other paints strippers were not tested for whatever reason. The paint strippers were tested by application of 375 ml on 1 m^2 of clipboard in a 15 m^3 room with an air exchange rate of 4. A total exposure time of 25 minutes (5 min application, 10 min affecting, and 10 min removing) was taken into account (ETVAREAD, 2004). Their lower air concentrations found may be explained by the high chosen air exchange rate. Results from ConsExpo 4.0 when taking similar circumstances into account showed an average exposure a factor two higher (data not shown) in comparison to the exposure levels observed by ETVAREAD and Ruehl

(ETVAREAD, 2004; Ruehl et al., 2004). The experimental results observed by Van Veen et al. (2002) were even lower than the air concentrations observed by ETVAREAD and Ruehl. A similar amount and release area was taken into account, but with lower ventilation rates. It is unclear that such unfavorable setting would result in such low air concentrations. A possible explanation could be the stripping of a horizontal surface at ground level. DCM is heavier than normal air and DCM particles might be at low altitudes while measuring DCM at a seemingly high level (1.60 m).
For consumer exposure estimations with ConsExpo 4.0, the time after stripping paint was also included. It is assumed that an individual will stay in the room to clean up and or repaint the surface. The total exposure time is therefore longer. When referring to the AEGL levels it is obvious that the same air concentrations for longer periods of time are more hazardous. Air concentrations may still be rising while a person is still completing his task. Besides, ConsExpo 4.0 only displays the average exposure to DCM during the activity, but peak exposures may be significant higher.
It seems that the estimations made with ConsExpo 4.0 are in the same range as several scientists have measured. Therefore it can be concluded that the estimations derived with ConsExpo 4.0 was valid for further use.

7.2 Selected critical effects

The characterization of risk and derivation of the DALY are based on the selected critical effects. For the acute health effects CNS depression was selected as critical effect. CNS depression as a result from exposure to DCM has a clear dose-response relationship. This dose-response relationship is partly described by the PBPK models adopted from Andersen et al. (1987). In the PBPK models a relation was detected between the air concentration and the concentration that resulted in the brain. Another toxic effect from short term exposure to DCM is the formation of COHb. The NAC/AEGL report on methylene chloride makes clear that COHb formation plays a major role in acute exposures longer lasting than an hour. The additional COHb formation is then considered as the critical effect. The additional formation of COHb was chosen instead of a benchmark, because the COHb percentage differs significantly amongst the population. COHb percentages are usually higher amongst smokers (NAC/AEGL, 2005). In addition, an increase of COHb formation can be more severe for individuals who have already a high level. Furthermore the formation of COHb or the level of COHb in relation to air concentrations is not as well understood as the relation between air concentration and CNS depression. Therefore CNS depression was selected to assess the risk for DCM exposure.
COHb formation is considered hazardous and can be lethal. It is known that persons with ischemic heart disease are more vulnerable to COHb. However, in regard to characterizing the risk for DCM exposure, it would not differ much when COHb formation was chosen.

7.3 Uncertainties in deriving DALY

The applied method to derive DALYs is very crude. The prevalence of certain symptoms related to an AEGL value is derived from the exposure distribution. Because exposure does not necessary leads to a health effect, the estimated prevalence is subject to error. Only a part of the distribution between AEGL levels will suffer from the acute symptoms. Therefore, logically, the derived DALY would be overestimating the ‘actual’ DALY for acute effects. Actual prevalence numbers of subjects having health effects due to exposure to DCM are not known or will not be reliable (underestimation due to registration or uncertainty in attributing the effect to DCM exposure). One could make an estimation of a sensitive population which most definitely will suffer from the heavier health effects. For instance, 5% of the possible individuals who exceed the AEGL3 level will die, the remaining will suffer from severe CNS effects. But, estimating a sensitive population for CNS depression is troublesome. A possible sensitive population is the slow metabolizer. The detoxification step by CYP450 2E1 will take longer for an individual and brain concentrations may reach higher levels as result (personal communication P.M.J. Bos, RIVM). These individuals are beforehand not identifiable and therefore the population at extra risk is hard to assess.

It must be noted in deriving the DALYs for DCM that dermal exposure was left out, which according to estimations obtained from ConsExpo 4.0 was approximately 10% of the total exposure. The dermal exposure plays a more important role in the chronic exposure than in acute exposure. Furthermore, amongst the estimated DIY population that is supposed to work with DCM, there are individuals that use these kinds of products even more than five times per year. The chronic exposure would be even higher for these individuals.

There are still other health effects that were not considered in the calculation of DALYs. The possible DALYs for the formation of COHb and the related health effects are not considered in this case. In the derivation of the DALY health effects resulting from COHb formation, irritations, and eye sensitization were not included. In banning DCM from consumer products it is expected that these health effects will also no longer occur. Therefore, the DALY calculated from consumer exposure to DCM could be higher.

The durations and disability scores are also point of discussion. The durations are expected to be very short for the acute effects and the acute effects are reversible. It was expected that the duration would be longer as the severity increases leading to durations of 1 hour to two days. The severities for those possible cases were determined by EuroQol scores. The scores are based on functional state of health (see Appendix 5.1) in which a certain individual will be when exposed to a certain level of DCM. The resulted score is the score for the period when the individual undergoes the disability and is not a disability weight for an entire year. A correction for the duration is therefore necessary.

Comparing disabilities with each other and using EuroQol scores to determine the disability weight is considered to be a valid method. The input data for estimating the DALY, i.e. exposure data and toxicology data, has uncertainties and as a consequence this uncertainty is found in the derivation of the DALY. It is important to pay attention to the assumptions made, because they influence the outcome.

7.4 Assumptions

To use the DALY concept for determining the health risk reduction a lot of assumptions have been made. For the assessment of consumer exposure it is difficult to determine the target population (actual users of DCM). There are no real numbers of individuals that use or ever have used DCM in their life. The point of departure was data from CBS to obtain estimation for the consumer population. The target population was set at 150,000; it is based on the

assumption that 5% of the DIY population have worked with DCM containing products. Since there are no sales numbers or production figures available this is considered the best estimation, based on the most recent data. Information on glue removers was also not available and therefore the population estimation for stripping paint has also been used for removing glue (target population is thus 150,000 for both DIY activities).
The frequency of usage is set as a default on once per year. Of course there are individuals who will never use such products or less often. On the other hand there are individuals who use the product more often, for instance hobbyists. The frequency is especially important for the chronic exposure and is therefore taken into account to show what results of repeated use. Therefore for paint stripping an additional scenario was calculated with a frequency of five times a year. This choice was arbitrary. Although some individuals may use DCM containing products more often than five times a year, using DCM containing products five times a year can be considered as a reasonable worst case scenario.
For paint stripping two scenarios were calculated. An average scenario and a worst case scenario were set as input data for ConsExpo 4.0 to obtain a distribution of the consumer exposure estimation. The release areas were set at 1 m^2 and 4 m^2. The latter is large in comparison to the 1 m^2 that was considered by ETVAREAD. However, stripping doors, furniture, and wooden bars can easily result in release areas of 4 m^2 or more. A release area of 4 m^2 can be considered as a reasonable worst case scenario. The release area was set at 5 m^2 for removing glue. In this case it is considered as an average release area.
Toxicity of DCM is clear and no assumptions have been made. The AEGL levels and the unit risk set up by EPA are widely accepted. For risk characterization it was assumed that all possible subjects between AEGL1 and AEGL2 are related to AEGL1 effects. Because possible health effects could differ significantly from each other, subjects between AEGL2 and AEGL3 were divided into two groups of equal size. One group was coupled with effects just above AEGL2 level (slight CNS depression) and the second group with more severe health effects (moderate to heavy CNS depression). Since it is not known were the transition takes place from slight to moderate effects in the dose-response relationship it was assumed that half of the sub-population would suffer from the slight effects.
For derivation of the DALY it was assumed that the duration of the acute effects would not last longer than two days for the most severe effects.

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Appendix 5.1

Determination of the EuroQol score was executed according to six dimensions, which varied in severity over three levels. The dimensions were: mobility, self care, daily activities, pains and other complaints, anxiety/depressions, and cognition. These dimensions describe the functional state of health of a certain individual with a certain disability. A score of 1 equals full health. A EuroQol score of 111111 will consequently result in a disability weight of 0. A score of 2 equals to a disability weight of 0.0833. A EuroQol score of 222222 will result in a disability weight of 0.5 (since all dimensions were scored as being half). A EuroQol score of 333333 will result in a disability weight of near 1. For details see a report by VTV (in dutch; 1997) and an overview of the Table is given below.

For the AEGL levels EuroQol scores were determined:

- AEGL1: 111211 corresponding to a disability weight of 0.083
- AEGL2(light): 212111 corresponding to a disability weight of 0.17
- AEGL2(severe): 213322 corresponding to a disability weight of 0.58
- AEGL3: 323323 corresponding to a disability weight of 0.83

Table A5.3. EQ-6. Dimensions with their 3 levels (no problem, some problems, many problems).

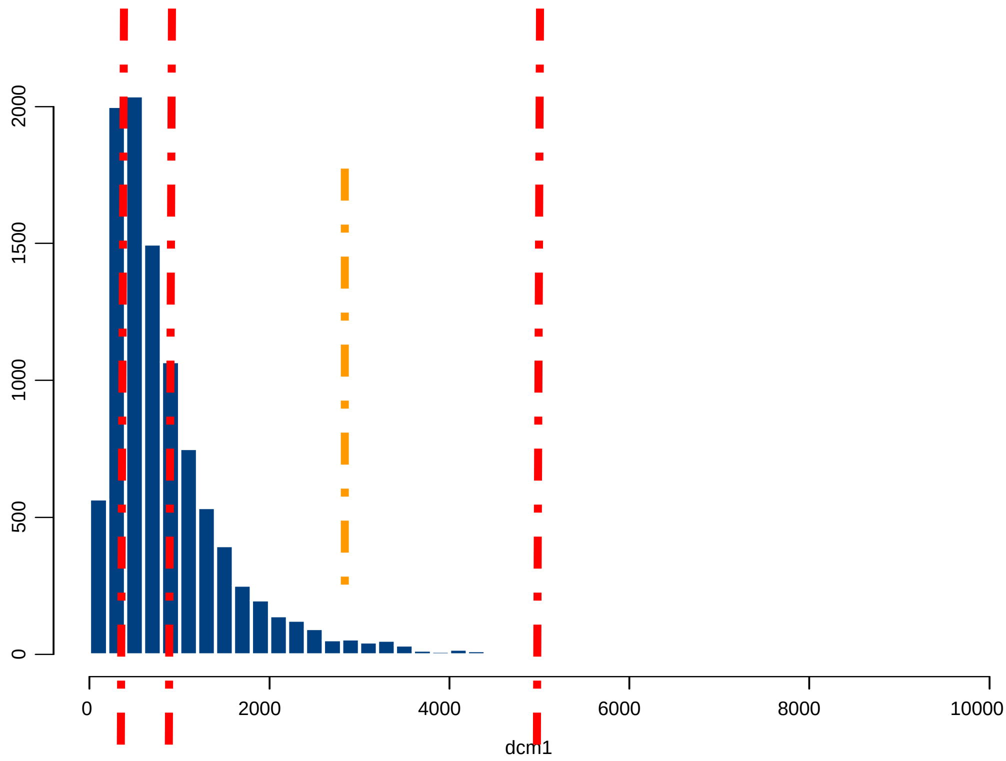
Dimension	Level	Score
mobility	No problems in walking about.	1
	Some problems in walking about.	2
	Confined to bed.	3
self care	No problems with washing or dressing self.	1
	Some problems with washing or dressing self.	2
	Unable to wash or dress self.	3
usual activities	No problems with usual activities (e.g. work, study, housework, family or leisure activities).	1
	Some problems with usual activities.	2
	Unable to perform usual activities.	3
pain / discomfort	No pain or discomfort.	1
	Moderate pain or discomfort.	2
	Extreme pain of discomfort.	3
anxiety / depression	Not anxious or depressed.	1
	Moderately anxious or depressed.	2
	Extremely anxious or depressed.	3
cognition	No problems with cognitive functioning (e.g. memory, concentration, coherence, IQ)	1
	Some problems with cognitive functioning	2
	Extreme problems with cognitive functioning	3

EuroQol (6 Dimensies) (EQ-6D). For more details see a report by VTV (in Dutch) (Van der Maas and Kramers, 1997) and Hoeymans et al., 2005a.

Appendix 5.2

DALY calculations

Acute health effects
The distributions of exposure to DCM as a result of stripping paint or removing glue are divided into segments by AEGL levels, whereby the exposure levels between AEGL2 and AEGL3 are divided in half. In the figure below the large dashed lines represent the AEGL levels, whereas the small dashed line represents the split-up of the AEGL2 exposures. The values in Table A5.2 represent the disability weights for all exposures between the dashed lines for AEGL1, 2a, 2b, and 3 respectively. The disability weights were determined via EuroQol scores (see Appendix 5.1)



Calculation of the DALY for acute health effects is as follows:

DALY = % distribution between dashed lines * target population * disability weight * duration disability

$DALY_{AEGL1}$ = 55.25% * 150,000 * 0.08 * 0.04/365 = 0.72 DALYs

The sum of DALYs per sub-population represents the total amount of DALYs for a certain DIY activity.

Chronic health effects
With help of the unit risk the virtual safe dose was calculated for 50 years exposure to DCM (See section 2.4). The actual exposure is then compared to the VSD to derive the additional risk.
With the additional risk one can determine the additional number of liver or lung cancer cases in the target population of 150,000. To derive the DALY for chronic health effects one needs the disability weights for liver and lung cancer (see Table A5.2). Besides that, one must determine the average duration of the illnesses and the average age of death to be able to determine the YLD and YLL. Both illnesses are taken together since the unit risk, derived by the EPA, does not discriminate between liver and lung cancer. From Havelaar and Melse (2003) the average YLL for cancer cases is set at 13.8 DALYs (no morbidity accounted). Assuming an average duration of five years with disease with an average disability weight of 0.335 will result in 15.5 DALYs per case (5 * 0.335 + 13.8 = 15.5).
The total amount of DALYs for chronic health effects would then become:

DALY = additional number of cases * DALY per case

$DALY_{\text{paint stripping, frequency=1}} = 16$

Appendix 6 Case report formaldehyde

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1. Introduction

This case addresses the influence of legislation on exposure to formaldehyde from consumer non-food products in the Dutch general population. Legislative measures regarding formaldehyde were expected to contribute potentially substantial to improved public health, as these suspected carcinogenic substances are present in several consumer products and exposure might be considerable.

2. Background

2.1 C, M, R or S legislation

Formaldehyde is classified under EU index no. 605-001-00-5 as follows:
Carc3; R40, R43 Possible risks of irreversible effects. May cause sensitization by skin contact;
T; R23/24/25 Toxic. Toxic by inhalation, in contact with skin or if Swallowed;.
C; R34 Corrosive. Cause burns.
It is noted that concentrations 1-5% is classified Carc3; R40, R43 and concentrations 0.2 to 1% classified R43.

The Dutch government constituted two laws in order to limit exposure to formaldehyde. In May 1987 the limit for formaldehyde in chipboard was set at 10 mg per 100 g chipboard. This law applies to all chipboard except that used in furniture.
The limit of formaldehyde in textile was set at 120 ppm (= 120 mg/kg textile) in April 2001. If the formaldehyde concentration in textile is 120 ppm or higher, the label in the fabric should indicate 'wash before use'. After washing following the instructions once, the concentration should be lower than 120 ppm.

In July 1976 the EU Cosmetics Directive 76/768/EEG guidelines for ingredients of cosmetic products have been drawn up. In this directive it is stated that if the cosmetic end product contains more than 0.05% formaldehyde or formaldehyde releasers the label should state 'contains formaldehyde'. For sprays it is not allowed to contain formaldehyde. The following specific guidelines have been set up (see Table A6.1).

Table A6.1. Dutch and European legislation (http://www.overheid.nl, http://ec.europe.eu/enterprise/cosmetics)

Product	Limit	Label	Date of enforcement	Legislation
Chipboard	10 mg/100g	-	01-05-1987	Dutch 'Spaanplaatbesluit (Warenwet)'
Textile	120 ppm	'Wash before use'	13-04-2001	Dutch 'Warenwetbesluit formaldehyde in textiel'
All cosmetics (except oral hygiene)	0.2%[b,c]	'Contains formaldehyde' for finished products with more than 0,05% formaldehyde	31-12-1983; 31-12-1986	EU cosmetics directive 76/768/EEG; 2nd amendment 82/368/EEC and 6th adaptation to technical progress 85/391/EEC
Oral hygiene	0.1%[b,c]	'Contains formaldehyde' for finished products with more than 0,05% formaldehyde	31-12-1983; 31-12-1986	EU cosmetics directive 76/768/EEG; 2nd amendment 82/368/EEC and 6th adaptation to technical progress 85/391/EEC
Nail hardeners	5%[b]	'Protect cuticle with grease. Contains formaldehyde'	31-12-1983	EU cosmetics directive 76/768/EEG; 2nd amendement 82/368/EEC

[a] If concentration exceeds limit
[b] Expressed as free formaldehyde
[c] Forbidden in sprays

The WHO advises 100 µg/m^3 as a 30 minutes average 'to prevent significant sensory irritation in the general population' (WHO, 2002). The Dutch Ministry of Housing, Spatial Planning and the Environment (VROM) is using 120 µg/m^3 for 30 minutes, and 10 µg/m^3 as limit for long term average indoor air concentrations (VWA, 2005).

The current occupational exposure limits, although not legally binding, are in 1987 set by the Health Council of The Netherlands at 1.5 mg/m^3 (1 ppm) TWA-8hr and 3 mg/m^3 (1.5 ppm) TWA-15 min. In 2003 however, an expert committee of the Dutch Health Council advised new occupational exposure limits of 0.15 mg/m^3 (0.12 ppm) TWA-8hr and 0.5 mg/m^3 (0.42 ppm) TWA-15 min, based on new research data (Health Council of the Netherlands, 2003).

2.2 General information

Formaldehyde (CAS nr 50-00-0) is a gas which is formed by the incomplete combustion of carbon-containing materials. Small amounts of formaldehyde are produced as a metabolic byproduct in most organisms, including humans. The substance is characterised as colourless and flammable and has a strong pungent odour.

Synonyms for formaldehyde are: methanal, oxomethane, oxymethylene, methylene-oxide, methylaldehyde, formic aldehyde, methylene oxide and formaline.

Formula: H_2CO

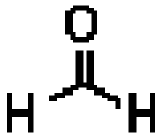

Figure A6.1. Chemical structure of formaldehyde

Besides its natural occurrence formaldehyde is also used in many industries as a preservative, disinfectant or solvent. Formaldehyde is produced by oxidizing methanol .
Formaldehyde can also be formed as a by-product of hydrocarbon oxidation processes.

Industrially, formaldehyde is used in the production of several resins. These resins are used as an adhesive or binder for, among other things, wood products, paper, textile and the production of plastics. It is also added to several consumer products as a disinfectant or preservative in house-hold cleaners, cosmetics and also in pharmaceuticals.

Formaldehyde can occur in products as free-formaldehyde and as formaldehyde releaser. Examples of these releasers are bromonitropropanediol, bromonitrodioxane and chloroallylhexaminium chloride. Formaldehyde releasers are often used in cosmetics as a preservative. The release of formaldehyde in these products depends on temperature and pH (Health Council of the Netherlands, 2003; Flyvholm and Andersen, 1993).

2.2.1 Exposure sources and routes

Formaldehyde is used in many industries to manufacture building materials and various household products. It is present in many products as free formaldehyde or may be emitted subsequently due to so called formaldehyde releasers.

Table A6.2 presents a selection of sources and routes of entry. Formaldehyde exposure can occur at home, outdoors and at work. The formaldehyde released from several sources can be inhaled, it can enter through the skin or can be ingested.

Table A6.2. Potential sources of formaldehyde exposure for consumers, based on expert judgement

Sources	Exposure routes		
	Inhalation	Dermal	Oral
Antiseptics		x	
Cigarette smoke	x		
Coloring agent, paints	x	x	
Cosmetics	(x)	x	
Diapers		x	
Drugs			x
Fertilizer	x	x	
Fiberglass		x	
Food products (preservative)			x
Gas cookers	x		
Glue	x		
Medicines		x	x
Musk aromatic substances	x	x	
Paper handkerchiefs		x	
Paper (napkins, kitchen/ paper towels, toilet)		x	
Perspiration (deodorants)		x	
Plaster cast		x	
Plastics	x	x	
Plywood	x	x	
Sanitary towels, tampons		x	
Smog	x		
Textiles		x	

2.2.2 Selection of exposure scenarios

As formaldehyde and formaldehyde releasers are used in numerous non-food products, the population exposed cannot be well-defined. However, within the general population some subgroups can be distinguished which may be higher exposed. Literature suggests that people who live in mobile homes may be exposed to higher concentrations of formaldehyde in indoor air due to the extensive use of light-weight chipboard in combination with small living spaces (Levin and Purdom, 1983; L'Abbé and Hoey, 1984; Imbus, 1985).

Dermal exposure to formaldehyde can also originate from numerous products like cosmetics and detergents. It is assumed that the whole population is in contact with one or more cosmetic or cleaning products on a daily basis. Dermal exposure to formaldehyde from textile is also calculated for the whole population.

Exposure scenarios included in the calculations are therefore:
1. Chipboard and plywood in houses

2. Textile (cloths and beddings)
3. Daily used cosmetics

3 Description of exposure

3.1 General

Exposure can occur as a result of air concentrations being inhaled or as concentrations in products where dermal contact can occur. Inhalation exposure to formaldehyde was an extensive research topic in the second half of the last century and is still studied. In 1968 The American Industrial Hygiene Association (Community Air Quality Guidelines, 1968) presented their Air Quality Guidelines based on literature review at 0.1 ppm formaldehyde in the atmosphere. Stating that at that level sensory irritation is not proven.

Exposure data of formaldehyde on the skin is rather limited. Some data is available on formaldehyde and formaldehyde-releaser concentrations in cosmetics and cleaners. One study in Denmark (Flyvholm and Andersen, 1993) performed a survey this matter. In literature, data on 22 formaldehyde releasers was found. In this study 30,900 PROBAS (Danish Product Register Data Base) registered products were scanned by means of product information on formaldehyde and formaldehyde releasers. The most frequent product categories containing these substances are cleaning agents, soaps, shampoos, paint/lacquers and cutting fluids. Formaldehyde mainly occurs in general cleaners, disinfectants, and dishwashing agents. The concentration is below 0.1% apart from the disinfectants which contain about 4% to 37% percentage formaldehyde.

It is also hypothesized that inhalation exposure may occur from products for dermal use. For example skin creams or shaving creams applied to the face may emit formaldehyde and with close proximity to nose and mouth inhalation exposure may occur. Currently TNO Quality of Life is conducting a study to test this hypothesis.

3.2 Background exposure

In Northern Europe urea-formaldehyde foam (UFFI) was used as an insulating material since the early 1960s. In the 1970s UFFI was used extensively as insulation in many buildings in the USA. By the end of the decade it was recognized that formaldehyde off-gassing was causing sensory irritation and suspicion rose that formaldehyde may be a potential carcinogen (Levin and Purdom, 1983; L'Abbé and Hoey, 1984). In the early 1980s also other sources of formaldehyde were present like chipboard, lacquers and adhesives, textile, cosmetics, paper and pharmaceuticals together with indoor and outdoor environmental exposure like cigarette smoke and traffic exhaust (Imbus, 1985; Solomons and Cochrane, 1984; Klus et al., 1985). Furthermore, the behavior of formaldehyde under different relative humidity conditions was studied (Samet, 1987) and the decline of formaldehyde concentrations in homes with UFFI after some time (IARC, 2004).

The latest estimates by IARC of formaldehyde levels in outdoor air are generally below 0.0001 mg/m^3 in remote areas and below 0.02 mg/m^3 in urban areas. Indoor air levels of houses are typically between 0.02 – 0.06 mg/m^3 and on average 0.5 mg/m^3 in mobile homes (IARC, 2004). The results of the measured indoor air concentrations are influenced by relative humidity, ventilation of the room, temperature, measurement and whether potential sources of formaldehyde are either coated or painted or untreated. Because building materials and requirements may differ quite largely between countries, there can be relatively large differences between different countries in indoor concentrations.

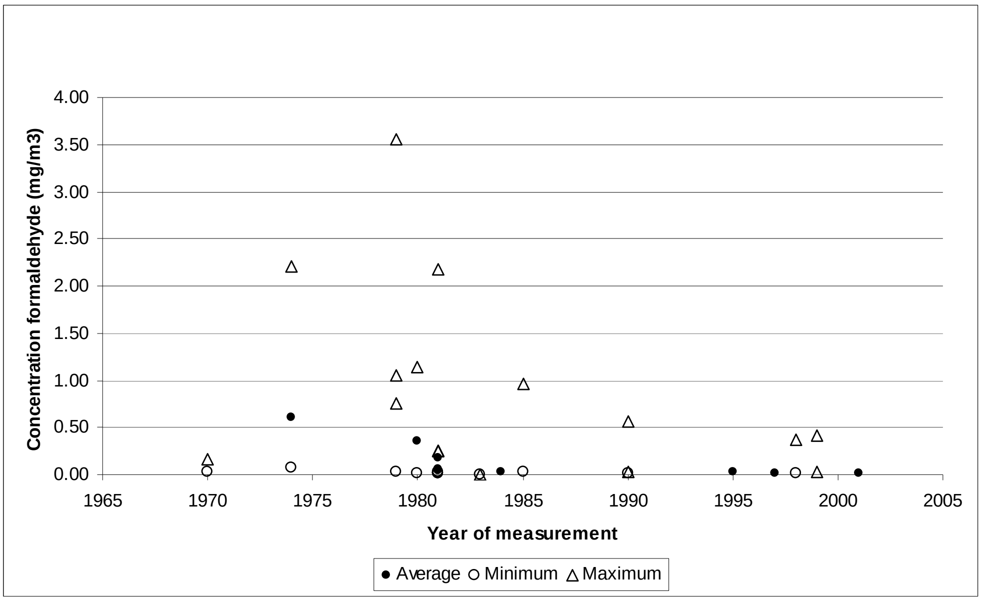

Figure A6.2. Indoor air concentrations (mg/m^3) (Levin and Purdom, 1983; L'Abbé and Hoey, 1984; Imbus, 1985; Solomons and Cochrane, 1984; OECD SIDS, 2002; Clarisse, 2003; Gordon, 1999; Suh, 2000; Manuel, 1999; WHO, 2002)

Figure A6.2 (with data from both North America and Europe, but no specific data from the Netherlands) shows that from 1990 onwards the indoor concentration of formaldehyde stays relatively stable with values between 0.02 mg/m^3 and 0.56 mg/m^3. The concentration measured in mobile homes, all in the US, range between 0.01 and 2.17 mg/m^3 (not in figure) (L'Abbé and Hoey, 1984; Spitzer, 1996; Chang and Gershwin, 1992).

In 1991 an inventory on formaldehyde was made by the WHO and results were presented in the IPCS (International Program on Chemical Safety) health and safety guide for formaldehyde. Their results on the contribution of various sources to the average daily intake are summarized in Table A6.3.

Table A6.3. Contributions of several sources to the average daily intake of formaldehyde in 1991 (IPCS, 1991).

Source	**Contribution (mg/day)**
Outdoor air	0.02
Drinking-water	0.2
Workplace	0.2-0.8
Environmental Tobacco Smoke	0-1
Indoor air (conventional building)	0.5-2
Indoor air (with formaldehyde source)	1-10
Workplace (with formaldehyde source)	4
Food	1.5-14

Based on these values it is plausible that for the general population the background exposure of formaldehyde is 9.7 mg/day. This is the sum of 0.02 mg/day from outdoor air, 0.2 mg/day from drinking water, an average of 0.5 mg/day from environmental tobacco smoke, an average of 1.25 mg/day from indoor air (conventional building) and an average of 7.75 mg/day from food.

In 2002 the WHO in Canada set up the Concise International Chemical Assessment Document 40 (CICAD 40) for formaldehyde (WHO, 2002). The concentrations of formaldehyde of sources relevant to our study are presented in Table A6.4.

Table A6.4. Formaldehyde concentrations in diverse sources.

Sources	**Concentrations formaldehyde**	**Area of measurements**
Drinking water	20 - 100 µg/L	International
Surface water	1.0 – 9.0 µg/L	Canada
Snow	4.9 µg/L	Germany
Rain	77 µg/L	Germany
Food	<60 mg/kg	International
Beverages	0.1-16 mg/kg	USA
Tobacco smoke (mainstream)	73.8 – 238.8 µg/cigarette	USA
Tobacco smoke (side stream)	1000-2000 µg/cigarette	USA

Using probabilistic techniques CICAD 40 estimated 24 hour average concentrations of formaldehyde exposure from air, only. Their results show that one in every two persons is exposed to about 0.024 mg/m^3 or higher from formaldehyde in air on a daily basis. As a worst case, one in every 20 persons is assumed to be exposed to approximately 0.094 mg/m^3 or higher (WHO, 2002).

In the same year, 2002, the Dutch National Institute for Public Health en the Environment (RIVM) published a study on aldehydes in cigarette smoke (Van Andel et al., 2002). In this study a daily intake from air of about 1 mg/day was calculated. This calculation was based on the following assumptions:
Daily respiratory rate of 20 m^3
100% retention and absorption

65% of their time people spend indoors
25% of their time at work
10% outdoors
The calculation was performed using data from a previous study by RIVM in 1992. Therefore, the data are considered to be relevant for 1992. This also accounts for the results by CICAD 40. The estimates in this study are based on data measured in 1989. However, based on the results shown in Figure A6.2 it is assumed that these estimates are still valid.

Based on these calculations, the background exposure of formaldehyde is assumed to be 1 – 10 mg/day for the general population. Diet will count for about 80%, and air for the remaining 20%. For an adult with a bodyweight of 70 kg, the daily exposure ranges from 0.014 to 0.14 mg/kg bw/day:

1 mg/day * 1/(70 kg bw) = 0.014 mg/ kg bw/day
10 mg/day * 1/(70 kg bw) = 0.14 mg/kg bw/day

Exposure to side stream tobacco smoke may increase indoor air concentrations significantly. Assuming a standard room of 53 m^3, 10 cigarettes being smoked in this room with little ventilation, and a contribution of 2000 µg/cigarette, the concentration in the room through this source may be 10*2000/53= 0.4 µg/m^3.

3.3 Chipboard and Plywood in mobile homes

Plywood and chipboard are a major source of formaldehyde in indoor air. TNO Built Environment & Geosciences measured emissions of plywood or chipboard, some samples were double-sided or one-sided coated or painted. The measurement strategy was based on NEN-EN 717-1[1]. The emission data is presented in Figure A6.3.

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[1] Personal communication with a research assistant of TNO Built Environment & Geosciences delivered a dataset with emission concentrations of formaldehyde from plywood and chipboard under laboratory conditions. The data set consists of 54 measurements of use conducted by order of commercial (anonymous) clients, local authorities and TNO Built Environment & Geosciences between 1992 and 2004.

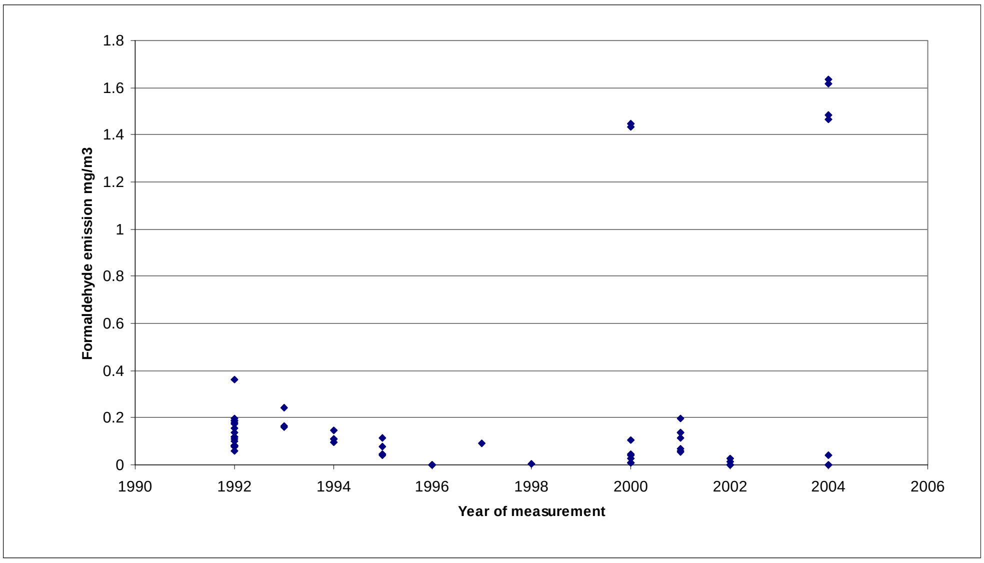

Figure A6.3. Formaldehyde emission from chipboard and plywood mg/m^3,1992-2004[2]

The formaldehyde emission was measured by a proportion of 5.25 m^2/m^3 in a room of 0.011 m^3 (with test piece of 0,058 m^2). Most board samples (48 of total 54) emit less than 400 μg/m^3 (0.4 mg/m^3). Six measurements exceed this level with 1000 μg/m^3 or more. Two of these samples were MDF (Medium Density Fibreboard) and three were multiply. The median of the complete dataset is 87 μg/m^3 (0.087 mg/m^3).

Plywood and chipboard come in many varieties; MDF, uncoated, double coated or one sided coated plywood. Whether a panel is coated or not does seem to influence the formaldehyde concentration. The off-gassing of formaldehyde from plywood decreases in time and plywood does not emit significant quantities after 2 to 5 years (Chang and Gershwin, 1992).

Also the content of formaldehyde was measured in plywood or chipboard by TNO Built Environment & Geosciences, some samples were double-sided or one-sided coated or painted. The measurements were performed using NEN-EN 120:1993[2]. The data are presented in Figure A6.4.

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[2] Personal communication with a research assistant of TNO Built Environment & Geosciences delivered a dataset with emission concentrations of formaldehyde from plywood and chipboard under laboratory conditions. The data set consists of 54 measurements of use conducted by order of commercial (anonymous) clients, local authorities and TNO Built Environment & Geosciences between 1992 and 2004.

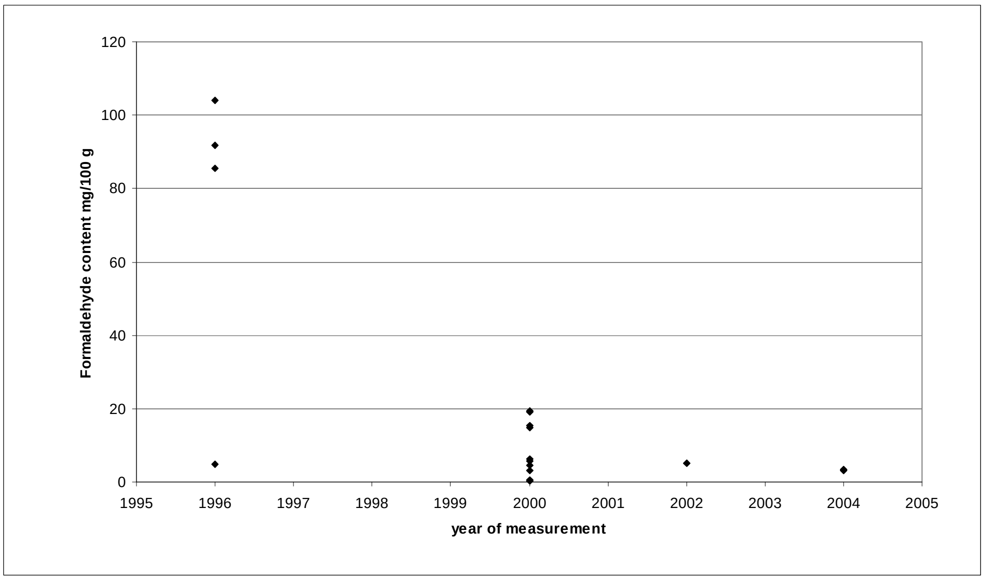

Figure A6.4. Formaldehyde content in chipboard and plywood mg/100g, 1996–2004.

In 1996 some high concentrations of formaldehyde were found in multiplex. However, the majority of formaldehyde came from the coating layer. Without this layer the formaldehyde concentration in multiplex was determined at 4.9 mg/100 g. In 2000 some pieces of MDF were examined with an average concentration of 19.2 mg/100 g formaldehyde. The remaining 9 measurements are well below the Dutch legislation of 10 mg/100 g formaldehyde. The median of all measurements is 5 mg/100 g.

It is estimated that the concentration of formaldehyde present in plywood is currently 5 mg/100 g. There are no measured data available from before 1985, but it is assumed to be much higher. Based on the data presented in Figure A6.2, two estimates of exposure of the periods 1970–1985 and 1986–2001 have been calculated using probabilistic analysis in '@risk'. The results are presented in Figure A6.4. Estimates of exposure to formaldehyde in indoor air; comparing two periods.

The cut-off point was determined at 1985, as in 1985 the Department of Housing and Urban Development in the United States of America designed regulation to ensure that the indoor air level of formaldehyde would be below 0.49 mg/m^3 (0.4 ppm). As 1985 is close to the Dutch chipboard regulation it is assumed that the results in this figure also represents the situation in the Netherlands.

Figure A6.1 shows that the average indoor concentration of formaldehyde has reduced from 0.28 mg/m^3 in the period 1970–1985 to 0.06 mg/m^3 in the period 1986–2002. The reduction in indoor formaldehyde exposure is then 80%. It is assumed that the main exposure in the earlier period is caused by formaldehyde in plywood and related products.

Assuming that people are indoors 90% of their time and with an average indoor air concentration of 280 μg/m^3 , and a outdoor concentration of 0.1 in rural areas to 20 μg/m^3 in

urban areas, the time weighted average exposure will be 252-254 µg/m^3, and 72-73 µg/kg bw per day.
(example) [280*0,9 (fraction spent indoors) + 0.1*0.1 (fraction spent outdoors)* 20 m^3/day]/70 kg= 72 µg/kg bw per day.

After 1985 the average indoor air concentration was 60 µg/m^3. In this situation the time weighted average exposure will be 54-56 µg/m^3 and 15-16 µg/kg bw per day.

Table A6.5. Inhalation exposure to formaldehyde in dwellings before and after measure to reduce formaldehyde in plywood

	before measure	**after measure**
Inhalation exposure	~ 250 µg/m^3	~ 55 µg/m^3
Systemic exposure	~ 70 µg/kg bw/day	~ 15 µg/kg bw/day

3.4 Textile worn by adults and children

Since 2001 the Dutch 'Warenwetregeling' Formaldehyde in Textile became effective, which prohibits trading in fabrics of which it is expected that they are in direct contact with human skin and contain more than 120 ppm formaldehyde, which corresponds to 120 mg/kg textile. It is also stated that if the fabric contains more that 120 ppm formaldehyde the label should state 'wash before use'.

In 2001 the Dutch Inspection Service tested if fabrics were in compliance with this regulation (Reus and Westerhoff, 2001). The tested cloths (n=153) were nightwear, underwear, shirts, trousers, socks, bedding and other fabrics. The textile was made of cotton, polyurethane, polyamide, polyester, linen, acrylic fibre and nylon in varying compositions. If testing showed a concentration of more than 120 ppm the fabrics were rinsed with water and retested. The results show that 3% of the fabrics show concentrations exceeding 100 ppm (138–259 ppm). These fabrics, bedding only, were made of 100% cotton and after rinsing the textile complied with the regulation of <120 ppm. Most fabrics (80%), however, contain a formaldehyde concentration of less than 20 ppm before rinsing, and another 15% below 60 ppm (Table A6.6).

Earlier Dutch studies dating from 1996 showed that exposure was also low before the measure was taken, with 98% of tested objects with levels <100mg/kg. In bed textile and baby clothing, 12% contained more formaldehyde than 100 mg/kg. For this period, no information could be retrieved of the exposure distribution. It is possible that exposure distribution was about the same as after the measure, but it is also possible that average exposure has decreased after the measure because of the attention to the measure, even if the percentage of exceeding >100 ppm was similar in both periods. Because no information is available, it is assumed that the exposure distribution in both periods was the same. Much older (foreign) studies showed much higher levels.

Table A6.6. Distribution of formaldehyde in textile in 2001 (Reus and Westerhoff, 2001)

ppm (mg/kg)	%
< 20	80
21 - 40	8
41 - 60	7
61 - 80	1
81 - 100	1
101 - 120	0
> 120 (max 259)	3

The following assumptions are made for assessment of exposure:

Each person has skin contact to new textile twice a month
The total weight of new textile is 300 gram
There is skin contact for two days before textile is washed
After the measure, all textile with >120 ppm formaldehyde is rinsed before use and the reduction in concentration is 60%. None of the other objects are rinsed.

Before the measure, on average 3% * 24 times per year is about one time per year lasting two days, people will be exposed to textile with >120 ppm formaldehyde.
After the measure, there is no exposure to textile >120 ppm assuming that people follow the instruction on the label.

For the period (close) before the measure a formaldehyde concentration of 20 ppm (20 mg/kg textile) is expected to be a reasonable scenario, taken the exposure distribution and the midpoints of exposure categories as average of those categories. Keely et al. (1999) found that after rinsing once, the formaldehyde concentration decreased with about 60%. Only exposure to new clothing will therefore be important. Clothing in close contact to the skin and bedding material will be washed after several days. Assuming a scenario of new clothing or bedding material of 300 gram per month (jeans weigh 500 gram, a t-shirt weighs 100 gram) and skin contact for two days before textile is washed, thus app. 20 gram per day of unwashed new textile and an absorption factor of 1, this will lead to the following exposure before the measure:

20 mg/kg textile * 20 g new textile = 0.4 mg formaldehyde
For an adult of 70 kg the exposure then will be 0.014 mg/kg bw:
0.4 mg /70 kg = 0.006 mg/kg bw per day.
For children it is assumed that the amount of textile worn and exposure per bodyweight is in proportion with that of an adult.

After the measure, the average concentration in textile is 17 mg/kg, leading to a dose of 0.005 mg/kg bw per day for an adult person.

Table A6.7. Exposure to formaldehyde through textile before and after labeling measure

	before measure	after measure
dermal exposure > 120 ppm	2 days per year	0 days
systemic exposure through dermal exposure	6 µg/kg bw/day	5 µg/kg bw/day

3.5 Cosmetics

Some studies have made estimates on formaldehyde release in cosmetics (Flyvholm and Andersen, 1993). Emulsions containing 0.02% bromonitropropanediol can release up to 15 ppm formaldehyde. Based on concentrations of this formaldehyde releaser would lead to 23 ppm formaldehyde in hair care products and 15 ppm in soaps. Chloroallylhexaminum chloride of 0.1% concentration contains 100 ppm free formaldehyde. Again, extrapolating this for the concentration of this releaser in soaps would result in formaldehyde concentrations of up to 100 ppm. DMDM hydantoin containing 0.5-2.0% free formaldehyde would result in concentrations of up to 150 ppm formaldehyde if the soap or shampoo has up to 0.15% of the releaser.

A number of substances has been recognized as formaldehyde releasing products and has been regulated in the EU Cosmetic Directive 76/768/EC. However, to check the compliance of these cosmetic products with this Directive it shows that during testing the substances decompose very rapidly to release formaldehyde when dissolved in aqueous/polar solvents (SCCNFP, 2002a). It was therefore stated, until better methods for testing would be developed, that in order to ascertain consumer safety the total content of formaldehyde in the finished cosmetic product must not exceed 0.2% (SCCNFP, 2002). The four formaldehyde releasers investigated in this latter study are presented in Table A6.8

Table A6.8. Free formaldehyde equivalent to maximum authorized concentration of certain formaldehyde releasers.

Compound	Maximum authorized concentration of the compound	Formaldehyde equivalent
Benzylhemiformal (containing 1.5 mole formaldehyde)	0.15%	0.044%
Sodium Hydroxymethylglycinate	0.5%	0.118%
Diazolidinyl Urea	0.5%	0.215%
Imidazolidinyl Urea	0.6%	0.186%

In one study from Denmark in 2000 an analytical control of preservative labeling on skin creams against the Cosmetic Directive was performed. Amongst other substances formaldehyde and formaldehyde releasers were examined on the label and tested in the product (Rastogi, 2000). In 34 (51%) of the skin creams tested formaldehyde and/or formaldehyde releasers were present. In 22 (33% from total) of them the label did not declare formaldehyde or formaldehyde releasers. In 1997 in Finland (Sainio, 1997), a study was performed on allergic ingredients in nail polishes. All nail polishes contained 0.08 to 11.0% toluene sulfonamide formaldehyde resins (TSFR) and 0.02-0.5% total formaldehyde. More TSFR resulted in a higher concentration of formaldehyde. A recent study by Sasseville (2004) shows that Quaternium-15 (1-(3-chloroallyl)-3,5,7-triazo-1-azonlaadamantane chloride) is a more common sensitizer than any other formaldehyde releaser. Table A6.9 presents the general concentrations of a few formaldehyde releasers in cosmetics and their potential for formaldehyde release.

Table A6.9. Formaldehyde releasers and formaldehyde concentrations in cosmetics.

Formaldehyde-releaser	**Concentration of formaldehyde releaser (%)**	**Formaldehyde release potential at 0.1% (ppm)**	**Maximum concentration in formulations (ppm)**
Quaternium 15	0.02 – 0.3	100	300
Imidazolidnyl urea	0.03 – 0.2	2.5	5
Bronopol	0.01 – 1	65	650
Dimethyloldimethyl hydantoin	0.1 – 1	20	200

It is assumed that in 50% of all consumer cosmetic products formaldehyde or formaldehyde from its releaser is present with an average content of 0.15% (based on the averages of the concentrations given in Table A6.9.it is also assumed that the whole Dutch population, to some extent, uses cosmetics and detergents. Based on a study from 2003 (SCCNFP, 2003) the average daily use of cosmetics is calculated:

	g per day
Total oral hygiene products	3.52
Total eye products	0.05
Total non rinse-off products	13.5
Total rinse-off products	0.72
Total	17.8 g/day

When 50% of all cosmetics contain 0.15% formaldehyde, the exposure is 13.4 mg per day. For an adult with a bodyweight of 70 kg, this leads to the following exposure:
13.4 mg/day * 1/(70 kg bw) = 0.19 mg/kg bw per day.

For formaldehyde, no information was available to estimate the exposure to formaldehyde prior to legislative measures on the formaldehyde contents in cosmetic products.

4 Description of toxicity

4.1 Introduction

The toxicology of formaldehyde has been studied extensively. The present evaluation is therefore based on the most recent evaluations available, e.g. Schulte et al. (2006), and Arts et al. 2006. In case relevant or additional information is available from other evaluations, or remarks are made with respect to the evaluations used, these will be specified as such.

It is to be noted that formaldehyde is present at low levels in most living organisms. Physiological amounts of formaldehyde are endogenously formed from serine, glycine, methionine and choline by demethylation of N-, O-, and S-methyl compounds. Enzymatic oxidation of formaldehyde leads to detoxification and is thought to protect from endogenous and exogenous levels of formaldehyde.

Furthermore it is noted that formaldehyde odor is detected and/or recognized by most human beings at concentrations below 1.2 mg/m^3. The absolute odor threshold for formaldehyde, defined as the concentration at which a group of observers can detect the odor in 50% of the presentations, has been reported to be between 0.06 and 0.22 mg/m^3.

4.2 Acute toxicity data

Upon dermal exposure, most of the formaldehyde will evaporate. In rodents between 3.6 and 16%, and in monkey circa 10% remained in the skin as demonstrated by exposure to ^{14}C labeled formaldehyde, where it is assumed that substantial amounts of topically applied formaldehyde reacts reversibly and irreversibly with biomolecules in the skin and hair (Schulte et al., 2006).
Upon inhalation, formaldehyde is rapidly metabolized, such that exposure to high concentrations (up to 18 mg/m^3 in rats) does not result in increased blood concentrations.

Formaldehyde demonstrated lethal effects in mammals: LD50 (rat, oral) 600 – 800 mg/kg bw, LC50 (rat, inhalation, 4 h) 578 mg/m^3. Inhalation of high concentrations (> 120 mg/m^3) of formaldehyde caused hypersalivation, acute dyspnea, vomiting, muscular spasms, convulsions and finally deaths. Histopathological examination showed respiratory tract irritation, bronchioalveolar constriction and lung oedema.
Formaldehyde was irritating to the eyes, and aqueous solutions of formaldehyde were irritating to the skin (NOAEC = 0.1%) and has corrosive properties when ingested. The Dutch Institute of Public Health established a NOAEL for skin irritation of 0.12 mg/cm^2 (LOAEL 0.57 mg/cm^2). As dose-response data are incomplete the reliability of these values is small (Janssen et al., 1998).
Data on formaldehyde specific reactivity in asthmatics under controlled exposure conditions are limited due to the small numbers of volunteers tested. The absence of significant formaldehyde-related differences in pulmonary function parameters comparing pre-exposure and exposure phases indicate that a formaldehyde-related increase in pulmonary dysfunction was not evident in asthmatics at concentrations of up to 3.6 mg/m^3.

Formaldehyde was found sensitizing in the guinea pig maximisation test and the local lymph node assay with mice. On the other hand, specially designed studies (IgE tests, cytokine secretion profiles of lymph node cells) did not reveal evidence of respiratory sensitization in mice. In human, the thresholds for elicitation of allergic contact dermatitis in sensitized subjects range from 30 mg/kg (w/w), aqueous solution, for patch testing to 60 mg/kg (w/w) for products containing formaldehyde. A threshold for induction has not been clearly established, but it is estimated to be less than 5 % aqueous solution (OECD SIDS, 2002). Allergic skin responses in sensitized subjects exposed to formaldehyde in aqueous solutions are reported to be rare at concentrations below 250 – 500 mg/kg (agency for Toxic substances and Disease Registry, 1999). It should be noted however that it is considered questionable if it is possible to discriminate between the protein cross-linking potential of formaldehyde at skin contact and observations like sensitization.
Upon exposure to formaldehyde, an increased number of DNA–protein cross-links has been found in the upper respiratory tract of monkeys and in the rat nasal mucosa, indicating that formaldehyde is a genotoxicant.

4.3 Chronic toxicity data

Repeated formaldehyde exposure caused toxic effects only in the tissues of direct contact after inhalation, oral or dermal exposure, characterized by local cytotoxic destruction and subsequent repair of the damage. Atrophy and necrosis as well as hyper- and metaplasia of epithelia may occur.
In repeated inhalation toxicity studies (up to 13 months) and chronic inhalation studies in rats, a high susceptibility of the nasal mucosa to formaldehyde was observed, resulting in increased incidences of nasal squamous cell carcinomas upon chronic exposure. No increased incidence of tumors was found in other organs than the nose after inhalation. Administration routes other than inhalation did not result in local or systemic tumor formation. The most sensitive No Observed Adverse Effect Levels (NOAELs) for morphological lesions were between 1.2 and 2.4 mg/m^3 for inhalation exposure and about 260 mg/l in drinking water.

The IARC (2004) concluded that the results of a study of industrial workers in the USA, supported by the largely positive findings from other studies, provided sufficient epidemiological evidence that formaldehyde causes nasopharyngeal cancer in humans. In addition, it was concluded that there is strong but not sufficient evidence for a causal association between leukaemia and occupational exposure to formaldehyde. In an extensive review by Heck and Casanova, however, it was shown that it is highly unlikely that formaldehyde is leukaemogenic. At present a biologically plausible mechanism how formaldehyde exposure could be related to leukemia is not available. Therefore, only an association rather than a causal relationship is assumed. Overall, IARC (2004) concluded that formaldehyde is carcinogenic to humans (Group 1) on the basis of sufficient evidence in humans (http://www.overheid.nl).

There are no indications of a specific toxicity of formaldehyde to fetal development and no effects on reproductive organs were observed after chronic oral administration of formaldehyde to male and female rats (OECD SIDS, 2002; Schulte et al., 2006; Arts et al., 2006).

4.4 Health risk levels for the inhalation route

Schulte et al. (2006) derived a safe level with regard to the induction of tumors in the upper respiratory tract including the pharyngeal region for human exposure. The ‘point of departure’ is cytotoxicity in rats and sensory irritation as a surrogate for this in man. It takes into consideration the dose response relationship and mechanistic information of relevant steps in the development of formaldehyde induced tumors in this anatomical region. It is noted that understanding the mechanisms underlying tumor induction by formaldehyde is critical for determining whether risks observed in animal experiments are of relevance to humans. Mechanistic considerations may also be used to define a practical threshold.
With respect to the genotoxic properties of formaldehyde *in vitro*, it is noted that a chemical agent can increase the risk of cancer either by damaging DNA or by increasing the number of cell replications, or both. Increased cell proliferation is by itself the basis for carcinogenicity induced by non-genotoxic agents. For non-genotoxic chemicals, particularly those acting by non-receptor dependent mechanisms, a threshold phenomenon will usually be involved, in many cases associated with cytotoxicity.

Concerning the tumors in the upper respiratory tract induced by formaldehyde, the steps in the induction of tumors are understood and include non-genotoxic mechanisms, which in the low concentration range are considered the most critical events in inducing carcinogenesis. Hence, a well founded level can be derived, considering the fact that genotoxicity at which tumor formation is demonstrated appears to be absent or at least negligible.

The analysis of the available human data suggests that an exposure level of 0.12 mg/m^3 formaldehyde can be regarded as a ‘safe’ level for the general population (Schulte et al., 2006). The proposed level of 0.12 mg/m^3 is 2 fold lower than the level derived from animal data by applying appropriate safety factors. This level is in good agreement with the MAC value of 0.36 mg/m^3 (0.3 ppm) which has been derived to protect humans at the working place (DFG, 2000), and the recommendation of the Dutch Health Council to establish a health-based occupational exposure limit of 0.15 mg/m^3 (0.12 ppm) formaldehyde in air, TWA-8 h, and a short term exposure limit, 15 min TWA, of 0.5 mg/m^3 (0.42 ppm) (Health Council of the Netherlands, 2003).
In the literature, a physiologically based model has been reported which has been applied to the animal data. From the reported calculations and their extrapolation to the human situation a level of 1.2 mg/m^3, 10 times the level proposed by Schulte *et al.*, was considered to be safe, as from both human and animal studies, it was concluded that at airborne levels for which the prevalence of sensory irritation is minimal (i.e., <1.2 mg/m^3), both in incidence and degree of respiratory tract cancer are considered to be negligibly low (Arts et al., 2006). Therefore, the level derived by Schulte et al. (2006) of 0.12 mg/m^3 seems to be a conservative estimate and is chosen for a threshold level of 1.2 mg/m^3.

5 Current risk assessment

5.1 Carcinogenicity

Formaldehyde is only acting at the site of entry and the concentration is the relevant exposure metric with regard to the induction of effects. As only concentrations which are capable to induce cytotoxicity (critical effect by inhalation) in the upper respiratory tract are considered to induce tumor formation, the cumulative daily dose and/or cumulative long term exposure are not considered of relevance for consumer risk. Furthermore, the development of nasal squamous cell carcinoma is likely to require repeated and prolonged damage to the nasal epithelium. As such, incidental short-peak exposure is considered of minor relevance for consumers. Exposure to a concentration of 1.2 mg/m^3 is considered not to induce cytotoxicity in the upper respiratory tract and hence can be regarded as a ‘safe’ level. Furthermore, this level is not regarded to induce other local or systemic effects.
It should be noted that the mechanism of tumor formation is based on the induction of irritation, cytotoxicity, and cell proliferation in the upper airways, which is primarily related to the concentration of formaldehyde exposed to. Considering this mechanism, the use of linear extrapolation to estimate human carcinogen risk will lead to erroneous conclusions. Therefore, a quantitative risk assessment is not considered possible using the current scientific methods available.

5.2 Sensitization

The critical effect after dermal formaldehyde exposure is considered the potential of formaldehyde to induce contact dermatitis. It should be taken into account that contact dermatitis may well be the result of the protein cross-linking potential of formaldehyde at skin contact, which mechanism is driven by both the concentration and, to a lesser extend, the duration of each exposure. With this respect it is noted that comparisons to a cumulative daily dose and/or cumulative long term exposure is not considered of relevance. Contact dermatitis is reported to occur at challenge concentrations as low as 30 mg/kg in aqueous solutions, or 60 mg/kg for products containing formaldehyde (OECD SIDS, 2002), whereas allergic skin responses in sensitized subjects exposed to formaldehyde in aqueous solutions are reported to be rare at concentrations below 500 mg/kg. According to the Dutch health council report on formaldehyde (2003) skin sensitization is caused by direct contact of the skin with more than 2% (v/v) formaldehyde solution. In this report it is estimated that 3% – 6% of the general population suffers from allergic contact dermatitis (based on data published by Bardane and Montanaro, 1991). In a publication of the WHO (2002), it is estimated that less than 10% of (North American) patients presenting with contact dermatitis may be immunologically hypersensitive to formaldehyde. The general population suffering from formaldehyde induced allergic contact dermatitis is therefore estimated at 0.3% - 0.6%. It is however noted that the mechanism inducing sensitization, and/or allergic contact dermatitis is unknown (Health Council of the Netherlands, 2003).

5.3 Conclusions current risk assessment

Based on the above, it is assumed that formaldehyde is associated with nasopharyngeal cancer as a result of a cytotoxic mechanism when exceeding a formaldehyde exposure to a concentration of 1.2 mg/m^3. Furthermore, it is assumed that formaldehyde causes contact dermatitis at a repeated minimum dermal exposure to 30 mg/kg in aqueous solutions, or 60 mg/kg for formaldehyde containing products, whereas it is estimated that circa 0.45% of the general population suffers from formaldehyde induced contact dermatitis.

6 Calculation of Public Health Gain

6.1 Decrease in exposure

6.1.1 Plywood

For indoor air formaldehyde concentrations, information could be retrieved from the public literature on the average indoor levels of formaldehyde in two relevant periods. The indoor concentration of formaldehyde is reported to be reduced from 0.28 mg/m^3 in the period 1970–1985 to 0.06 mg/m^3 in the period 1986–2002. When outdoor concentration is negligible, average daily exposure decreased from about 0.25 to 0.06 mg/m^3. The large difference between concentrations before and after 1985, when plywood legislation was enforced, seems to be the positive effect of this legislation, assuming that plywood is the main source of indoor formaldehyde exposure.

6.1.2 Textile

Washing cloths before wearing is advised by the label, which is obligated by law when the formaldehyde level exceeds the limit. Washing is assumed to reduce the concentration with about 60%. Given the exposure information before and after the measure, it is expected that the number of days that exposure exceeds 120 ppm reduces from 2 to 0 days per year if instructions are followed.

6.1.3 Cosmetics

Currently no information is available on dermal exposure to formaldehyde or formaldehyde releasers before 1976 (time of enforcement of the EU Cosmetics Directive 76/768/EEG). No detailed information is currently available on the formaldehyde content in cosmetics to estimate dermal exposure.

Table A6.10. Exposure reduction per product

Product	Exposure		Legislation	Reduction
	Before	After		
Plywood; inhalation exposure	~ 250 µg/m^3	~ 55 µg/m^3	Dutch 'Warenwet'	78%
Plywood; dose	~ 70 µg/kg bw/day	~ 15 µg/kg bw/day	Dutch 'Warenwet'	78%
Textile; dose	6 µg/kg bw/day (20 ppm)	5 µg/kg bw/day (17 ppm)	Dutch 'Warenwet'	17%*
Textile; exposure > 120 ppm	2 days per year	0 days	Dutch 'Warenwet'	100%*
Cosmetics; dose	-	0.19 mg/kg bw (0.15%)	EU Cosmetics Directive 76/768/EEG; 2nd Amendment 82/368/EEC and 6th Adaptation to technical progress 85/391/EEC	-
Background	0.014 to 0.14 mg/kg bw			

* only valid if people rinse new textile if labeled so.

6.2 Increase Margin of Safety

The margin of safety (MOS) approach is another method to describe the effect of the decrease in exposure. Generally, a reference MOS describes the margin which is allowed between human exposure and the dose at which no adverse affects are observed in animals or humans. When the MOS is too low, efforts should be made to reduce the exposure until the desired MOS is reached.

For consumers, inhalation exposure as a result of formaldehyde from plywood, and dermal exposure via textile and cosmetics are considered of relevance (see Table A6.10).
For exposure via inhalation, an exposure limit of 1.2 mg/m^3 is considered not to induce cytotoxicity in the upper respiratory tract as well as other local or systemic effects and is therefore regarded as a 'safe' level.

For dermal exposure, human contact dermatitis is reported to occur at levels as low as 30 ppm in aqueous solutions, or 60 ppm for products containing formaldehyde. It is noted that cosmetics are considered to contain formaldehyde (releasers) in aqueous solutions, whereas textile is related to products containing formaldehyde. Furthermore, effects are only found at site of contact (local effects), whereas no systemic effects are foreseen. Therefore, not the daily exposure (per kg bw), but the concentration in the product is of relevance.

The MOS calculations are performed using the exposure limits of 1.2 mg/m^3 for inhalation, and 30 ppm in aqueous solutions, or 60 ppm for products containing formaldehyde at dermal exposure. MOS values exceeding 2 (for age effects only, considering local effects, which are based on concentrations, and as the limits are based on human exposure) are considered not of concern.

In Table A6.11, the MOS approach using the exposure levels of formaldehyde exposure before and after the reduction are presented.

Table A6.11. Margin of Safety before and after reduction in exposure levels

Exposure scenario	**Exposure**		**MOS**		**Concern**	
	before	**after**	**before**	**after**	**before**	**after**
Inhalation exposure via plywood	~ 250 µg/m^3	~ 55 µg/m^3	4.8	22	no	no
Dermal exposure via cosmetics	-	0.15 % (1500 ppm)	-	0.02	unknown	yes
Dermal exposure via textile	20 ppm	17 ppm	3.0	3.5	no	no

Using the MOS approach, only for cosmetics a MOS exceeding the exposure limit is found. Although no information was available on the levels of formaldehyde in cosmetics before measures were taken, it is expected that they were of concern..

6.3 Decrease in incidence of effect

For the exposure scenario 'inhalation exposure via plywood', the exposure decrease due to measures is estimated to be 195 µg/m^3 (from ca. 250 µg/m^3 to ca. 55 µg/m^3). As an exposure below 1200 µg/m^3 is not considered to induce cytotoxicity in the upper respiratory tract, this decrease in exposure is not considered to lead to a decreased incidence of effects. As the MOS calculations are performed using average exposure levels, a decrease in effect might be assumed for high exposure groups. However, as no exposure data are available for these groups, this assumed decrease cannot be calculated.

For the exposure scenario 'dermal exposure via cosmetics', a decrease in exposure might be expected. However, as no exposure data are available before measures were taken, this assumed decrease cannot be calculated.

For the exposure scenario 'dermal exposure via textile', a decrease in exposure is calculated, assuming that consumers will follow the labelling instructions and will wash textile containing more than 120 ppm formaldehyde before use. A decrease in exposure of 3 ppm (from 20 ppm to 17 ppm) in textile is expected (1 µg/kg bw/d). As for formaldehyde related contact dermatitis a repeated minimum dermal exposure to 60 ppm in products is considered, the exposure is well below the limit inducing contact dermatitis. Although a decrease in exposure is calculated, this will not lead to a decreased incidence of effects as a result of the measures taken.

6.4 Derivation of DALY

6.4.1 Plywood

With respect to formaldehyde exposure via inhalation, it is assumed that cytotoxic effects occur when a formaldehyde exposure exceeds a concentration of 1.2 mg/m^3 on a chronic basis. The estimate of indoor air exposure is reported to be reduced from 0.28 mg/m^3 in the period 1970 to 1985 to 0.06 mg/m^3 in the period 1986 to 2001.

In the toxicology description of formaldehyde it is discussed that cytotoxicity in the upper respiratory tract is the critical effect after inhalation exposure to formaldehyde. The concentration exposed to is the major factor inducing the adverse effect. Furthermore, tumor formation is depending on repeated and/or prolonged exposure before it will become apparent. In this respect it is noted that incidental short-peak exposure is considered of minor relevance for consumers. Considering this mechanism, the use of linear extrapolation will lead to erroneous conclusions.

The MOS calculations indicate no concern both before and after measures taken. As such the calculation of a DALY is not considered possible for formaldehyde for this endpoint.

6.4.2 Cosmetics

The average content of formaldehyde (either as formaldehyde or as formaldehyde releaser) in 50% of the cosmetic products containing formaldehyde, is assumed to be 0.15% (1500 mg/kg, see section A6.1.5). This is well above the minimum dermal exposure level which might induce contact dermatitis at repeated exposure: 30 mg/kg. As such, contact dermatitis cannot be excluded for consumers via cosmetic use. The relevance of this however, is highly depending on the type of product and its use.

Formaldehyde, or formaldehyde releasers, present in an emulsion intended as skin crème, will be applied in a very thin layer (relative small amount of formaldehyde per cm^2), with a relative long dermal exposure time. However, in case of e.g. soap, shampoo, etcetera, a short (minute) exposure period can be considered, whereas the product is also diluted with water during use. For the latter group, not the concentration in the product, but also the contact time, as well as the conditions during exposure (wet hands/hair gives dilution of the product) are considered of relevance with respect to a possible health effect.

For cosmetics, concentrations, contact time and conditions during use are to be taken into account before a DALY can be elaborated. Considering the broad range of use, no DALY calculation for the group of cosmetics as a whole can be made. For calculations using subgroups of cosmetics with comparable use, insufficient information is available. Therefore, no DALY calculations were performed.

It is noted that no data are available for formaldehyde levels in cosmetics before the measure has become effective.

6.4.3 Textile

The average content of formaldehyde in textile have been estimated at 20 mg/kg and 17 mg/kg, before and after measures has become effective, respectively. As a result of the intervention, the mean exposure is decreased with 3 mg/kg.

It is noted that for (dry) textile, most of the formaldehyde has to become available in gaseous form before dermal exposure can take place considering the fibre structure of textile. Dermal effects can be initiated, only after the formaldehyde ‘gas’ is dissolved in the aqueous fraction of the skin. However, gas tends to flow towards a lower concentration most likely away from the skin, and air replacement is much higher at the non skin side than at the skin side of textile. Most of the gaseous formaldehyde is expected to flow away from the body. The exposure limit of 60 mg/kg for products containing formaldehyde at dermal exposure is therefore considered to be a rather arbitrary level for textile, although the mean formaldehyde levels are below the level expected to induce effects.

The critical effect after dermal formaldehyde exposure is contact dermatitis. The concentration finally exposed to is considered the major factor inducing the adverse effect, although the absolute amount per cm^2, and the contact time, are also of relevance. Furthermore, it is noted that the induction of contact dermatitis is most likely related to the cumulative exposure via air, cosmetics and textile.

The MOS calculations indicate no concern both before and after measures taken. As such the calculation of a DALY is not applicable for contact dermatitis induced by formaldehyde exposure via textile.

7 Discussion

7.1 Target population

Indoor air concentrations, textile worn by adults and children, and cosmetics
Information on exposure in homes is primarily focused on the general population. This assumes the whole Dutch population, which is known accurately. Within the general population, there are some groups with an assumed higher risk, e.g. people living in mobile homes and houseboats. This group is relatively small (0.4% of the population) and can be estimated rather accurately. For this group, however, no specific exposure data are present. Also, the total population is potentially exposed via textile and cosmetics and thus the population at risk can be estimated accurately.
Overall, the error in estimating the target population sec is small.

7.2 Exposure

7.2.1 Indoor air concentrations
There is no information on exposure levels in Dutch homes, prior to taken measures as well as after taking measures. Currently, a project is carried out in which a.o. formaldehyde concentrations will be measured in a large number of Dutch homes to obtain a representative overview of their health quality (Onderzoek gezondheidskwaliteit woningvoorraad; VROM). Estimates used in this case are based on foreign studies. Since building materials and criteria can vary largely between countries, real average exposure levels in the Netherlands can be under or overestimated with presumably several factors. Also, since concentrations decline with age of the products, for interpretation of the results the age of the formaldehyde containing material should be taken into account as well as information on decline in emission rates. This information has not been taken into account, introducing additional errors.
The error in average exposure is likely to be moderate. However, because of the shape of the exposure-response relationship, with a clear threshold value for carcinogenicity, is it crucial to have information on the chance of exceeding threshold levels and the frequency of high exposures since it is assumed that effects occur only after prolonged exposure to high concentrations. This information is not available. Since exposure levels are relatively close to the given threshold level, exceeding of threshold levels may occur. Since there is no information available either on the number of people exposed to levels above the threshold level, this means that the validity of the conclusions about health gain related to reduction of formaldehyde in plywood can not be estimated.
No evaluation has been made of the method used to determine formaldehyde in air and the representativeness of the objects in the study. Both could have affected presented results. Especially the restricted representativeness might lead to relatively large errors.

7.2.2 Textile
Information on exposure levels in different products was available before and after the measure. Although a relatively large number of (different) objects was studied, the error in exposure assessment with respect to exceeding the level of 120 mg/kg can not be estimated. Since generally studies by VWA are focused on finding products with high concentrations, there may be an overestimation of products with high formaldehyde levels. This means that the actual health effects and the actual reduction in exposure may be lower than suggested by the calculations.
For the calculations of the number of days that people are exposed to materials with >120 ppm formaldehyde rather crude assumptions had to be made. The error in the number of days with high exposure is potentially up to several factors.
Besides, the toxicological information does not give information on the threshold level above which people might get allergic skin reactions by contact with textile. Since the available Dutch information on exposure before and after the measure suggest that exposure did hardly change, lack of data will hardly affect the effect estimate.

7.2.3 Cosmetics

The estimations on exposure to formaldehyde lack relevant data on crucial elements. There is no accurate information on formaldehyde levels in products, and for the available information the representativeness is not known. No distinction has been made with respect to different type of products with different application procedures. For the potentially experienced health effect, this information is crucial. The total potential error in exposure through use of cosmetics is therefore considered to be large.

The total experienced health effect by use of cosmetics with high formaldehyde concentrations is very difficult to estimate and can only be based on assumptions of duration of effect and frequency of contact to products containing dermal effects. It is unknown to what extent people might link effect to the use of specific products. It can be assumed that when the true cause is expected, people will shift within reasonable short time to other products. No information is available on the correlation between type of product (e.g. shampoo) and formaldehyde concentration, and between the price category and concentration. With high correlation, the same people might be affected more often and longer than in case of no or low correlations. The error in estimated days of exposure may be moderate.

7.2.4 Other exposure sources

Inhalation exposure to formaldehyde may occur through many different sources. For the health endpoint under study, there is a threshold value. For effects through inhalation, the air concentration is relevant. The outdoor background value is in polluted urban areas about 1-2% of the threshold value of 1.2 $\mu g/m^3$. Smoking can contribute significantly to the indoor concentration in case of heavy smoking e.g when multiple smokers are present is a badly ventilated room. Errors in input information and deviating smoking circumstances may cause that total exposure to add up to over the threshold level in (most likely being) occasional circumstances. This will invalidate the conclusion about potential gain in health effect.
For dermal exposure, also many potential sources have been indicated. Since in this case there is also a threshold value for the health endpoint, simultaneous local exposure to products containing formaldehyde even below the threshold value may increase the risk of experiencing contact dermatitis. This restricts the validity of the conclusions about health effects and potential health gain.

7.3 Toxicology

Chronic formaldehyde exposure via inhalation is associated with nasopharyngeal cancer as a result of a cytotoxic mechanism when exceeding a formaldehyde exposure to a threshold concentration of 1.2 mg/m3.
Furthermore, it is assumed that formaldehyde causes contact dermatitis at a repeated minimum dermal exposure to 30 mg/kg in aqueous solutions, or 60 mg/kg for formaldehyde containing products, whereas it is estimated that ca. 0.45% of the general population suffers from formaldehyde induced contact dermatitis.

7.4 DALY calculation

For inhalation exposure, cytotoxicity in the upper respiratory tract is the critical effect after exposure to formaldehyde, i.e. for inducing local tumour formation. The concentration exposed to is the major factor inducing adverse effects, but tumor formation is depending on repeated and/or prolonged exposure above the threshold level before it will become apparent. Considering this mechanism, the use of linear extrapolation clearly is not applicable here. As the MOS calculations indicate no concern both before and after measures taken, the calculation of a DALY by exposure via inhalation is not considered possible.

The critical effect after dermal formaldehyde exposure is contact dermatitis. The concentration exposed to is considered the major factor inducing adverse effects, although the absolute amount per cm^2 and the contact time are factors which have to be taken into account too. As clear thresholds for induction are identified here, a threshold risk assessment is performed.

Considering the broad range of use of cosmetics, no DALY calculation for the group of cosmetics as a whole can be made. For calculations using subgroups of cosmetics with comparable use, insufficient information is available. Therefore, no DALY calculations were performed. However, concern of dermal exposure via cosmetics is indicated by the small MOS calculated for the period after measures were taken. It is noted that no data are available for formaldehyde levels in cosmetics before the measure has become effective.

For dermal exposure via textile, the MOS calculations indicate no concern both before and after measures taken. As such the calculation of a DALY is not applicable for contact dermatitis induced by formaldehyde exposure via textile.

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Appendix 7 Case report lamp oil

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1. Introduction

In the discussion on which cases to choose for the calculation of health gain after a measure was introduced, the ban on the sale of coloured lamp oil was mentioned as a success. The incidence of lamp oil intoxications as monitored by the Dutch Poison Information Centre (NVIC) was namely reduced after the measure. This case was also included as an example substance for acute toxicity.

2. Background information on lamp oil intoxications

2.1 General information

In the early years of 1990 the reported number of poisoning of children by lamp oil at the Dutch Poison Information Centre (NVIC) was increased. NVIC conducted a study to establish the circumstances of exposure, the frequency and severity of clinical effects and the treatment provided. Some specific information on the actual exposure and the products involved was also collected (Van Zoelen et al., 1997). Data collection forms were returned and completed in 66% of the 165 cases, consequently 109 cases were included. The majority (82%) of these patients was aged 1-2 years, mostly within the range of 15-26 months. The ingested dose was reported in 79 cases and varied from 1-150 ml, in 84% of these cases the volume was small (1-10 ml). In 68% of the cases the children drank from the lamp and in 23% ingestion from the bottle was reported. Usually these lamps and containers were easily accessible to the children. In a few cases they were able to open the childproof screw-caps of the containers. Symptoms were reported in 77% (n=84) of the patients. The effects most frequently observed were coughing (52 cases), vomiting (20 cases) and lethargy or drowsiness (18 cases). Chemical pneumonitis was reported in 9 cases and fever in 12 cases. No fatalities were reported in the 12 month investigation period. In 39% of the cases (n=42) patients were sent to a hospital and 55% of these patients remained under observation, usually for 1 day (range 1-21 days). A chest x-ray was performed in 41 cases and abnormalities on the x-ray were reported in over 50% of these cases. In this study, ingestion of lamp oil resulted in clinical effects in the majority (77%) of the 109 cases. Drinking lamp oil directly from the lamp clearly needed more attention: people may be notified by warnings on the packages. With regard to the bottle, improved childproof screw-tops and improved labelling can add to the prevention and reduction of exposure. It was concluded that lamp oil ingestions involved a considerable risk of aspiration and chemical pneumonitis. This was also underlined in a study by Melis et al. (1990) were 5% of patients with chemical pneumonitis had accidentally ingested lamp oil. It was concluded that lamp oil belong to the top five chemicals inducing chemical pneumonitis in patients.

Other European countries reported similar increases in lamp oil poisonings. In 1986 papers in a Norwegian and Swedish journal were published on the serious increasing problem of lamp oil intoxications (Orderud et al. (1986) and Nielsen and Hansen (1986), respectively). The Swiss Poison Centre conducted a study in 1995 because of increasing number of lamp oil intoxications (Van Zoelen et al., 1997). German poison centres received in 1994 1100 information requests on lamp oil (Hahn et al., 1997).

2.2 Legislation

This increase in intoxications was the reason for designing a new legislation in Europe to ensure that children do not suffer from damage to the lungs by drinking lamp oils or similar fuels, which may appear tempting because of their colour or smell. If these types of fluids are consumed, a few drops may easily enter the lungs and cause damage.
The legislation under Directive 76/769/EEG (the so-called (‘verbodsrichtlijn’) covers the sale of lamp oils and similar fuels when the products contain colouring or perfume, and can cause damage to lungs (with a viscosity of less than $7x10^{-6}$ m^2/sec)– and therefore carry the risk phrase R65 on the label, and are sold in packaging of 15 litres or less. The adaptation was published in Document 31997L0064 (1997) of Commission Directive 97/64/EC (adapting Annex I to Council Directive 76/769/EEC). It was implemented in July 2000.
The legislation also covers the sale of colourings as an accessory to colourless lamp oils.
The following applies to lamp oils and similar fuels which are covered by the legislation:
Sale of lamp oils and similar fuels which contain colouring or perfume is prohibited.
Lamp oils and similar fuels which are sold commercially must be labelled: ‘Keep lamps which contain this fluid out of reach of children’. The text must be easy to read and in indelible text.
It is not permitted to sell colourings as an accessory to colourless lamp oils. The ban does not apply if, due to taxes and duties, the substance or product is required to contain colouring.
In the Netherlands, this legislation is implemented in the “Warenwet”.
“2.3 Warenwetbesluit algemene chemische productveiligheid.
Artikel 2. 1.4 Onverminderd het bovenstaande mogen stoffen en preparaten geen kleurstof bevatten, tenzij dat om fiscale redenen vereist is, noch geurstof noch beide bevatten indien deze stoffen en preparaten:
- gevaarlijk zijn bij inademing en gekenmerkt worden als ‘schadelijk: kan longschade veroorzaken na verslikken’, in de zin van de criteria in bijlage VI van de stoffenrichtlijn en
- als brandstof in sierlampen kunnen worden gebruikt en
- in een verpakking met een capaciteit van 15l of minder op de markt worden gebracht.

3 Description of exposure

Several papers and reports from different countries were found on the subject of lamp oil intoxication. An overview of the cases and studies, more or less per country, is given at the section 3.2 Exposure to lamp oil.
A clear distinction needs to be made. This specific case is about lamp oils which are used for decorative lamps. Other oils such as perfume oils (which are used for aroma therapy) do not lead to aspiration. Substances used as lamp oils are exclusively highly purified petroleum distillates such as kerosene or isoparaffins to which odorous and colouring substances might have been added (Hahn et al., 1997).

3.1 Target Population

The target population for this case are children in the age of about 1 to 3 years. Information is included from different countries; however the definitive calculations will be performed for the Dutch situation. In the Netherlands, the number of children between 0 and 5 is about 1,000,000 (Statistics Netherlands (CBS), 2005). For children in the age of about 1 to 3 years, the population will be around 500,000.

3.2 Exposure to lamp oil

Germany

In a publication in a series on medical aspects of consumer health by the BgVV (Federal Institute for Health Protection of Consumers and Veterinary Medicine in Germany), poisoning (accidental exposure) of infants and small children by lamp oil was taken into account (Hahn et al., 1997). Intoxication by lamp oil was second on the list of toxicants involved in private homes and amounted around 19% of the cases. In 99% of the lamp oil accidents, infants or small children were affected. Since 1990, 3 casualties after lamp oil ingestion had been notified to the Centre for Documentation and Evaluation of Poisoning. In 1996, there was a particular accumulation of severe cases in a comparatively small total number of cases.

According to the surveys conducted by BgVV, since 1970 an increased number of inquiries to German poison control centres about lamp oil has been registered; particularly noticeable since 1989 (see Table A7.1).

Table A7.1. Number of inquiries of lamp oil ingestion in Germany based on data of German poison control centres. (Hahn et al., 1997)

Year	Number of cases
1989	109
1990	429
1991	626
1992	905
1993	966
1994	964
1995	886
1996	842

A medium-sized paediatric hospital serving circa 720,000 residents (with about 140,000 children) in the eastern part of Berlin reported to the BgVV 23 cases of ingestion within 3 years. Approximately 50% of the children developed a chemical pneumonia, with a very severe course in some cases (Hahn et al., 1997).

A BgVV study (published in 2001, Hahn et al) included 107 reported lamp oil ingestions requesting clinical care in 2001 for investigation. Questionnaires were sent out and 65 were received. In 30 cases, the physicians reported chemical pneumonias.

The year report of 2004 from the BfR (Federal Institute for Risk Assessment; former BgVV) reported 56 cases of poisoning with lamp oil in 2004, all concerning children. In half of the cases the health impairment was moderate/severe. Furthermore, 2 cases with fatal outcome were reported, regarding two infants after ingestion of colourless and unscented lamp oils containing paraffin (Hahn et al., 2005). In this report, the BfR mentioned the ESPED study Lamp oil poisoning in Germany in which poisoning cases are recorded in collaboration with the clinical registration unit for rare paediatric diseases in Germany. The results up to 2004 are reported in Table A7.2 In total over the period of 1 March 2000 till 31 December 2004, the BfR received 616 case reports from ESPED with a total number of 458 questionnaires being returned. 411 of these cases could be validated as lamp oil ingestion with a 40% rate of pneumonia (in 165 infants and young children). In the majority of cases (61%), pneumonia was caused by lamp oils containing paraffins or petroleum distillates that were either old products (i.e. coloured or scented products sold before the ban) or uncoloured and unscented products not subject to the ban so far.

Table A7.2. Number of notifications (paraffin-containing products) under 16e Chemicals Act from 2000-2004 in Germany (Hahn et al., 2005)

Year	Number of cases	Of these with pneumonia
2000	76	36
2001	57	23
2002	63	26
2003	38	16
2004	39	20

Denmark
In Odense, in a 13-year period (1980-1992) a total of 1751 cases of poisonings in the 0-6 year age group were registered. In 482 children, accidents occurred with household chemicals. There was an increase in the number of poisonings with lamp oil (from 0 cases in 1980-81 to 22 cases in 1986-87). It is noteworthy that 67 of the 69 poisonings over the 13-year period with lamp oil occurred in the 0-3 year age group. Sixty of the children poisoned with lamp oil were admitted to the hospital. During the following years the number of accidents with lamp oil declined again. Whether or not this was the result of greater precautions in the home or a decline in the use of oil lamps and hence lamp oil is not known. (Johannsen et al., 1994).

United States of America
A letter submitted in 1999 to a journal called for attention on a recent increase in the incidence of lamp oil exposure in Europe and the United States (Martins et al., 1999). It mentions 1100 reported cases in Germany in 1994 including 3 deaths that occurred after the study was complete. The Illinois Poison Centre reported 21 cases in 1997. Furthermore, an 8-year analysis conducted during 1983 and 1989 identified five lamp oil fatalities in the United States and an additional death in 1990 was reported to the American Association of Poison Centres (Litovitz and Manoguerra, 1992). This letter was supposed to alert the public to the dangers of lamp oil and its sources. They recommend secure childproof containers and purchasing childproof lamps. The manufacturers should include warning labels and remove the colours and pleasant scents from the oils which allure small children. Also, parents should be advised to place the oil lamps out of reach of children.
Between 1988 and 1998 an estimated 8500 ± 2100 incidents of lamp oil ingestion and/or aspiration by children less than 5 years old were reported in the US CPSC National

Electronic Injury Surveillance System (NEISS). An estimated 31% of these poisoning victims were hospitalized, considerably higher than annual hospitalization rate usually associated with paediatric poisonings reported in NEISS. The Consumer Product Safety Commission (CPSC) in-depth investigations suggested that many (43/52) of these potentially serious lamp oil exposures occur directly from lamps rather than childproof bottles. (Aitken et al., 2000).

In New York City, a retrospective review was conducted to all human exposures to paraffin lamp oil in patients not older than 18 reported to the regional poison control centre between January 1, 2000 and February 1, 2003. Reports were investigated to ascertain the frequency of occurrence of paraffin lamp oil exposures on the Jewish Sabbat and Jewish religious holidays. This investigation was prompted by an apparent increase in paraffin lamp oil exposure during the Jewish Sabbath. Many orthodox Jews maintain a burning lamp that uses paraffin lamp oil as fuel. During these 25 months, 45 cases were reported. No fatalities occurred. Orthodox Jews accounted for 32 cases (71%), 4 cases (9%) occurred in children who were not orthodox Jews, and demographic data were unavailable in 9 cases (20%).
24 Cases (53%) occurred within 10 hours before or during the Jewish Sabbath or Jewish religious holidays. The relative risk of orthodox Jewish children to ingest paraffin lamp oil, calculated by using census data, is 374 times that of other children. (Hoffman et al., 2004).

The Netherlands
The Dutch Poison Information Centre (NVIC) reports every year on the information requests on many different substances, amongst them are household products/chemicals (Van Gorcum et al., 2003; Van Velzen et al., 2004; Van Gorcum et al., 2005). In these annual reports an increase was found for lamp oil ingestions in the middle nineties (see Table A7.3). In 1996 NVIC conducted a study on this specific case (Van Zoelen et al, 1997) which is discussed in section 2.1. In Europe, the measure on banning coloured and scented lamp oil was introduced in 2000, and a decrease in reported intoxications was found. However, in recent years, the requests for information after lamp oil ingestions increased again. The total number of reports also increased, but not enough to explain the increase.
The found increase resulted in a new study performed by NVIC in 2005 which is recently released (De Vries, 2006). The aim of the report was to get more insight in the circumstances, frequency, nature and seriousness of the poisonings with different kinds of lamp oil. From April till December 2005, 152 cases of lamp oil were reported, 110 cases had a follow-up obtaining additional information. In total 79 of the patients (72%) had complaints including prickling cough, vomiting, feeling of sickness, drowsiness etcetera. In about 20% indicators of a chemical pneumonitis (such as shortness of breath, faster breathing and fever) were found, in 9 cases this was seen on a lung picture.

Table A7.3. Number of reported cases of lamp oil ingestion in the Netherlands in different years. (NVIC Annual reports, 2001-2004)

Year	Number of cases
1993	50
1994	145
1995	170
1996	225
1997	254
1998	225
1999	168
2000	117
2001	95
2002	87
2003	111
2004	146
2005	264

3.3 Results

No exposure calculations were made for exposure to lamp oil.
The decrease in number of lamp oil intoxications was determined by using the highest intoxication number (254) before the measure and the lowest intoxication number (87) after the measure. This provided a maximum decrease of lamp oil intoxication cases of 167.
It is assumed that the decrease shown (in Table A7.3) is a result of the measure. The increase later on cannot yet be explained.

4 Description of toxicity

Toxicological data from animal studies with kerosene or paraffins (e.g. LD_{50} oral 2-5 g/kg bw in rat and mouse) did not formally identify any relevant risk for man. Pharmacokinetic studies in man have shown that kerosene is only absorbed in very low quantities from the gastro-intestinal tract. Kerosene/paraffin is a convincing example demonstrating that the assumption of a substance having a risk only in case of systemic availability can lead to errors in evaluation. The hazard potential stems from the special physical-chemical properties of these lamp oils. Swallowing even the smallest amount (less than one gram) can lead to the oils creeping into the lungs and causing severe inflammation there, so-called chemical lung inflammation. Lung inflammation is also called pneumonitis.
Even when very low amounts of kerosene are introduced through thin cannulas directly into rat lung, amounts of only 0.1 ml kerosene can cause death. The risk of aspiration pneumonitis caused by petroleum distillates is inversely proportional to volatility and directly proportional to viscosity and surface tension. (Hahn et al., 1997)
Ingestion of lamp oil by children or adults results in a range of different clinical symptoms. Some patients experience amongst others, persistent coughing, vomiting, nausea, lethargy or somnolence, drowsiness, shortness of breath, and pneumonitis.

Medical care may consist of admittance to a hospital, sometimes for more than 1 day to the intensive care unit. Some patients were endotracheally intubated and mechanically ventilated. (Hahn et al., 1997)

5 Current risk assessment

This is not applicable for the present case.

6 Calculation of Public Health gain

6.1 Decrease in exposure

This is not relevant for this case.

6.2 Increase of Margin of Safety

This is not relevant for this case.

6.3 Decrease in number of reported intoxications

In the Netherlands, the highest number of intoxications in the years before the measure, was 254 (in 1997, see Table A7.4). The Directive was effective from July 2000 on. After that date, the NVIC observed a decrease in the number of information requests on lamp oil ingestions. The smallest number was reported in 2002, namely 87 cases. In recent years (see Table 3) the number of cases was increasing again. It might be possible that this increase results from the presence of coloured lamp oil on the market again. Producers claim that these coloured lamp oils have a higher viscosity, because they are made from vegetable oils. For that reason they could be less toxic after intake (Van Gorcum et al., 2005).
An investigation in 2005 of NVIC (De Vries, 2006) showed that almost all of the reported cases were exposed to paraffin containing lamp oils (although with higher viscosity). In 20% of the cases exposure was to coloured lamp oil, and 68% to white lamp oil. In some cases the oil lamp itself was from coloured glass.
Still, we assume that the found decrease is a result of the measure. For this calculation, we choose for the highest possible decrease to be calculated, a decrease of 167 cases.

6.4 Derivation of DALYs

Direct effects that were mentioned in the different reports included coughing, vomiting, nausea, fever and chemical pneumonitis. From the study by NVIC (Van Zoelen et al., 1997), the following information could be extracted (using 109 cases).

Table A7.4. Symptoms after ingestion of lamp oil (Van Zoelen et al., 1997).

Symptom	**Percentage (%)**
Nausea	11
Vomiting	18
Persistent coughing	48
shortness of breath	7
Pneumonitis	8
Fever	11
drowsiness	17

The symptoms nausea/vomiting/coughing/shortness of breath and drowsiness were taken together in total as acute effects. The disability weights that were set for these symptoms are based on the Dutch burden of disease study. They are determined by their score in EuroQol (see Appendix 7.1). The scores for these effects on mobility, self-care, daily activities, pains and other complaints, anxiety/depressions, and cognition were set at 122212, resulting in a weighing factor of 0.33. Acute effects are assumed to occur in all intoxication cases of lamp oil; the duration of these effects is set at 1 day (as reported in the study by NVIC, 1996).
For the longer lasting effect of pneumonitis two different ways of calculating the DALY can be used. The existing weighing factor of 0.1 from the Dutch burden of disease studies (VTV, 1997) can be used. This factor is established for this effect over a year. The other way is to gather it under acute effects, using a duration of 14 days, and calculating a weighing factor using the EuroQol method (see Appendix 7.1). Pneumonitis was scored as 323312, resulting in a weighing factor of 0.67.
In reports from the German colleagues, percentages of 10-23% (Hahn, 1997) and 48% (Hahn, 2001) for chemical pneumonitis were mentioned. The Dutch study (Van Zoelen et al., 1997) mentions a 10% (rounded) percentage of pneumonitis. For this calculation we take the Dutch data, and assume a percentage of 10%.

Table A7.5. Overview of DALY calculation

	Weighing factor		**Duration**	**Number of cases**	**%**	**DALY**
	EuroQol	**VTV**				
Acute effects	0.33		1 day	167	100	0.2 [1]
Pneumonitis	0.67		14 days	167	10	0.4 [2]
		0.1	1 year	167	10	1.7 [3]
Total						0.6-1.9

Calculation:
[1] 100% x 167 x 0.33 x 1/365 = 0.15
[2] 10% x 167 x 0.67 x 14/365 = 0.43
[3] 10% x 167 x 0.1 = 1.7

In this case, the preference is given to using the EuroQol method, because the intoxications with lamp oil concern acute effects, including pneumonitis. The total amount of DALY then amounts 0.6.

7 Discussion and conclusion

For this case of acute intoxications, the DALY calculation resulted in a low value of 0.6. However, the number of reported lamp oil ingestions may be not the actual number. There is no duty to report this kind of intoxications (in the Netherlands), which might result in an underestimation of the number of cases. There is no knowledge on the percentage of not-reported cases, thus the actual value might be 2 times (50% underreporting) or 10 times higher (90% underreporting). Comparing the Dutch data (145) with the German data (1000) in for example1994 with the total population results in somewhat higher reportings in Germany (The total German population is about 5 times larger than the Dutch (for 1994: 15.4 million with 73.2 million (Eurostat, 2005))). It might be assumed that the amount of DALY certainly will be higher. On the other hand, there seems to be a trend in increase of lamp oil intoxications from 2002 onwards. It is unknown what is responsible for this increase. The health benefit from the measure will deteriorate due to this increase. From the 2005 NVIC investigation, it seemed that oils with higher viscosity not really resulted in less serious effects (De Vries, 2005).
The relationship of the seriousness of the complaints to the weighing factors is complicated. In this report it was simplified by assuming a lot of symptoms together as acute effects, and using the EuroQol method to appoint a weighing factor. The more seriousness effect of pneumonitis was assessed in a similar way, using the same method. A few reports mention more permanent lung damage, up to 8 -14 years after the intoxication. In the present calculation, this was not taken into account.
The derivation of DALYs is based on the Dutch situation, as monitored by the NVIC, using the most recent data. However, some German data show more serious effects after lamp oil ingestion. In 2004, the German Federal Institute for Risk Assessment (BfR, July 2004) reported on two new child fatalities caused by lamp oil. This happened despite repeated warnings and a series of risk-reducing measures. Both had ingested small amounts of paraffin-containing, clear and non-perfumed lamp oils. In 1994 there were between 250 and 300 cases of chemical lung inflammation in infants in conjunction with the around 1,000 inquiries. When a fatal case (as in Germany) is included in the calculations, the DALY at once increases with about 70.
The use of the DALY in this specific case might be subject of some discussion. The large decrease in cases (with 66%) is felt to be not expressed in the low resulting DALY of about 1. However, in many cases, children were taken to a hospital after lamp oil ingestions, had to stay there for a day or longer, with might be stressful for the children and their parents. It is a feeling that the severity of this is also not expressed in the DALY. That might be more an aspect of risk perception which is not taken into account.

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Appendix 7.1

Determination of the EuroQol score was executed according to six dimensions, which varied in severity over three levels. The dimensions were: mobility, self care, daily activities, pains and other complaints, anxiety/depressions, and cognition. These dimensions describe the functional state of health of a certain individual with a certain disability. A score of 1 equals full health. A EuroQol score of 111111 will consequently result in a disability weight of 0. A score of 2 equals to a disability weight of 0.0833. A EuroQol score of 222222 will result in a disability weight of 0.5 (since all dimensions were scored as being half). A EuroQol score of 333333 will result in a disability weight of near 1. For details see a report by VTV (in dutch) (1998) and an overview of the table is given below.

Table A7.6. EQ-6. Dimensions with their 3 levels (no problem, some problems, many problems).

Dimension	Level	Score
mobility	No problems in walking about.	1
	Some problems in walking about.	2
	Confined to bed.	3
self care	No problems with washing or dressing self.	1
	Some problems with washing or dressing self.	2
	Unable to wash or dress self.	3
usual activities	No problems with usual activities (e.g. work, study, housework, family or leisure activities).	1
	Some problems with usual activities.	2
	Unable to perform usual activities.	3
pain / discomfort	No pain or discomfort.	1
	Moderate pain or discomfort.	2
	Extreme pain of discomfort.	3
anxiety / depression	Not anxious or depressed.	1
	Moderately anxious or depressed.	2
	Extremely anxious or depressed.	3
cognition	No problems with cognitive functioning (e.g. memory, concentration, coherence, IQ)	1
	Some problems with cognitive functioning	2
	Extreme problems with cognitive functioning	3

EuroQol (6 Dimensies) (EQ-6D). For more details see a report by VTV (in Dutch) (Van der Maas and Kramers, 1997) and Hoeymans et al., 2005a.

Appendix 8 Case report Nickel

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1. Introduction

Contact allergy to nickel is a frequently occurring disease. Denmark was the first country to take measures on nickel in objects in direct and prolonged contact with the skin. The measure was intended to decrease the release rate of nickel in objects to less than 0.5 µg Ni/cm^2/week in the late eighties. A somewhat adapted measure on nickel was adopted by Europe in the nineties. However, it took some time before a standard European test was accepted for enforcement purposes.
In recent years, several nickel compounds were subject of discussion in the Existing Chemicals Program in Europe. In those reports, evidence is included that the Danish legislation that restricted the release of nickel has resulted in decreased prevalence of skin sensitisation in the younger population. This suggests that this reduced release rate contributes to the prevention of new cases of nickel allergy. The Risk Assessment Report on Nickel (May 2005) concluded that more research is needed. Meant by this was that effects of the EU Directive and the associated EN 1811 standard should be similarly monitored in the wider European population to ensure that the threshold set in the Directive is adequate to prevent new cases of nickel allergy.
For the present report, nickel was chosen as case compound, because adequate human data were available on the impact of the measure. Furthermore, a large number of people are exposed to nickel, and the toxicological endpoint is different compared to the other selected cases, i.e. skin sensitisation.

2. Background information on nickel and contact allergy

2.1 General information

2.1.1 Nickel legislation

Nickel metal and nickel sulphate are known skin sensitizers in humans and are classified with risk phrase R43, which indicates that the substance may cause sensitivity to the skin upon contact (Annex I, according Directive 67/548/EEC). It was considered necessary to include a proposal for setting a specific release limit for the classification of alloys containing nickel for skin sensitisation. It is recognised that the limits for expressing this threshold is related not to the concentration of nickel in the metal or alloy but rather to the rate of nickel release expressed in µg Ni/cm^2/week from the material. A draft specific concentration limit based on a new Note relating to the labelling of preparations in the Foreword to Annex I has been agreed by the C&L Health Effects Working group. The draft note reads: ‘Alloys containing nickel are classified for skin sensitisation when the release rate of 0.5 µg Ni/cm^2/week as specified in the European Parliament and Council Directive 94/27/EC and as measured by the European Standard reference test method EN 1811 is exceeded.’

The use of nickel and nickel-containing alloys in certain applications is regulated by Directive 94/27/EC (EC, 1994). This Directive was introduced at Community level following Danish regulations adopted in 1991. It has since been amended (Directive 2004/96/EC, EC, 2004).
The Danish regulation covered a variety of specified products. These included objects in direct and prolonged contact with the skin, piercing posts for ear-rings, and hairclips. The regulations were based on the nickel-release rate from the material, using a threshold of 0.5 µg/cm^2/week, as measured by the dimethylglyoxyme (DMG) assay. Nickel-containing materials in close contact with the skin were not permitted for sale if the nickel release rate exceeded the threshold.
Directive 94/27/EC, which is often referred to as 'the Nickel Directive', was adopted in 1994 and amends the Annex to Directive 76/769/EEC, regarding dangerous substances and preparations, by regulating the use of nickel and its compounds in certain products. The Annex describes the products covered by the Directive.
The requirements of the first indent deals with nickel-containing objects intended for pierced ears and other pierced parts of the body. These requirements were at first (EC, 1994) based on the nickel content of the alloy, with a requirement for an essentially nickel-free alloy: '*in post assemblies which are inserted into pierced ears and other pierced parts of the human body during epithelisation of the wound caused by piercing, whether subsequently removed or not, unless such post assemblies are homogeneous and the concentration of nickel - expressed as mass of nickel to total mass - is less than 0.05 %;*' This requirement has since been amended (EC, 2004) to read: '*in all post assemblies which are inserted into pierced ears and other pierced parts of the human body during epithelisation of the wound caused by piercing, whether subsequently removed or not, unless the rate of nickel release from such post assemblies is less than 0.5 µg/cm^2/week (migration limit)'*,
The second indent deals with nickel products coming into direct and prolonged contact with the skin. '*In products intended to come into direct and prolonged contact with the skin such as: - earrings, - necklaces, bracelets and chains, anklets, finger rings, - wrist-watch cases, watch straps and tighteners, - rivet buttons, tighteners, rivets, zippers and metal marks, when these are used in garments if the rate of nickel release from the parts of these products coming into direct and prolonged contact with the skin is greater than 0.5 µg/cm^2/week.*'
The third indent deals with the same type of products as listed in the second indent, but which have been covered by a non-nickel-containing layer: in products such as those listed in point 2 where these have a non-nickel coating unless such coating is sufficient to ensure that the rate of nickel release from those parts of such products coming into direct and prolonged contact with the skin will not exceed 0.5 µg/cm^2/week for a period of at least two years of normal use of the product.
With the amendment to the first indent, all the requirements are based on the rate of release of nickel from the surface of the metal or alloy rather than on the nickel content.
The Directive recognises that test methods are required for the Directive to be operational and accepts the need for a European Standard. The date for the specified measures to come into effect was related to the date of publication of references to the Standards by the Commission.

Reference to these standards was published as a Commission Communication in 1999 (EC, 1999), over five years after the publication of the Parliament and Council Directive. The

Communication lists three standards which specify test methods for each of the three indents in the Annex: EN 1810 (CEN, 1998a) dealing with the measurement of the nickel in piercing assemblies; EN 1811 (CEN, 1998b) dealing with measurement of the nickel release rate; and EN 12472 (CEN, 1998c) dealing with the accelerated wear and corrosion to be used for the detection of nickel release from coated items.
Nickel is mentioned in some other directives, which are not under discussion here. This includes Directive 98/83/EC (EC, 1998) which sets a limit for nickel in drinking water of 20 µg/l, Directive 89/109/EEC on materials and articles intended to come into contact with foodstuffs (EEC, 1989) which has been repealed and replaced by Regulation (EC) No 1935/2004 (EC, 2004) and comes into effect in December 2004, Council Directive 90/385/EEC on active implantable Medical Devices, Council Directive 93/42/EEC on Medical Devices and Council Directive 98/79/EEC on *in vitro* diagnostic Medical Devices, Council Directive 88/378/EEC on the Safety of Toys, Council Directive 89/106/EEC on Construction Products, and Directive 2001/95/EC on general product safety.

3. Description of exposure

Most of the information given below was extracted from the Risk Assessment Report on nickel and the accompanying Background Report (RAR, May 2005).

3.1 Target Population

The selected population for this case is the population wearing nickel-containing alloys against their skin, which means the total population. All people might develop a contact allergy to nickel. In the Netherlands this means a population of 16 million people.

However, a percentage of this population already has a contact allergy to nickel. There are many investigations into the occurrence of nickel allergy. In order to quantify this problem, two methods can be used. Clinical patch test studies can be used which involve collection of data from consecutively patch tested patients at dermatological centers. Secondly, epidemiological investigations of different populations, the general population included, can also be used. The first method is a relative inexpensive method for monitoring the skin sensitisation pattern in a given population, whereas the latter method is necessary in order to measure the frequency of sensitized individuals in the general population, even though the technique is much more expensive.
Table A8.1 below shows the results of several, more recent, clinical patch test studies:

Table A8.1. Results of clinical patch test studies (copied from Nickel RAR, May 2005)

Study *	Country	Year	Number of patients tested			Percentage positive to nickel		
			Male	Female	Total	Male	Female	Total
Lunder (1988)	Yugoslavia	1972-76			1945			6.7
		1977-81			2082			6.3
		1982-86			2373			9.1
Enders et al. (1989)	Germany	1977-83			11962	2.6	13.7	9.2
		1987			1845	4.5	23.9	16.7
Christophersen et al. (1989)	Denmark	1985-86	696	1470	2166	5.1	20.7	15.6
Storrs et al. (1989)	North America	1984-85			1123			9.7
Nethercott & Holness (1990)	Canada	1981-87	335	294	629	5.1	16.7	10.5
Shehade et al. (1991)	UK			4719				18.5
Nethercott et al. (1991)	North America	1985-89	2170	2876	5046			10.5
Lim et al. (1992)	Singapore	1986-90	2634	2923	5557			17.7
McDonagh et al. (1992)	UK		248	364	612	4.4	32.7	21.2
Schnuch et al. (1997)	Germany				36720	4.8	18.3	12.9
Marks et al. (1998)	North America	1994-96			3108			14.3
Dawn et al. (2000)	Scotland	1982	307	493	800	7	22	16
		1997	191	669	860	7	26	22
Johansen et al. (2000)	Denmark	1985-86	397	835		4.2	18.3	
		1997-98	423	844		4.9	20.0	
Kanerva et al. (2001)	Finland				1693			14.6

* Table reproduced from RAR (May 2005), see for references the Nickel RAR.

Some results of epidemiological investigations of different populations, the general population included, are given in Table A8.2, which shows the prevalence of skin sensitisation. The prevalence is the proportion of already sensitized persons in the total population at risk, at a given point in time.

The outcome of the studies presented is rather uniform, with a prevalence among females in the most recent studies above 20% (ranging from 7 to 38.8%) which is much higher than the prevalence among men (ranging from 0.8 to 17%). The population already sensitized in the Netherlands is estimated to be 2 million (12.5%). This number is based on the assumption that 20% of the women (total 8 million) and 5% of the men (total 8 million) suffer from nickel allergy. The reason that women have higher prevalence number than men, is due to the fact that women are generally higher and more often exposed to nickel, for instance, via jewellery. Women are not more susceptible to nickel.
The different studies must be compared with caution because the investigated groups are more or less selected and the age structure differs among the studies.

Table A8.2. Prevalence of nickel allergy in different populations (copied from Nickel RAR, May 2005)

Reference *	Study population	Number of persons investigated			Prevalence %		
		M	F	Total	M	F	Total
Menné (1978)	Female non-dermatological inpatients	-	213	213	-	9.4	
Prystowsky et al. (1979)	Paid adult volunteers	460	698	1158	0.9	9.0	
Peltonen (1979)	General population	478	502	980	0.8	8.0	
Kieffer (1979)	Veterinary students	247	168	415	2.8	9.8	
Magnusson & Möller (1979)	Orthopaedic patients	106	168	274	1.0	10.0	
Menné et al. (1982)[1)]	General population	-	1976	1976	-	14.5	
Boss and Menné (1982)	Hairdressers – school	-	53	53	-	20	
Menné and Holm (1983)	Female twins	-	1546	1546	-	9.6	
Larsson-Stymme and Windström (1985)	Schoolgirls	-	960	960	-	9.0	
Schmiel (1985)	Surgical inpatients and hospital staff	244	259	503	1.6	7.7	
von Hums (1986)	Schoolchildren	135	131	266	-	7.0	
van der Burg et al. (1986)	Nursing (school)	29	188	217	-	13	
	Hairdressers (school)	12	74	86	17.0	27.0	
Widström & Erikssohn (1987)	Young men (military service)	216	-	216	1.4		
Dotterud & Falk (1994)	School children	223	201	424	8.5	21.9	14.9
Meijer et al. (1995)	Young men (military service)	520	-	520	1.9		
Mangelsdorf et al. (1996)	Aged population (age 68-87)	35	47	82			6
Mattila et al. (2000)	University students	96	188	284	3.1	38.8	26.8
Nielsen et al. (2001)	Adult population 1990			290	2.2	16.9	
	Adult population 1998			469	2.1	17.2	

1) In the investigation by Menné et al. (1982) the nickel allergy was diagnosed by history only.
* Table reproduced from RAR (May 2005), see for references the Nickel RAR.

3.2 Exposure to Nickel

3.2.1 General information

The most important nickel exposure results from nickel containing objects in close contact with the skin such as earrings, clasp of necklace, zipper, finger rings, medallions, metal identification tags, buttons, wire support of brassiere cup, buttons on jeans, watchbands, bracelets, spectacle frames et cetera.

Lidén et al. (1996) interviewed 111 subjects with allergic contact dermatitis (ACD, the clinical terminology of the effect of skin sensitisation) to nickel. The following objects were reported to have caused ACD most frequently (see Table A8.3).

Table A8.3. Sources of nickel objects which are common causes of allergic contact dermatitis (Liden ét al., 1996).

Type of object	% of subjects reporting symptoms
Ear ornament	76
Wristwatch	67
Button	49
Necklace	42
Finger ring	41
Zipper	41
Bracelet	28
Spectacle frame	12

All these articles are worn in prolonged and close contact with the skin. Earlier studies have indicated significant release from some of these articles.
Piercing with either ear posts or other body ornaments involves direct contact with a wound during the period of epithelisation, and following epithelisation, a contact similar to the “direct and prolonged” contact described above. Piercing of the ear lobes seems to be the main etiological factor leading to high prevalence of nickel allergic hypersensitivity in the population (Hostýnek et al., 2002).

Other exposures
There are other exposures to nickel than from jewellery, in particular exposure to coinage. In the draft report (Nickel RAR, May 2005) professional exposure was used as the basis of the evaluation of consumer exposure to coins. An exposure estimate was made based on the attachment of Nickel on fingertips after counting coins. Worst case estimations reached levels of 120 μg/day/840 cm^2 for adult men (is equal to 1 μg/cm^2/day, twice as high as norm in Directive) (see Appendix 8.1). Also, some other articles might result in skin exposure to nickel, including belt buckles, bottle openers, candle holders, hip flasks, key ring fobs, money clips, torch bodies, casings for pens and pencils, model railway lines, heads of golf clubs, swimming pool handrails, sliding gates for computer discs. Other possible sources of nickel exposure are the whole range of domestic kitchen appliances (cookers, fridges, freezers, dish washers, washing machines), tableware (knives, forks, and spoons), pots and pans, and kettles.
Metals and alloys are used as food contact materials, mainly in processing equipment, containers and household utensils but also in foils for wrapping foodstuffs. (Council of Europe 2001). High nickel levels in flour may originate from contamination during milling.

In addition, fats can contain nickel, probably owing to the use of nickel catalysts in commercial hydrogenation. Margarine normally contains less than 0.2 µg/g, but levels up to 6 µg/g have been found (Grandjean, 1984 quoted in IARC, 1990). The average contribution of kitchen utensils to the oral intake of nickel is unknown, but they could augment alimentary exposure by as much as 1 mg/day (Grandjean et al., 1989 quoted from IARC, 1990).
The presence of nickel in food (such as beverages, cereals, fish, milk) and in drinking water result in an estimated the daily uptake of 400 µg (Council of Europe, 2001). Other investigations confirm an average daily intake of nickel between 0.1 and 0.7 mg/day.

When assessing the risk of skin sensitisation the total nickel dose via the skin is not the most relevant dose metric. A better parameter relating to sensitisation is the amount of nickel ion per cm^2 skin (Kimber et al., 2001; Farage et al., 2003; Griem et al., 2003). To assess the risks of different nickel containing surfaces following direct and prolonged contact, data describing the nickel release rate/cm^2/week is used for the risk characterisation.
It is reasonable to assume that the release after epithelial piercing is higher than after direct and prolonged contact, since the release rate to plasma resulted in the release of twice as much nickel compared to artificial sweat (LGC, 2003). The release data using artificial sweat cannot be used, because prolonged contact caused corrosion of the alloy. Corrosion of the alloy does not occur when transiently exposed.
It is reasonable to assume that the release after transient contact is considerable lower than after direct and prolonged contact.

3.2.2 Nickel release from products before and after the measure

In Sweden, Lidén and Johnsson conducted a study in 1999, measuring the nickel release in 725 items intended for direct and prolonged contact with the skin. In 25% of the items, nickel release, as shown by a positive DMG test, was detected. In 15 posts intended for use during epithelisation after piercing, 60% contained more than 0.05% nickel. These products do not comply with the requirements of the nickel Directive (Lidén and Johnsson, 2001). In a follow-up study (2002/2003), it was shown that 8% of 786 items released nickel and that 17% of 18 piercing posts contained too much nickel. This indicates a significant reduction of items with nickel release and means that producers and retailers have made serious efforts to adapt to the requirements (Lidén and Norberg, 2005).
In Denmark, 250 ear studs/rings, bracelets and necklaces from Danish school girls in 1999 were tested using the DMG test and none was found positive. The only metallic items found positive were inexpensive hairpins and old wrist watches where the plating had worn off (Jensen et al., 2002).
In the Netherlands the Dutch Food and Consumer Product Safety Authority (VWA) investigated the effects of the nickel Directive. In January 2001, the Inspectorate for Health Protection started a pilot to monitor the nickel content of jewellery at the start of the implementation of the law. Twelve percent of the samples (total of 164) exceeded the legal limit. These products were mainly jewellery (toys) and buttons. A second control was performed in September 2002. Two samples out of 118 exceeded the legal limit (<2%). It was concluded that since the introduction of the legislation, the number of products with high release of nickel on the Dutch market has decreased (Bosman, 2003).

3.2.3 Nickel allergy cases before and after the measure

There is evidence that the Danish legislation limiting the use of nickel in objects in direct and prolonged contact with the skin to a release less than 0.5 µg Ni/cm^2/week as measured by the dimethylglyoxime assay has resulted in decreased prevalence of sensitisation in the younger population (Johansen et al., 2000; Nielsen et al., 2001; Veien et al., 2001; Jensen et al., 2002). In Denmark, patch-test results from eczema patients were collected in a 6-month period in 1985-1986 and again in 1997-1998. Nickel was the most common contact allergen in both studies. In children (0-18 years of age) the frequency of nickel allergy decreased from 24.8% in the first study period to 9.2% in the second study period (Johansen et al., 2000).
In another study by Veien et al. (2001), from 1986 to 1989, 35 of 1135 (3.1%) men and 628 of 3024 (20.8%) women patch tested had positive reactions to nickel. From 1996 to 1999, 48 of 1104 (4.3%) men and 424 of 2193 (19.3%) women had positive patch tests to nickel. However, during the first period, 155 of 702 women under the age of 20 (22.1%) had positive patch test to nickel, compared to 54 of 324 (16.7%) during the second period.
Jensen et al. (2002) tested girls in public and high schools in the period March 1999 to March 2000. It was found that 17.1% of the girls in the high school group (17-22 years, 275 girls) demonstrated a positive patch test reaction to nickel. In contrast, the prevalence of nickel sensitisation in the public school group (10-14 years, 427 girls) was only 3.9%. However the comparison of different age groups is not valid in this case, because the younger girls can still develop nickel allergies. The prevalence of the latter group may be increased when they reach higher age. Comparing girls with and without pierced ears, the prevalence of nickel sensitization was significantly higher in girls with ears pierced before, but not after, 1992 (Jensen et al., 2002).
Schnuch et al. (2003a/b) presented data from Germany on a large group of patients tested between 1992 and 2001. The annual frequency of sensitization to nickel was analyzed in women and men in four age subgroups. In young women (<31), the prevalence of contact allergy to nickel decreased significantly from 36.7% in 1992 to 25.% in 2001. In young men in the same age group, the prevalence dropped from 8.9% to 5.2% in 2001. This decrease was not found in the older age groups.

These results (presented together in Table A8.4) suggest that the lower release rate contributes to prevention of new cases of nickel allergy. The reduction in prevalence observed by Johansen et al., (2000) was approximately 60% amongst youngsters (both sexes combined). In the study by Veien et al. (2001) no such pronounced effects were observed, for all women a reduction of approximately 10% could be derived. Remarkably, the effect of the measure was higher amongst young women in that study (approximately 25%). A preliminary conclusion may be that youngsters, of which a large part has not yet developed nickel allergy, will benefit more from the measure than the other part of the population. Optimistically, a reduction of 60% in nickel allergy prevalence could be achieved. A reduction of 30% is probably more realistic and thus will be used in DALY calculations.

Table A8.4. Overview of investigations from literature on the effect of legislation on nickel

Reference	Study population	Age group (year)	Years of investigation	Incidence of nickel sensitization	Reduction
Johansen et al. (2000)	children	0-18	1985-1986	24.8%	±60%
			1997-1998	9.2%	
Nielsen et al. (2001)	women/men	15-22 and 23-41	1990	16.7% / 0% and 17.0% / 2.8%	Not to ±18%
			1998	11.8% / 2.6% and 20.3% /1.7%	
Veien et al. (2001)	women	<20 (all)	1986-1989	22.1 % (20.8%)	±25%
			1996-1999	16.7% (19.3%)	
Jensen et al. (2002)	girls	10-14	1999-2000	3.9%	
		17-22		17.1%	
Schnuch et al. (2003a/b)	women/men	<31	1992-	36.7% / 8.9%	±30% / 44%
			2001	25.8% / 5.2%	

There is also evidence that the Danish legislation has also prevented current eczema in nickel sensitive patients (Menné, 1998). This suggests that this rate of release is sufficient to prevent elicitation of symptoms in a significant proportion of nickel-sensitized individuals. It is possible that not all subjects with nickel allergy in all circumstances of exposure will be protected by the 0.5 µg/cm^2 limit as studies with nickel sulphate has shown that the lowest concentration resulting in a positive patch test in nickel sensitive subjects corresponds to 0.05 µg Ni/cm^2 (Uter et al., 1995). Exposure to nickel sulphate in a patch test lasting 48 hours can be considered as a direct and prolonged contact. Whilst it is not possible to equate this figure of 0.05µg Ni/cm^2 with the release rate of 0.5 µg Ni/cm^2/week, the result would suggest that a lower release rate would be needed to ensure that symptoms are prevented in all nickel sensitive patients in all circumstances.

In the Netherlands, on request of the Dutch Food and Consumer Product Safety Authority (VWA), a pilot study was performed by dermatologists (at the AMC in Amsterdam). In 2001, 2701 patients were tested using a patch test. At 428 patients (15.8%) a positive reaction on nickel was found. Of the positively tested patients 4.6% were males and 26% were females. Some questions were asked by telephone afterwards among 152 positively tested patients. From these interviews it could be concluded that the number of complaints by nickel allergy patients was decreased from 64 to 4% (Bosman, 2003). For risk characterisation it will be assumed that the decrease in exposure is 100%, thus leading to zero exposure after the measure.

4. Description of toxicity

Most of the information given below was extracted from the Risk Assessment Report on nickel and the accompanying Background Report (draft RAR, May 2005).
Nickel is well known as a skin sensitizer, and is one of the most frequent skin sensitizers in man. The Ni^{2+} ion is considered exclusively responsible for the immunological effects of nickel (Menné, 1994). Nickel allergy is a Type IV allergic reaction. Characteristic for this type of reaction is that it is cell mediated (mediated by T-lymphocytes) and delayed (the reaction appears 24-72 hours after exposure).
Nickel allergy manifests itself as allergic contact dermatitis, which is an inflammatory reaction in the upper part of the skin (epidermis) with erythema, infiltrations, and vesicles. Dermatologists use the terms allergy and sensitisation synonymously, as well as eczema is used as a synonym for dermatitis. Menné (1992 as reported in RAR, May 2005) describes that initially in 1889 nickel dermatitis was recognised as 'Das Galvanizierekzem'. In 1925 patch testing proved nickel allergy to be the cause of dermatitis in the electroplating industry. Occupational nickel dermatitis was common in the 1920's and 1930's while consumer nickel dermatitis first appeared in the early 1930's.

No animal data on sensitisation with nickel metal have been found. However, some studies on skin sensitisation in guinea pigs have been performed with nickel sulphate (mostly positive) or nickel chloride (see Nickel Background document, 2005). There is an abundance of reports on human sensitisation with nickel (see for more information chapter 3).
Nickel related sensitisation is normally diagnosed by patch testing with 5% nickel sulphate in petrolatum applied to the back of the person tested under occlusion for 2 days. The reaction to the patch test is not immediate, and for this reason the result is read after 2 days, at which time a positive effect is clearly visible.
Individuals sensitized to nickel fall into three groups:

- those with previous eczema present under nickel-releasing objects in direct and prolonged contact with the skin. They do not show signs of eczema, as they avoid contact with nickel objects;
- those with current eczema, because they are currently exposed to nickel released from items in direct and prolonged contact with the skin;
- those suffering from chronic vesicular hand eczema.

It is commonly accepted by dermatologists that sensitisation (induction) requires more intense exposure than elicitation of nickel dermatitis in already sensitized persons. Among already sensitized persons the degree of reactivity to nickel varies. Many have been shown to react to 5% nickel sulphate in petrolatum which is the concentration used in diagnostic patch testing. A minority can react at concentrations as low as 0.001% (Uter et al., 1995). The threshold for reactivity is lower when the area is occluded compared to when it is not occluded, and further the threshold is lower on irritated skin compared to normal non-irritated skin in the absence of any form of occlusion (Menné and Calvin, 1993 as reported in RAR, May 2005) as well as on closed exposure (Allenby and Basketter, 1993 as reported in RAR, May 2005).

Both in the Uter (1995) and the Andersen studies there are patients reacting to very low nickel doses representing the very most sensitive persons in the population. The biological relevance of the results is supported by the reactivity in nickel sensitive patients to alloys with a very low nickel release rate. On the basis of the available data it is not possible to set a scientifically based threshold for elicitation (NOEL) in nickel sensitized individuals. Data gathered after the Danish legislation limiting nickel release from consumer items came into force suggest that the majority of the population are protected by a release rate of 0.5 µg Ni/cm^2/week for items in close and prolonged contact with the skin.

Eczema is often obvious to the affected person. Exposure to nickel from consumer products, when recognized, can be avoided rather easily. A much larger problem related to nickel allergy is however the increased risk of hand eczema, which in the general population appears with a prevalence of 10%. In populations sensitized to nickel, up to 40% have been shown to develop hand eczema, indicating that nickel allergy is one of the most prominent risk factors for hand eczema (Menné et al., 1982, Meding and Swanbeck, 1990). A study by Wilkinson and Wilkinson (1989 as reported in RAR, May 2005), examined both the prevalence of nickel sensitivity in patients with hand eczema as well as the prevalence of hand eczema in nickel-sensitive patients. In the former instance, they found that nickel sensitivity in hand eczema patients appeared to be in the range of 12 to 17 percent; in the latter instance, the incidence of current hand eczema in nickel-sensitized patients appeared to lie between 17 to 24 percent. Hand eczema related to nickel allergy may result in chronic suffering, sick leave, change of jobs, early retirement, and large costs for the society (Menné and Bachman, 1979 as reported in RAR, May 2005).
It should be underlined that even though nickel allergy is a risk factor for hand eczema, it is not understood how these two diseases are connected mechanistically. Epidemiological studies demonstrate that there is a high risk of hand eczema in populations sensitized to nickel. In individual cases, interpretation is more difficult.

5. Current risk assessment

The suggested level of nickel release from nickel-containing alloys to prevent induction after direct and prolonged contact in a substantial proportion of a non-sensitized population is 0.5 µg Ni/cm^2/week as measured by EN1811. This conclusion is based on the experience acquired in Denmark following the introduction of legislation with a cut-off of 0.5 µg Ni/cm^2/week as measured by the DMG assay. This experience suggests that this rate of release contributes to the prevention of new cases of nickel sensitisation.
The suggested level of nickel release from nickel-containing alloys to prevent elicitation after direct and prolonged contact in a substantial proportion of a nickel-sensitized population is 0.5 µg Ni/cm^2/week as measured by EN1811. This conclusion is based on the experience acquired in Denmark following the introduction of legislation with a cut-off of 0.5 µg Ni/cm^2/week as measured by the DMG assay. This suggests that this rate of release is sufficient to prevent elicitation of symptoms in a significant proportion of nickel-sensitized individuals. However, complete protection for the most sensitive nickel-sensitized persons may only be achieved at levels that could be an order of magnitude lower than the cut-off of

0.5 µg Ni/cm^2/week as measured by EN1811. On the basis of the available data it is not possible to set a scientifically based threshold for elicitation (NOEL) in nickel-sensitized individuals, as depicted above.
It is not possible to set thresholds for induction and elicitation after intermittent and semi-direct exposures.

6. Calculation of Public Health Gain

6.1 Decrease in exposure

Studies by Lidén (2001 and 2005) and by the VWA (Bosman, 2003) showed a decrease in the presence and release of nickel from alloys (see section 3 of this Appendix). In the Netherlands, nickel release above the limit was only found in less than 2% of the tested items. For the present case, it is assumed that the exposure will decrease further, and exposure will be below the legal limit.

6.2 Increase in Margin of Safety

The Margin of Safety was not determined.

6.3 Decrease in incidence of the effect

The effects of the Nickel Directive are twofold, which are described separately.
The first effect is the incidence of skin sensitisation itself. The utmost goal of the Nickel Directive is to protect people from getting a nickel allergy. By removing or decreasing the possibility just like the decrease in amount to be exposed to nickel, the number of newly sensitized people by nickel will decrease. However, only prevalence numbers are available. These numbers are indicative for the number of individuals who would have been sensitized to nickel when the measure was not amended.
The second effect is elicitation resulting in contact eczema. People who are already sensitized are less or not at all exposed to nickel because of the reduced release of nickel from consumer products. Thus, patients still do have nickel allergy, but they do not have clinical complaints anymore.
For this case, it is difficult to assess the potential health gain, because people having a nickel allergy would have already tried to avoid exposure as much as possible, before the measure was taken. This, however, is an ideal situation, because a part of this subpopulation is still exposed incidentally (subject is not aware of nickel content) or is highly sensitive to nickel. Therefore, for this case it is assumed that 10% of the subpopulation will still be affected by their nickel allergy (which is a guessed estimate).

1.) The decrease in incidence of skin sensitisation:
In chapter 3 information is provided from a few studies on the prevalence of nickel allergy in young age groups, before and after the measure. It is expected that these youngsters will benefit most from the measure, because a large part is not yet sensitized. Furthermore it is known that the prevalence of nickel allergy amongst women is 20% and for men 5%. Then,

as a starting point for calculating the decrease of incidence the birth and mortality rates could be used, because certain percentage of the newborns will be sensitized in the future when policy is unchanged. From Statistics Netherlands; on average over 2001 to 2004 101,660 boys and 96,784 girls are born annually (adjusted for mortality during first 10 years of life which is 1,304, indicating that these figures represent number of newborns still alive at age ten).
For the present case it will be assumed that children aged 0 to 10 years have not yet developed nickel allergy. If the policy remains unchanged 20% of the girls and 5% of the boys would become sensitized every year. This mounts up to a total of 24,400 (rounded).
A reduction in prevalence was observed of maximally 60% due to the measure (see subsection 3.2.3). In the present case we use a reduction of 30% which provides an incidence after the measure of 17,100 (rounded). The decrease in incidence of skin sensitisation is thus 7,300 (rounded).

2.) The decrease in incidence of elicitation (thus the prevention of persons having complaints of contact dermatitis):
As mentioned above, a population of 12.5% of the total Dutch population already has obtained a nickel contact allergy. The population that might improve by this measure is 0.125 x 16 million = 2,000,000. However, assuming that only 10% really has complaints and suffers from the disease (percentage on avoiding behaviour established by estimation), the affected population is smaller, namely 200,000.
After the measure, the number of subjects affected by nickel allergy are also (see above) assumed to decrease by 30%. This assumption is based on the fact that the reason of still being affected is caused by unforeseen incidental exposures rather than dependent on the sensitivity of the individual. Although there are known cases, where subjects react to very low amounts of nickel.
After the measure 140,000 subjects will still have complaints, this indicates a reduction of 60,000 subjects affected by nickel.

Table A8.5. Overview of the calculations of the public health gain; incidence and DALYs (see section 6.4 for more information)

Effect of measure: decrease in	Target population	Decrease in incidence [3]	Calculation	DALYs
sensitization	24,400 [1]	7,300	x 60 x 0.1 x 0.07 [4]	3,066
elicitation	200,000 [2]	60,000	x 0.07	4200

1 ± 101,000 boys and ±97,000 girls born each year x 5% (boys) or 20% (girls) [= sensitized each year] = 24,400
2 12.5% [of Dutch population with nickel allergy] x 16 million x 10% [= having complaints] = 200,000
3 decreased with 30% (from Table 4)
4 60 = years lived after onset disease, set at 15 years
0.1 = percentage of people with nickel allergy with complaints
0.07 = weighing factor for constitional eczema (here used for contact eczema)

6.4 Derivation of DALYs

There is no derived weighing factor for contact eczema. In the National Public Health Compass, the weighing factor of constitutional eczema is used, which is 0.07. This is also used for the nickel allergy in this case, although it might overestimate the health impact.

1.) The decrease in incidence cases of sensitization:
In the previous section 6.3 the reduction of incidence was estimated at 7,300 newly sensitized subjects per year. To translate this number in terms of health benefit is rather difficult. One requires the average year of onset of disease, the number of years a person lives with nickel allergy, and how long a person suffers from contact eczema. Furthermore, as a subject learns to avoid nickel the percentage still being affected should be applied. In short, information on the course of the disease is desired.
The average year of onset stems from the assumption that people starting from ten years of age become sensitized and that people above 20 years of age will not be affected much by the measure. Therefore the average age of onset is set at 15 (based on above and expert judgment). The life expectancy is set at 75 years (Statistics Netherlands) which results in 60 years living with nickel allergy. As nickel allergy does not cause lethality in the population, the DALY is solely based on YLD. Contact eczema was assigned a disability weight of 0.07, which is used in the derivation of DALYs (see above). As mentioned above, just ten per cent of sensitized subjects will be affected by nickel.
Using these data, the amount of DALYs which can be 'gained' annually is the product of 7,300 * 60 * 0.1 * 0.07 which equals to 3,066 DALYs.

2.) The decrease in elicitation (thus the prevention of having complaints for allergic contact dermatitis):
The health benefit can be calculated using the weighing factor of 0.07 for contact dermatitis and the above calculated number of people (about 60,000) potentially protected by the measure. The DALY is thus based on the assumption that these people would otherwise still have complaints.
The amount of DALYs 'gained' by the measure is then: 60,000 * 0.07 = 4200 DALYs.

The total amount of possible health benefit caused by implementing the Nickel Directive is thus 4200 DALYs per year plus an additional 3,066 DALYs per year.

7. Discussion

The health gain from the measure was divided into subjects who were prevented from becoming sensitized and into subjects who no longer are affected by nickel exposure (prevention of elicitation). For this case of skin sensitisation, the estimated DALYs that could be 'gained' resulted in high values. It was estimated that annually 3,000 (rounded) DALYs could be ascribed to prevention of becoming sensitised and 4000 DALYs (in total 7000; rounded) from prevention of obtaining clinical effects in the sensitized population. This high value is mainly determined by the large number of subjects affected by nickel allergy and the

relative young age at onset of disease. The clinical aspect of nickel allergy is not regarded severe as the disability weight is set at 0.07.
There are, however, uncertainties in the derivation of the DALY. Below are described the assumptions and resulting uncertainties which influence the outcome.

- *Difference in prevalence and population rates as a measure for incidence rates*

The decrease in newly sensitized individuals is clearly a result of the Nickel Directive. Studies have shown that the percentage of consumer products with too high nickel releases has decreased due to the Nickel Directive. Further, studies conducted in European countries have shown that the prevalence numbers of nickel allergy decreased over time. For the DALY calculations for prevention of sensitisation, the Danish situation was regarded. Two studies, by Johansen et al., 2000 and Veien et al., 2001, described a decrease in nickel allergy prevalence in Denmark. The reduction in prevalence in these studies ranged from approximately 5% to 60% and showed that youngsters would benefit most from the measure, because a larger fraction is not yet sensitized. On average it was decided to use a decrease in prevalence of 30%.
Because the Nickel Directive was also affective in the Netherlands, it was assumed that a similar decrease in prevalence would also occur in the Netherlands. It is unknown, however, what the actual decrease in newly sensitized individuals is. Nevertheless, the difference in prevalence numbers is considered valid here, because the results showed consistency around Europe.
The prevalence only provides an indication of the amount or percentage of the population that has not been sensitized in regard to a similar age group a few years ago. It does not directly display the decrease of incidence (number of new sensitized subject per year) of nickel allergy. To derive the incidence of newly sensitized subjects to nickel, birth and mortality rates were used in combination with the prevalence numbers before and after the measure. Since newborns are not sensitized by birth a fraction would become sensitized in coming years (assumption from the age of ten). The important assumption made, was that the prevalence would remain the same over time in an unchanged situation (no measure taken). This provides an approximation of the incidence rate of nickel sensitisation. The number of newborns was corrected for mortality up until the age of ten, but no correction was made after the age of ten. This may lead to an overestimation, because subjects may have died before they obtained nickel allergy. However, this overestimation is considered marginal since the mortality rate between 10-30 years is annually 1,300 on a total population of 196,000 (Statistics Netherlands).

- *Calculating DALY for previous sensitized individuals*

The other large determinant in deriving the health benefit from the Nickel Directive, is the protection of already sensitized individuals. Already nickel sensitized individuals constitute a large part of the population (2 million). Hence the derived DALY for this subpopulation is mainly determined by the number of the population. However, this derived DALY value is also subject to uncertainty.
As mentioned above the reduction observed in Denmark was assumed to be valid for the Dutch situation. This reduction in prevalence does not influence the individuals already sensitized. However, this figure (-30%) is still indicative for the size of subpopulation that would still be affected by nickel (two assumptions used in the calculation, namely 10% or

100% of the sensitized subjects). Hereby, a linear relation between sensitisation and elicitation was assumed in individuals. In other words, the percentage still affected was reduced from 10% to 7%. Whether this linear relationship between sensitisation and elicitation is realistic is unknown. In the case that the elicitation threshold is found to be disproportional lower than the sensitisation threshold the derived DALY should also be lower, because the reduction is derived from the same relationship.

- *Course of disease: nickel allergy*

Nickel allergy is the most common skin allergen known to humans. The prevalence of nickel allergy is considerably high. Therefore, nickel allergy is well recognised and registered. Still there are uncertainties about nickel allergy. The average age of onset of the disease was set at 15 years based on the assumption that subjects will become sensitized between the age of ten and twenty. This is strengthened by the observation that subjects above twenty did not benefit much from the measure (Veien et al., 2001). There is no specific information on the onset of nickel allergy, but generally subjects become sensitized when starting to wear jewellery.

How subjects will be affected by nickel allergy is difficult to describe. Once sensitized, even very low amounts of nickel may be sufficient to elicit an effect. As a consequence subjects will learn to avoid contact with nickel. However, it was assumed that subjects would still be affected by nickel allergy due to incidental exposure or highly sensitivity to nickel. The release rate addressed in the Nickel Directive was set arbitrarily and not scientifically based. Actually, the release rate is rather crude, since in some cases the larger part of nickel is released in the first two days and the nickel release is then evened over the week (Gawkrodger, 1996). The high exposure in the first two days might already be sufficient to cause contact dermatitis. It was assumed that 10% of the subpopulation would still have clinical effects during their lives which is a guessed estimate. Further, detailed information on the frequency and duration of clinical effects are lacking. It was decided to use the average age of onset (sensitisation cases) or average age of subpopulation (elicitation cases) combined with the severity of contact dermatitis to derive the DALY. Likely, this is an overestimation of the actual situation, because it is not expected that the clinical effects will last for an entire year or consequent years.

For the reasons above the derived DALY values for the protection of already sensitized individuals and prevention of becoming sensitized are subject to uncertainty.

In conclusion, the health benefit to restrict nickel release from alloys to 0.5 $\mu g/cm^2$/week is clearly visible from the decrease in prevalence of nickel allergy and its symptoms. The derived DALY values are subject to uncertainty and should be regarded in orders of magnitude rather than point values.

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Appendix 8.1

Exposure estimation

The estimated values for professional dermal exposure of 0.04 mg Ni /day (typical) and 0.120 mg Ni/day (worst-case) as assessed in the Nickel RAR (2005) are used as the basis for the evaluation of consumer exposure. The exposure is for both hands (surface area 840 cm^2). It is however recognised that this will in many cases be an over-estimate and in some cases a considerable over-estimate.
The estimation of the above value is derived as described below (information from Nickel RAR, May 2005).
Fournier and Govers (2003 as reported in RAR, May 2005) investigated how much nickel, copper and zinc attaches to fingers after short contact with coins (Euros and Francs). Volunteers counted coins and the metal deposited on the inside surface of the three fingers used in counting (thumb, index, and middle finger) were collected by wipe sampling. For comparison the study included sampling of metals from fingers of persons doing everyday activities. The data obtained are tabulated below (Table A8.6). For shortness, the table does not include data for contact with Francs. Unfortunately Fournier and Covers do not specify the surface area of the fingers. Thus it is not possible to assess the exposure in terms of mass of nickel per surface area of the skin.

Table A8.6. Dermal exposure to nickel after short contact with coins (Euros). As an average the skin-metal contact lasted 2.6 seconds per coin (Fournier and Govers, 2003). (Table copied from RAR, May 2005).

Metal	**Mass (µg) deposited on three fingers by one manipulation of a single coin (Arithmetic average and 90% confidence limits)**			**Mass (µg) on three fingers from everyday activities**
	Unwashed [1] coins	**Washed [2] coins**	**Polished [3] coins**	
Ni	0.23±0.06	0.26±0.07	0.012±0.006	3.0±0.5
Cu	1.4±0.2	1.3±0.2	0.10±0.01	11±2
Zn	0.26±0.03	0.28±0.05	0.07±0.03	18±3

1: The coins had been in circulation from 2-5 months. 2: The coins were washed (ultrasonic bath) in demineralised water. 3: The coins were thoroughly rubbed 10 times on each side using the same type of wipes as used to sample metals deposited on the fingers.

Bang Pedersen et al. (1974, as reported in RAR, May 2005)) investigated how much nickel attaches to hands after short contact with coins. The study included four sub-groups of persons as tabulated below.

Table A8.7. Dermal exposure to nickel after short contact with Swedish 1-crown coins containing either 5% or 25% Ni (Bang Pedersen et al., 1974). (Table copied from RAR (May 2005)).

Sub-group of persons	**N** [2]	**Dermal exposure (both hands) to Ni µg/person**	
		Range	**Mean**
Persons counting 100 pieces of ether-washed 1-crown coins for 5 minutes	13	5-70	32
Persons counting 100 pieces of used 1-crown coins for 5 minutes	30	6-122	37
Employees in a department store were examined after 4 hours at work [3]	5	17-96	50
Patients at a department of dermatology. The patients had no particular contact with nickel on the day of the sampling.	10	10-18	16

1: At entry of the experiment persons washed their hands thoroughly for 3 minutes with water and soap. At the conclusion of the experiment they washed their hands in one litre of distilled water and soap containing no nickel. This portion of water was concentrated 10 times by evaporation, after which it was analysed for content of nickel. The sub-group of patients had not washed their hands before coming to the department of dermatology.
2: Number of observations.
3: One of the employees worked at the information desk, where she also had to count the coins coming from the bank. Two employees sold cosmetics, one sold bicycles and toys and one sold clothes. The four last-mentioned persons took payment for the goods.

For the ether-washed coins immersed for 24-h in synthetic sweat Bang Pedersen et al. (1974 as reported in RAR, May 2005) reported the nickel release rate at a level of 8.5 µg/cm^2/24-h (1-crown, 5% Ni) and 12.2 µg/cm^2/24-h (1-crown, 25%). Most of the available data on nickel release from current European coins are given for coins immersed in sweat for one week. Although it is difficult to compare the data on nickel release given by Bang Pedersen et al. (1974) to other more recent data sets it appears prudent to consider the measured data (Table A8.6) on dermal exposure useful for the assessment. Per coin it is noted that the mass of nickel deposited on the skin (Table A8.7) was rather similar to the recent data (Table A8.6 reported by Fournier and Govers (2003 as reported in RAR, May 2005). The typical exposure was estimated as the median of the tabulated means for the three sub-groups of persons exposed to coins. The typical level (≈40 µg/person) was seen for persons counting used 1-crown coins. The tabulated data have no information on the 90th percentile. Taking the size of the data sets into consideration the worst-case exposure was estimated at the upper limit of the range of exposure observed for the large data set (30 observations) of persons counting used 1-crowns. Thus the worst-case exposure was estimated at a level of ≈120 µg/person. It has to be noted that estimated levels are considered valid for full-shift exposure although the data were obtained for a short period of rather intensive counting of coins.
The measured data (Table A8.6) on exposure were obtained by the washing of both hands. For a man the mean surface area for both hands, including the fingers and back of the hands is 840 cm^2 (US EPA, 1997). This area would allow an estimate of exposure in terms of mass of nickel per surface area and day. As a hypothesis the fingertips of persons exposed to coins may by contrast to other parts of the hands have a high load of nickel. It is noted that no data

are available for testing the validity of such hypothesis, but it has to be expected that an estimate per surface area and day may bias the exposure of fingertips towards low levels. It is noted that some of the measured data were collected for a short-term (5 min) intensive counting operation. In principle the cumulative mass of nickel deposited on the skin must, to some extent, be positively correlated to the number of coins counted per unit time and the span of the counting period. Thus the estimated typical and worst-case full-shift exposure levels should be considered biased towards low levels. For the assessment the nickel deposited on the skin is considered being all metallic. The typical and reasonable worst-case dermal exposure of the hands is estimated as given below.

Table A8.8. Estimated typical and reasonable worst-case dermal exposure of the hands after short contact with tools and coins

Nickel species [1]	**Typical exposure** [2]			**Worst-case exposure** [2]		
	Nickel species as % of 'total' nickel	**Exposure to 'total' nickel (µg/day)**	**Exposure to nickel species (µg/day)**	**Nickel species as % of 'total' nickel**	**Exposure to 'total' nickel (µg/day)**	**Exposure to nickel species (µg/day)**
M	100	40	40	100	120	120

1: M = Nickel is considered to be all nickel metal. 2: The exposure is for both hands (surface area 840 cm^2).

For consumer use of coins it may be assumed that exposure is lower than professional exposure.

Appendix 9 Case report Nitrosamines

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(TNO)

1. Introduction

This case addresses the influence of legislation on exposure to N-nitrosamines from consumer products in the Dutch general population. Legislative measures regarding nitrosamines were expected to contribute potentially considerably to improved public health, as these suspected carcinogenic substances are present in several consumer products and exposure might be considerable.

2.1 Background information

2.1 C, M, R or S, Legislation

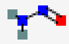
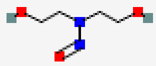
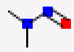
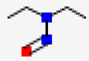
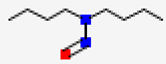
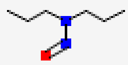
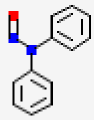
Nitrosamines (N-nitroso di-n-alkanol amines (NDAA)) are a large group of chemical compounds. Table A9.1 gives an overview of the most common nitrosamines to which humans are exposed. For those mentioned in the table, only NDMA (n-nitroso dimethyl amine) has been classified, as follows:

- Carc. Cat. 2; R45 (may cause cancer)
- T+; R26 (Very toxic by inhalation)
- T; R25-48/23/24/25 (Also toxic: danger of serious damages to health by prolonged exposure through inhalation, in contact with skin and if swallowed)

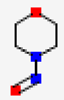
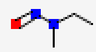
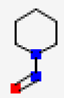
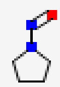
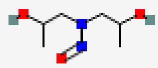
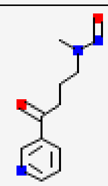
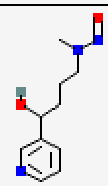
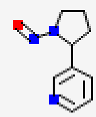
Next to that, several of the nitrosamines consumers are exposed to are evaluated by the Agency for Research on Cancer (IARC) as Group 2a: probably carcinogenic to humans (NDEA, NDMA) or as Group 2b: possibly carcinogenic to humans (NDBA, NDELA, NDPA, NMOR, NMEA, NPIP, NPYR, NNK).

Relevant legislative documents concerning nitrosamines in consumer products are described below for different sources of exposure.

Table A9.1. Overview of the most common nitrosamines to which humans are exposed

Abbrev.	Full name	CAS-number	Formula*	Structure*
NDAA	nitrosamine	35576-91-1	H_2N_2O	
NDELA	n-nitroso diethanol amine	1116-54-7	$C_4H_{10}N_2O_3$	
NDMA	n-nitroso dimethyl amine	62-75-9	$C_2H_6N_2O$	
NDEA	n-nitrosodi-ethylamine	55-18-5	$C_4H_{10}N_2O$	
NDBA	N-Nitrosodi-n-butylamine	924-16-3	$C_8H_{18}N_2O$	
NDPA	n-nitrosodi-n-propylamine	621-64-7	$C_6H_{14}N_2O$	
NDP(h)A	n-nitroso-di-phenylamine	86-30-6	$C_{12}H_{10}N_2O$	

rivm

Abbrev.	Full name	CAS-number	Formula*	Structure*
NMOR	n-nitrosomorpholine	59-89-2	$C_4H_8N_2O_2$	
NMEA	N-nitroso-methylethylamine	10595-95-6	$C_3H_8N_2O$	
NPIP	N-Nitrosopiperidine	100-75-4	$C_5H_{10}N_2O$	
NPYR	N-Nitrosopyrrolidine	930-55-2	$C_4H_8N_2O$	
NDiPLA	n-nitroso diisopropanol amine	53609-64-6	$C_6H_{14}N_2O_3$	
NNK	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone	64091-91-4	$C_{10}H_{13}N_3O_2$	
NNAL	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol	76014-81-8	$C_{10}H_{15}N_3O_2$	
NNN	N'-nitrosonornicotine	64162-58-9	$C_9H_{11}N_3O$	

2.1.1 Teats and soothers

The European Union has adopted a Directive (93/11/EEC) concerning the release of nitrosamines and nitrosatable substances from teats and soothers.
The migration of nitrosamines and nitrosatable substances during 24 hours at 40 °C in saliva simulant shall not exceed:
- N-nitrosamines, in total: 0.01 mg/kg rubber product
- N-nitrosatable substances: 0.1 mg/kg rubber product

The Netherlands has more extensive national legislation on teats and soothers. Teats and soothers must comply with Chapter III of the Packaging and Food-Utensils Regulation (Food and Commodities Act). The Regulation classifies teats and soothers as category I (baby bottle teats and articles intended to be taken into the mouth by babies or young children). This implies that only those starting substances and aids that have been approved for this category may be used. Furthermore, compared to category II rubber products, the specific migration limit (SML) has been lowered with a factor 10, considering the low body weight of babies and young children compared to adults. The specific migration limit (SML) of approved substances is determined in mg/teat. The overall migration from teats and soothers shall not exceed 20 mg/teat. For teats the overall migration and specific migration limits must be divided by 5, as it is assumed that a child uses 5 bottle teats a day (VWA, 2002).

2.1.2 Cosmetics

In Annex II of Directive 76/768/EEC it is stated that cosmetic products shall not contain nitrosamines or secondary dialkanolamines (No: 410 and 411), because of the carcinogenic properties of nitrosamines. Nitrosamine contamination of cosmetics may be caused by nitrosamine-contaminated ingredients or through the nitrosation of amines present in the finished product by nitrosating agents.
An exception was made for products for which the following ingredients were used:
- Dialkanolamides of fatty acids (Annex III; no. 60)
- Monoalkanolamines (Annex III no. 61) and
- Trialkanolamines (Annex III no. 62)

These substances are frequently used in cosmetics as emulsifying agent and surface active agents. For both the use and the quality of these raw materials conditions have been set with respect to the formation of nitrosamines in the end products.
It was determined that these ingredients
- should contain at maximum 50 µg of N-nitrosodialkanolamines (NDAA)/kg
- are not to be used in combination with nitrosating agents
- are not to be stored in recipients that contain nitrite,
- the level of secundary alkanolamines (easily nitrosatable substances) may not exceed:

(i) 5% of dialkanolamides of fatty acids, and
(ii) 0.5% of monoalkanolaminen and trialkanolamines

(Source: VWA/KvW Noord rapport NDCOS017/04, januari 2004)

2.1.3 Balloons

The Ministry of Health, Welfare and Sports, and the suppliers or importers of balloons in the Netherlands made an agreement to put a warning on the labels: 'Warning! For safety reasons do not take balloons into the mouth and only inflate with a balloon pump'. This warning should be present on the labels from May 1st 2004. In 2006 additional legislation became into effect, setting a maximum level of nitrosamines and nitrosatable substances in balloons.

2.1.4 Other measures

In addition to these legislative measures, other developments might have influenced total exposure to nitrosamines, such as changes in food manufacturing, and campaigns to discourage smoking and to prevent children from being exposed to environmental tobacco smoke ('Smoking, not around children!').

Table A9.2. Overview of legislative measures with regard to nitrosamines and date of enforcement

Product	**Limits**	**Date of enforcement**	**Legislation**
Soothers and teats	0.01 mg nitrosamines /kg product 0.1 precursors mg/kg product	29-05-1991	Directive 93/11/EEC; Food and Commodities Act
Cosmetics	50 µg/kg	30-06-1993	Directive 76/768/EEC cosmetic products; Directive 92/86/EEC
Balloons	0.01 mg nitrosamines /kg rubber (nitrosatable substances 1 mg/kg rubber)	28-03-2006	Policy measure regarding safety of balloons, Ministry VWS, Staatscourant nr. 62 March 23 2006

2.2 General Information

2.2.3 Substance information

Nitrosamines (N-nitroso di-n-alkanol amines (NDAA)) are a large group of chemical compounds that have been found to be carcinogenic in all species of animals tested and are also suspected to be carcinogenic in man. There are more than 300 different nitrosamines. The names, abbreviations and CAS-numbers of the most common, most frequently measured/reported, nitrosamines, to which humans are exposed are presented in Table A9.1. Nitrosatable substances (or nitrosamine precursors) are substances which can be converted into nitrosamines by reaction with nitrosatable agents such as nitrite and/or nitrogen oxides and therefore may form a cancer risk too.

N-nitrosamines and/or nitrosatable substances are present, usually in trace quantities, in various environmental media such as tobacco and tobacco smoke, in certain food products such as beer and cured meat products, in cosmetics, in drugs, pesticides, indoor air and often in relatively high concentrations in certain occupational conditions, especially in the rubber and metalworking industries. N-nitrosamines and precursors that are present in rubber products originate from certain accelerators (carbamates) used for the vulcanization of rubber. Table A9.3 gives an overview of a selected number of exposure sources and routes. Not all of the nitrosamines that are presented in Table A9.1 are present in detectable amounts in all potential sources. In general, NDMA is most frequently measured as it has been measured in tobacco smoke, food, cosmetics, rubber products, pesticides and in several other potential sources of exposure such as interior air of new cars, alkylamine drugs and tanneries/dyes. The nitrosamines NDELA, NDiPLA and NMOR are frequently detected in cosmetics, whereas NNK, NNAL and NNN are tobacco-specific.

Table A9.3. Potential sources of exposure to nitrosamines for consumers (both adults and children).

	Exposure routes			Target population	
	Inhalation	Dermal	Oral	Consumer	
				children	Adults
Rubber consumer products					
Household gloves, garden hoses, bath mats, door mats, hot-water bags, band-aids, rubber stamps, slippers, erasers, etc.		X		LIMITED	YES
Electric cords, rubber tyres, rubber tiles		X		NO	YES
Erotic products and condoms		X	X	NO	YES
Rubber toys and other products					
Soothers and teats			X	YES	NO
Balloons		X	X	YES	YES
Rubber mouthing toys, snorkel, etc.		X	X	YES	YES
Rubber tiles at playgrounds, flippers, masks, etc.		X		YES	NO
Cosmetics					
Shampoo, shower gel, suntan lotion etc.		X		YES	YES
Background exposure					
Foods (cured meats, bacon, fish, beer)			X	LIMITED	YES
Endogenous formation	N/A	N/A	N/A	?	YES
Tobacco smoke - active	X			NO	YES
Tobacco smoke – passive	X			YES	YES
Pesticides	X	X	X	?	?
Drugs			X	?	?

2.2.4 Selection of exposure scenarios

For babies and toddlers, it is assumed that the main exposure will result from mouthing of rubber teats and soothers and potentially also from rubber balloons, and from use of children's cosmetics (care products). For adults, it is assumed that the main exposure through

consumer products results from dermal contact with nitrosamine containing cosmetic products. Dermal contact to rubber products most likely results in a relatively small contribution. Next to this it is likely that exposure by active and passive smoking (inhalation), and consumption of food (oral), leads to considerable background exposure among adults and children.
The exposure resulting from most other possible sources, such as dermal contact with other miscellaneous rubber products, dermal contact or inhalation of pesticides and the use of drugs will not be taken into account because contribution to the average exposure of the total population is assumed to be small and there are no legislative measures which have been implemented lately which have influenced exposure through these sources.
There is very little information available on exposure to nitrosamines or nitrosatabe compounds by the use of condoms. Two publications yield contradicting results: Proksch (2001) states that exposure is a 1000 to 10,000 fold lower than exposure by food, whereas Altkofer et al. (2005) state that exposure might exceed exposure through food by a factor 1.5 to 3. Because of the lack of information on the possible exposure through condoms the effect of condom use will not be regarded in this case.
Occupational exposure, although usually to relatively high concentrations, is beyond the scope of this study.
Endogenous formation of nitrosamines is suspected to contribute considerably to the total internal exposure to nitrosamines. However, as the amount of endogenously formed nitrosamines is uncertain and subject to intra-individual toxicokinetic variance and most likely depends on –unknown- dietary factors, in this report we focus on exposure to exogenously formed nitrosamines only.

Exposure routes included in the calculations are therefore:

- Rubber teats and rubber soothers
- Other rubber products that are mouthed by children (such as balloons)
- Cosmetics (shampoo, bath foam, shower gel, suntan lotion).

Besides, these two types of background exposure routes are evaluated since these are considered a major source of nitrosamine exposure in the general public:

- Active and passive tobacco smoking
- Food.

Further, dermal contact to miscellaneous rubber products as other source of background exposure will be evaluated for:

- Household gloves.

3 Description of exposure

3.1 General

As the sources that contribute to the total nitrosamine exposure differ considerably between adults and children, the calculations are performed separately for adults and young children. In addition, as both the body weight of children increases very rapidly and therefore exposure expressed per kg bodyweight, and behaviour (such as suckling and mouthing) also changes over time, the exposure was calculated according to four age strata for children: 0-6 months; 6-12 months; 12-24 months; 24-48 months.
For oral and inhalation exposure, internal dose is assumed to be 100% of the exposure, whereas for dermal exposure information on skin penetration is taken from the literature. Exposure has been adjusted for these values.
For all the sources, we assumed that exposure determinants such as exposure duration was the same before and after legislative measures to be able to compare the influence of the legislative measures, without bias caused by changes in exposure by other reasons.

Table A9.4 summarises the evaluated exposure sources and routes for specified subpopulations. For calculations for different sources, as far as possible concentrations measured in Dutch products (or products sold on the Dutch market) are used.

Table A9.4. Routes of exposure to nitrosamines for both adults and children

	0-6 months	**6-12 months**	**1-2 years**	**2-4 years**	**Adult men**	**Adult women**
Rubber products						
Rubber teats	+	+	+	-	-	-
Soothers	+	+	+	+	-	-
Balloons	-	-	-	+	-	-
Cosmetics						
Skin washing	+	+	+	+	+	+
Hair washing	+	+	+	+	+	+
Tobacco smoke						
Active	-	-	-	-	+	+
Food						
Malted alcoholic beverages	-	-	-	-	+	+
Cured meat	-	+	+	+	+	+
Cheese	-	+	+	+	+	+
Sea food	-	+	+	+	+	+

3.2 Exposure through different sources and routes

Exposure through sources and routes will be discussed below. Exposure information used for the calculations is described.

3.2.3 Rubber teats

Exposed population

Children drinking from bottles with rubber teats can be exposed to nitrosamines in the teat. In The Netherlands, each year about 200.000 children are born.
The percentage of children drinking from bottles was estimated from data from the Central Bureau of Statistics and the national inquiry of milk feeding practices (Lanting, 2005). Data are given in Table A9.5 Additionally, a 50% breast feeding-50% bottle feeding is assumed for 10% in the age group 0-6 months, and 15% for the age group 6-12 months.

Tabel A9.5. Number of bottles per day, average feeding time and percentage using bottles per age category

	Complete bottle feeding		
Age	**Number of bottles/day**	**% using bottles 1984**	**% using bottles 2002**
0-6 months	6	56	47
6-12 months	3	72	47
1-2 years	3	50*	50*

* assumptions

Exposure

The percentage of teats with detectable nitrosamine concentration and nitrosamine concentration was based on two reports from two Dutch retail surveys, one based on 29 samples in 1983/1985 (Ellen et al., 1987) and one based on 14 samples in 2001 (Bouma et al., 2003). Weight of teats was set at 7.5 g (Westin et al., 1990). Information on the nitrosamine content of teats is given in Table A9.6.

Table A9.6. Nitrosamine exposure from bottle teats, determined by 24-hour extraction using artificial saliva, expressed in µg/kg rubber

		% positive	**Leaching Rate µg/kg/24 hrs**			**Source**
			Mean	**Min**	**Max**	
1984	Nitrosamines	83	23.7	4	56	Ellen, 1987
	Precursors	83	1067	26	4900	Ellen, 1987
2002	Nitrosamines*	86	0.43	0.2	0.7	Bouma et al., 2003
	Precursors	36	4.72	0.5	21	Bouma et al., 2003

* NDMA, NDBzA

The daily exposure of a child drinking from bottles with rubber teats is calculated as follows:

$$Exp = \frac{t * \left[\left(LR_{NA} * pos_{NA} + CF * LR_{NC} * pos_{NC} \right) * W_N \right]}{W_C} \quad \text{(formula 1)}$$

Where
Exp = average exposure (µg NA/kg bodyweight per day)
t = total drinking time per day (min) (= # bottles per day * 10 minutes per bottle)
posx = proportion of teats with detectable nitrosamines or nitrosatable compounds, respectively (Table A9.6)
LRNA = Average Leaching Rate for nitrosamines (µg/kg rubber product per min) (TableA9.6)
LRNC = Average Leaching Rate for nitrosatable compounds (µg/kg rubber product expressed per minute) (Table A9.6)
CF = correction factor; proportion of nitrosatable compounds which are converted to nitrosamines (1%; Van Leeuwen et al., 2003)
WN = weight of teat (kg)
WC = weight of child (kg) (Table A9.7)

Averaged over the whole child population the exposure per child has to be adjusted for proportion of bottle users:
BU = average proportion of bottle use, which is proportion of bottle users plus 0.5 * proportion of users of combination bottle/breast feeding

The following assumptions have been made to calculate exposure through teats:
The average drinking time per bottle is 10 minutes.
Children < 6 months drink 6 bottles a day
Children between 6 months and 2 years drink 3 bottles of milk
Bottle use for children 1-2 yrs is 50%
Children older than 2 do not use bottle teats
From the start, all other drinks (non-milk drinks), such as apple juice, are drunk from a normal cup.
CF is 1% (Van Leeuwen et al., 2003)

For calculations of exposure before and after measures, bottle use is assumed to be constant and the average of both periods is taken. Table A9.7 gives the input data which vary according to age category and the average exposure values.

Table A9.7. Input data and exposure data for use of rubber bottle nipples

		Complete bottle feeding		Combination with breast feeding			
Age	Before/ after measures	# bottles per day	proportion bottle users	# bottles/ day	proportion bottle users	body weight (kg)	average exposure per child (ng/kg/day)
0-6 months	Before	6	0.515	3	0.1	5.25	0.96
	After	6	0.515	3	0.1	5.25	0.01
6-12 months	Before	3	0.67	1.5	0.15	8.16	0.37
	After	3	0.67	1.5	0.15	8.16	0.00
1-2 years	Before	3	0.5		0	9.85	0.23
	After	3	0.5		0	9.85	0.00

Other input variables: Weight of nipple: 7.5 gr, % pos and exposure levels, see Table 3.3, CF 1%.

3.2.2 Rubber soothers

Exposed population

Many children use soothers for some time. No data is available on the percentage of the children using soothers in different age categories. For calculations for the total population, the average mouthing time is taken (see below).

Exposure

Table A9.8 gives information on the default mouthing time for soothers per day. The default mouthing time for soothers was taken from the RIVM Childrens Toys Factsheet (Bremmer and Van Veen, 2002). It is assumed that the default mouthing time is an estimator of the average mouthing time.

Table A9.8. Default mouthing time of soothers, per age category

Age	Default mouthing time per day (min)	Value is default at age:
0-6 months	285	4.5 months
6-12 months	82	7.5 months
1-2 years	62	18 months
2-4 years	31 (50% of 1-2 yrs assuming 50% still using a soother)	18 months

Average daily exposure is calculated analogous to that for bottle teats (see formula 1). In that formula, t stands for the average mouthing time. No adjustments have to be made for % of using a soother because this is already accounted for in the average mouthing time. The weight of the soother (kg) is the same as of a bottle teat: 7.5 g.

The percentage positive soothers and nitrosamine concentration were taken based on two reports from two Dutch retail surveys, one based on 22 samples in 1983/1985 (Ellen et al.,

1987) and one based on 5 samples of soothers in 2001 (Bouma et al., 2003). Exposure information for soothers is given in Table A9.9

Table A9.9. Nitrosamine exposure from soothers, determined by 24-hour extraction using artificial saliva, expressed in µg/kg rubber

		% positive	**Leaching Rate µg/kg/24 hrs**			**Source**
			Mean	Min	Max	
1984	Nitrosamines	64	27	7	94	Ellen, 1987
	Precursors	64	1294	42	5100	Ellen, 1987
2001	Nitrosamines	60	1.43	1.3	1.6	Bouma, 2003
	Precursors	20*	234			Bouma, 2003

* 1 out of 5 tested positive

For the calculations of exposure the following assumptions are made:
Default mouthing time of children does not change over the years within an age category.
For 2-4 years old, mouthing time of soothers stays the same for those still using a soother (62 minutes), but half of the children will no longer use a soother, resulting in a default time of 31 minutes.
Results of the calculations are given in Table A9.10.

Table A9.10. Exposure to nitrosamines through soothers

Age	**Before/ after measures**	**Average mouthing time per day**	**Weight of child**	**average exposure per child (ng/kg/day)**
0-6 months	Before	285	5.25	7.08
	After	285	5.25	0.37
6-12 months	Before	82	8.16	1.31
	After	82	8.16	0.07
1-2 years	Before	62	9.85	0.82
	After	62	9.85	0.04
2-4 years	Before	31*	13.3	0.30
	After	31*	13.3	0.02

- Assuming 50% still using a soother and using default mouthing time of child at age of 18 months.
- Other input values: weight of nipple: 7.5 gr, % pos and exposure levels, see Table A9.9, CF 1%.

3.2.3 Mouthing of other rubber products, such as balloons

Exposed population

Children are often orally exposed to rubber toys. Balloons were and probably still are often inflated by mouth, despite the warning on the package to use a pump. The age category highest exposed will be somewhere between 5 and 10 years, whereas also parents of young children will be exposed because they inflate the balloons for the children. However, within the scope of this case exposure will be estimated for children aged 3-4.

Exposure
The average daily exposure to nitrosamines from balloons is calculated analogous to formula 1, with the following adjustments:
t = mouthing time per day
WN = weight of the mouth piece (270 mg, as measured by Van Leeuwen et al., 2003).

The default mouthing time for balloons was taken from the RIVM Childrens Toys Factsheet (Bremmer and Van Veen, 2002). The average daily mouthing time for 'other objects' for children between 19-39 months old is 2 minutes/day.

It is assumed that children < 3 do not inflate balloons. Hence, to estimate the average exposure within the age group 2-4 years, the exposure is divided by 2.

Table A9.11. Nitrosamine exposure from balloons, determined by extraction using artificial saliva, expressed in µg/kg rubber

		% positive	Leaching Rate µg/kg/24 hrs			Source
			Mean	Min	Max	
1984	Nitrosamines	100 *	*55* **		110	Ellen et al., 1987
	Precursors	100 *	*1400* **		2800	Ellen et al., 1987
2001	Nitrosamines	84	72		750	VWA, 2005***
	Precursors	84	650		3200	VWA, 2005***

* No percentage 'positive' reported. Assumption: 100%
** Only maximum reported. Mean calculated as (0+110)/2=55 µg/kg/24hrs and (0+2800)/2=1400 µg/kg/24hrs
*** Extraction time 1 hour instead of usual 24 hours

Nitrosamine levels of balloons in 1983/1985 were provided by Ellen et al. (1987). Balloons were found to contain high levels of extractable nitrosamines and nitrosatable compounds, at levels up to 110 and 2800 µg/kg/24 hrs, respectively. Van Leeuwen et al. (2003) estimated the average total precursor levels in balloons at 1510 µg/kg/1 hr. For this case, we used nitrosamine levels published in a VWA report (ND04o063/02, 2005), based on a sample of 57 different balloons, as recent exposure. In that report it was stated that only 16% (9/58) complied with the migration limits. The % of positive balloons is therefore set to 84%. The leaching rate into artificial saliva is presented in Table A9.11.

For the calculations of exposure the following assumptions are made:
- Because of the age indication "3+", we assumed that younger children are not given balloons to mouth. Hence, of the group 2-4 years old, only 50% (the 3-years old) was exposed to balloons.
- Default mouthing time did not change over time.
- All balloons were assumed to be 'positive' in 1983/1985.

Table A9.12. Exposure to nitrosamines through balloons

		Exposure (ng/kg bw/day)			
Sub population	**Exposure source**	**Before**	**After***	**Absolute reduction**	**% Reduction**
0-6 months	Balloons	0	0	-	-
6-12 months		0	0	-	-
1-2 years		0	0	-	-
2-4 years (3-4 yrs)		$0.97*10^{-3}$	$0.94*10^{-3}$	$0.03*10^{-3}$	3

* no exposure data present after the 2006 measure on nitrosamine content. Earlier data used for calculation of effect.
Input values: weight of mouth piece: 0.27 gr, % pos and exposure levels, see Table A9.11 CF 1%, weight of child, see Table A9.7.

3.2.4 Cosmetics

Exposed population

Potentially the whole population is exposed to nitrosamines through use of cosmetics.

Exposure

Several cosmetic products have been shown to contain nitrosamines. We assumed that dermal exposure to nitrosamines follows the following steps

- washing the skin– using soap or washing gel directly on the skin and than rinsing it off or bath foam (bubble bath) diluted in the bath water
- washing the hair– using shampoo
- suntan lotion – rubbing the skin with suntan lotion

As no Dutch levels were available for body lotion and no information was found in the scientific literature, we assumed that the levels in these products were negligible.

Exposure by dermal contact with cosmetics is calculated with the following formula:

$$Exp = \frac{Amt * fy * \%pos * Conc * DF * SP}{W * 365} \quad \text{(formula 2)}$$

Where

Exp = average daily exposure (µg NA/kg bodyweight)
Amt = amount of cosmetic used each time (g)
fy = frequency per year
% pos = percentage of positive samples
Conc = mean concentration in product (µg/kg product)
DF = dilution factor if diluted in bath water
SP = skin penetration (fraction)
W = bodyweight (kg)

The factor 365 adjusts exposure per year to exposure per day. In Table A9.13 the frequency of application is given.

Table A9.13. Defaults for frequency of use per year of several cosmetic products per age category (Bremmer et al., 2002).

Age	**Shampoo**	**Shower gel**	**Bath foam** *	**Suntan lotion** **
0-6 months	260	0	329	75
6-12 months	260	0	208	75
1-2 years	260	0	156	75
2-4 years	260	100	104	75
Adults	260	329	104	75

* Default times were only provided for adults. We assumed that baby's and infants are bathed more frequently and that this gradually decreases until they are 2 years old and children do not use shower gel up to an age of 2 years. For 0-6 months: 5x/week=329/year; for 6-12 months: 4x/week= 208/year, for 1-2 years: 3x/week=156/year. We assumed that children between 2-4 use 100 times a year shower gel.

** 75 = 25 days per year, three times per day

The default amounts used of cosmetic products were taken from the RIVM Factsheet on cosmetic products (Bremmer et al., 2002).

Table A9.14. Nitrosamine concentration in several cosmetic products

		% positive	**Concentration µg/kg**			**Source**
			Mean	**Min**	**Max**	
1980-1991	cosmetics	32.7	620	130	1150	Ellen et al, 1980 Montfort and Groenen, 1981
	suntan lotion*	72	1887	60	20520	Vaessen et al., 1995
2004, 2005	shampoo	26	427	25	2191	VWA, 2006**
	shower gel	15	284	24	102	VWA, 2006**
	bath foam	11	307	88	649	VWA, 2006**
	baby bath foam/soap	33	79			VWA, 2006**
	baby shampoo	22	340	232	448	VWA, 2006**
	baby suntan lotion	0				VWA, 2006**

* As presented in Vaessen et al. (1995; Table 2): literature values of NMPABAO levels in cosmetic samples, mostly sun creams. Average concentrations 1987- 1991.

** NDELA

Figures for the years before 1995 did not distinguish between shampoo, shower gel and bath foam. We therefore assumed the average concentration to be representative for all three of these groups.

The input values lead to the calculated exposure values as given in Table A9.15.
We found two studies that described skin-penetration by nitrosamines into human skin. We distinguish between creams applied directly to the skin, and products that are rinsed off relatively quickly after use.

Walters et al. (1997) found in vitro dermal absorption of NDOMA to be 10% for a finite dose (emulsion) over 48 hours, based on the amounts recovered from the receptor fluid and the skin itself. For NDMA, the same laboratory using a similar experimental set-up found a dermal absorption of NDMA of 5.4% for a finite dose (Brain et al., 1995). The finite doses used reflected in use conditions. We used the mean of these two values: 7.7% for a finite dose (such as suntan lotion) directly applied to the skin. This value was not adjusted for contact time since we assumed that the contact time for suntan lotion was long enough to approach the value based on a contact time of 48 hrs.
For NDOMA present in shampoo minutes, followed by rinsing and applied in finite dose) Walters et al. (1997) found a skin absorption of 7.4%, whereas Brain et al. found a skin penetration of 1.2% for NDMA. Hence, we used the mean of these values (4.3%) for shampoo. We did not correct for shampoo contact time as the results of the NDOMA experiments indicated that the in vitro washing procedure was not very efficient, as 48 h later still 13% of the applied amount was recovered from the skin surface. Therefore the contact time was in fact much longer than the intended 10 minutes. As in vivo washing procedures are likely to be much more efficient, the absorption figures determined in vitro probably represent a worst case with respect to contact time.

Table A9.15. Exposure to nitrosamines through cosmetics.

		Exposure (ng/kg bw/day)			
Subpopulation		Before	After	Absolute reduction	% Reduction
0-6 months	shampoo	24	8.7	15	63
6-12 months		15	5.6	9.7	63
1-2 years		13	4.7	8.1	63
2-4 years		9.4	3.5	6.0	63
adults		1.8	0.97	0.82	46
0-6 months	bathing foam	$3.7*10^{-3}$	$0.47*10^{-3}$	$3.2*10^{-3}$	87
6-12 months		$1.5*10^{-3}$	$0.19*10^{-3}$	$1.3*10^{-3}$	87
1-2 years		$0.93*10^{-3}$	$0.12*10^{-3}$	$0.81*10^{-3}$	87
2-4 years		$0.45*10^{-3}$	$0.06*10^{-3}$	$0.39*10^{-3}$	87
adults		$0.09*10^{-3}$	$0.01*10^{-3}$	$0.07*10^{-3}$	83
0-6 months	shower gel	NA	NA	NA	NA
6-12 months		NA	NA	NA	NA
1-2 years		NA	NA	NA	NA
2-4 years		1.6	0.13	1.5	92
adult men		0.39	0.08	0.31	79
0-6 months	suntan lotion	41	0.00	41	100
6-12 months		26	0.00	26	100
1-2 years		22	0.00	22	100
2-4 years		16	0.00	16	100
adults		3.1	0.11*	3.0	96
	Total of all products				
0-6 months		65	8.7	56	87
6-12 months		42	5.6	36	87
1-2 years		35	4.7	30	87
2-4 years		27	3.6	24	87
adults		5.3	1.2	4.1	78

* no data after measure. It is assumed that concentration in all products is maximum allowable level of 50 µg/kg product.

Input values: The default amounts used (RIVM fact sheet on cosmetic products (Bremmer et al., 2002): 20 grams of shampoo; 8.7 g of shower gel, 17 g of bath foam, 10 g of suntan lotion. As bath foam is diluted in the bath water, we used a dilution of 7000 times (17 g gram (= 17 ml) in 120 litre) for a normal bath and the same dilution for a baby bath. Skin penetration: 4.3%, except 7.7% for suntan lotion.

For shampoo, bathing foam, shower gel and suntan lotion a reduction is expected based on the available information. This information, however, is not very specific since no distinction was made in exposure data before measures were taken between these categories.

3.2.5 Background exposure

Diet

The exposure of adults to nitrosamines from the adult diet was determined by 24-hours duplicate portion measures, based on 201 and 110 samples respectively by Stephany and Schuller (1980) and Ellen et al. (1990).
The exposure of children was determined by multiplying the amount of consumption with the nitrosamine concentrations in cured meat (mean 0.5 µg/kg; max 3.6 µg/kg), sea food (mean 0.4 µg/kg; max 2.1 µg/kg), and cheese (mean 0.1 µg/kg; max 1.1 µg/kg).

Table A9.16 Nitrosamines (NDMA µg/day) in duplicate portions of adult diets.

		Intake µg/person/day			**Source**
		Mean	**Min**	**Max**	
1980	all	0.38*		4.4	Stephany and Schuller, 1980
	men	0.49*			
	women	0.13*			
1990	all	<0.1		1.5	Ellen et al., 1990

* Including beer, otherwise 0.11 µg/person/day

Since the information for 1980 was most complete, we used the same information for estimating exposure through food for later periods. The total exposure is estimated by calculating the contribution of different sources. Consumption of food and drinks is obtained from the Dutch Feed Consumption Monitor (VCP '97-98; Voedingscentrum, 1998) for adults and separately for children based on 'Zo eten jonge peuters' (Breedveld and Hulshof, 2002). Since the 1980's, exposure through food has been decreased considerably due to adjusted food production methods.

Tobacco smoking

The internal exposure (in µg /kg bw/day) of adults to nitrosamines from tobacco smoke was determined as follows:

$$Exp = \frac{\%sm * \#cig * Conc_{NA}}{W}$$

Where
Exp = average exposure (µg NA /kg bw/day)
% sm = % smokers
# cig = average number of cigarettes smoked per day by smokers
ConcNA = mean concentration of NA in cigarettes (µg)
W = average body weight (kg)
We assumed a 100% uptake in the body for the inhalation exposure route.

Table A9.17. Tobacco specific nitrosamines in mainstream smoke in filter cigarettes.

	N	**Amount of NA per cigarette (ng)**			**Source**
Type of NA		**Mean**	**Min**	**Max**	
NNN	12	86 *	9	163	Fischer, 1990
NNK		53.5 *	5	102	Fischer, 1990
Total		140	14	265	

* calculated as the mean of the min and max value: NNN (9+163)/2=86 and NNK (5+102)/2=53.5

The percentage of persons that is smoking was found at CBS Statline database, as was the average number of cigarettes smoked per day (by smokers). This information and the calculated exposure is given in Table A9.18.

Table A9.18. Percentage smokers, number of cigarettes smoked per day, and exposure to nitrosamines through smoking

	Before measures		**After measures**		**Before and after measures**
Gender	**% Smoking actively**	**Number cig's/day**	**% smoking actively**	**Number cig's/day**	**Exposure (ng/kg bw/day)**
Adult men	44	18.8	36.2	15.6	15.6
Adult women	31.3	16.9	29.3	15	12.1

For the calculations, it has been assumed that the number of smokers remains constant over the evaluated period. The values for the period before the measures have been taken to calculate the background exposure.
No information was available for calculations of exposure through passive smoking.

Household gloves
RIVM (Janssen and Van der Zee, 2005) performed a risk assessment for exposure to nitrosamines through the use of household gloves. Estimates were made for single use latex gloves as well as for multiple use latex gloves. The 75 percentile reasonable worst case exposure estimates were 46 and 71 µg/person per year, respectively. Adjusted for daily exposure per kg bw this corresponds to 2-3 ng/kg bw per day for an adult of 70 kg. It is assumed that the average exposure per person will not exceed 1 ng/kg bw per day.

4. Description of toxicity

4.1 Introduction

Most toxicological assessments of nitrosamines focus on their carcinogenic and mutagenic properties. Little is known on other toxicological endpoints (see amongst others (USEPA, 1993a/b/c/d/e/f; USEPA, 1994, Health Council, 1999). Therefore the present evaluation will be restricted to the carcinogenic potency of these chemicals. Several of the nitrosamines consumers are exposed to are evaluated by the Agency for Research on Cancer (IARC) as Group 2a: probably carcinogenic to humans (NDEA, NDMA) or as Group 2b: possibly carcinogenic to humans (NDBA, NDELA, NDPA, NMOR, NMEA, NPIP, NPYR, NNK) (see the following webpage of IPCS INCHEM: http://www.inchem.org/pages/iarc.html).

4.2 Carcinogenicity of nitrosamines in animals

More than 300 different N-nitroso compounds have been extensively tested in 40 different animal species, and caused cancer in everyone of them. Of the three relevant exposure routes, only the respiratory and/or the oral route have been tested for the various nitrosamines. Before exerting their carcinogenic effects, most N-nitrosamines first have to be converted by oxidative enzyme systems in the host organism into substances that may cause the DNA mutations, which are thought to initiate carcinogenesis. N-nitrosamines are mostly systemically acting genotoxic carcinogens, that is they cause cancers after having entered the bloodstream (Haugen, 1991; Schuller, 1997).

Animal cancer tests can be analysed quantitatively to give an estimate of the carcinogenic potency of chemical carcinogens. Various mathematical models such as the linearized multistage, the Weibull, or the one-hit procedure have been proposed to fit the dose-response relationships in long-term animal experiments. Once the curve has been established, the potency can be expressed in various ways. Frequently used potency indices are the TD50 (defined as the chronic dose rate in mg/kg bw/day that will halve the probability of remaining tumour free throughout the standard life span), and the cancer incidence per unit of exposure, i.e., the quantitative unit risk estimate. In Table A9.19, the N-nitroso compounds are ranked according to carcinogenic potency using the rat TD50-values as a starting point. The rat TD50-values are considered more suitable for ranking of the N-nitroso compounds since these TD50s were calculated in a standardised way. The quantitative unit risk estimates by USEPA are considered less suitable for ranking of the N-nitroso compounds according to carcinogenic potency since they have been calculated using different mathematical extrapolation models. The TD50-values and the quantitative unit risk estimates have been taken from the Carcinogenic Potency Database (CPDB) (Gold et al., 1993).

The N-nitrosamines listed in Table A9.19 show a wide variation in their carcinogenic potency. The factor between the most potent carcinogen, i.e., NDEA with a TD50 of 7.87 x 10-3 mg/kg bw/day, and the least potent carcinogen, i.e., NDP(h)A with a TD50 of 116 mg/kg bw/day, amounts to approximately 15,000.

Table A9.19. Relative potency of some N-nitroso compounds (ranking order)

Nitrosamine	TD50 (mg/kg bw/d)	Nitrosamine	TD50 (mg/kg bw/d)
NDEA	0.00787 [1]	NPYR	0.409 [7]
NMEA	0.0503 [2]	NDBA	0.691 [8]
NDMA	0.0587 [3]	NDiPLA	0.813 [9]
NMOR	0.127 [4]	NPIP	1.57 [10]
NNK	0.182 [5]	NDELA	1.9 [11]
NDPA	0.186 [6]	NDP(h)A	116 [12]

It should be noted that these differences in potency are not directly interpretable in terms of additional cancer risk, as the TD50 is a relative measure of cancer-free survival and depends on the background incidence of the ‘critical’ tumour, but they do give an impression of the order of magnitude of the differences in potency in terms of additional cancer risk.

In view of the huge differences in potency, all nitrosamines consumers are exposed to should be dealt with separately when evaluating health risks, in order to avoid over- or underestimation of the risks involved. Furthermore, a distinction should be made between tumours caused by local effects, e.g. after respiratory exposure, which cannot be extrapolated to other routes of exposure, and systemic effects which may be extrapolated to other routes (although route-specific metabolism may render extrapolation invalid). In order to ensure the evaluation of all nitrosamines will be internally consistent, their (additional) cancer risk values should be derived using the same extrapolation method. In the Netherlands, linear extrapolation is the method of choice (Health Council, 1995; Janssen, 1997). At the moment, consistently derived cancer risk values covering all nitrosamines discussed here, are lacking, and, therefore, still need to be derived, using the available studies. Within the scope of this study, this is not feasible. For the same reason, no 'average’ cancer value for a combination of nitrosamines can be used, as comparable data are still lacking. Also this approach would introduce an additional insecurity: depending on the relative importance of the various nitrosamines consumers are exposed to, risks would be over- or underestimated. However, in order to get an impression of the possible health gains of the measures taken to reduce consumer nitrosamine exposure, a ‘reference’-nitrosamine can be chosen and evaluated. As NDMA appears to be present in all potential sources (e.g. food, cosmetics, rubber products) and is most commonly detected (see a.o. section 3), this individual nitrosamine is chosen as such a reference. In view of the relatively high potency of NDMA (see Table A9.19), this approach will probably lead to an overestimate of the risk connected to exposure to nitrosamines in cases where other nitrosamines than NDMA are comprised in the nitrosamine exposure estimates.

4.3 Carcinogenicity of NDMA

4.3.1 Introduction

The carcinogenicity of NDMA has been evaluated by WHO (WHO, 2002), Dutch Health Council (1999), DFG (1999), RIVM (Speijers et al., 1989) and ATSDR (1989) and IARC (1972a, 1978a). The more recent evaluations (end eighties, early 21st century), are all based on data generated until the early eighties. However, the most recent evaluations had re-evaluations some of these data at their disposal. The present description is largely based on the most recent evaluation by WHO (WHO, 2002), which also has been published in public literature (Liteplo and Meek, 2001) and the Dutch Health Council Report (Health Council of the Netherlands, 1999).

4.3.2 Animal studies

Besides oral and inhalatory animal studies, a number of studies in which the test substance was administered by the subcutaneous, intramuscular or intraperitoneal route, have been performed. These latter studies are considered to be less relevant for estimation of long-term cancer risk than dermal, inhalation and oral studies, and are not further discussed here. No dermal studies were found.

Oral cancer risk value

NDMA has been tested in rats by oral administration through drinking water, gavage and diet. The main target organ upon long-term oral administration is the liver, although also tumours in lungs and kidneys have been reported. The most comprehensive oral long-term carcinogenicity study has been conducted by Peto and co workers (Peto et al. 1991a/b cited in Health Council of the Netherlands, 1999), who examined in detail the dose-response relationship for the effects of NDMA on various types of liver cancer. This nitrosamine was given at 16 different doses in drinking water for lifetime. The dose range varied between 0.033 and 16.896 ppm in drinking water (equivalent to 0.001 and 0.697 mg/kg bw/d). The main target organ for tumour formation by NDMA was the liver, although NDMA also caused a few tumours of the lung. The tumorigenic dose05 (TD05; i.e., the dose level that causes a 5% increase in tumour incidence over background) was calculated in the WHO-evaluation by fitting a multistage model to the dose–response data obtained at many relatively low doses (WHO, 2002). The lowest TD05 was 34 µg/kg body weight per day for the development of biliary cystadenomas in female rats (95% lower confidence limit 18 µg/kg bw/d). This equates to a unit risk of 1.5×10^{-3} per µg/kg body weight (i.e., 0.05/34) (95% upper confidence limit 2.8×10^{-3} per µg/kg bw/d). As this unit risk was derived by taking into account the dose response-curve, it is considered to be the most reliable estimate based on the available data. As a consequence, the 95% upper confidence limit is quite close to the median value. However, this is not a measure of the uncertainty of the unit risk when applied to humans, as the uncertainty of the extrapolation from animal to human was not taken into account nor the uncertainty associated with fitting a multistage model to the dose–response data. In general, the multistage model is considered to be a conservative approach, which overestimates the carcinogenic risk provoked by the animal exposure. Overall the uncertainty surrounding the unit cancer risk in humans can not be quantified, but it may be several orders of magnitude.

Respiratory cancer risk value

Several of the inhalation studies summarised by the Dutch Health Council [Health Council of the Netherlands, 1999] allow an estimation of the additional life-time cancer risk under life span conditions of exposure. An inhalation experiment with rats published by Klein et al. (1991, cited in Health Council of the Netherlands, 1999) appears to be the most sensitive and most reliable study for estimation of the potential risk of cancer. Female rats were exposed to atmospheres containing 0, 0.04, 0.2 or 1.0 ppm NDMA in air (corresponding to 120, 600 and 3000 $\mu g/m^3$) four times per week, 4-5 hours per day, for 207 days. The median survival time of animals exposed to 1 ppm NDMA was nine months less than that of untreated controls owing to toxicity. The median survival of animals given 0.04 ppm was two months longer than that of control rats. Tumours occurred mainly in the nasal cavity, with the highest incidences in the groups receiving 1.0 and 0.2 ppm NDMA (19/36 and 31/36 tumour-bearing animals); in the lowest exposure group in 13 out of 36 animals nasal tumours were observed. No nasal or respiratory tract tumours were seen in control animals. At 1 ppm 47% of the tumours were aesthesioneuroblastomas, whereas only 6% and 15% of this tumour type was observed following inhalation of 0.2 and 0.04 ppm NDMA, respectively. In the 0.2 and 0.04 ppm group mucoepidermoid tumours represented the greatest proportion. The lowest concentration (120 $\mu g/m^3$) resulting in the induction of the tumour of interest, i.e. tumours of the nasal mucosa was used as starting point to calculate the unit risk, resulting in a value of 0.1 $(\mu g/m^3)$-1. Like for the oral unit risk, the uncertainty associated with the respiratory unit cancer risk for humans cannot be quantified, although it is probably greater than for the former, as in this case no dose-response fitting was executed.

Dermal cancer risk value

No dermal studies are available to derive a cancer risk value for NDMA, and it needs to be inferred from studies for the other routes. The respiratory cancer risk value is substantially higher than the value derived from the oral studies. However, while the tumours in the oral study are clearly systemic in nature (liver), the tumours in the respiratory study are not (nasal mucosa) and may very well be local in nature: they are not observed in the oral studies, although lung tumours do occur. Therefore, the unit risk derived from the respiratory study is considered route-specific, and should only be used to evaluate the health risks of respiratory exposure. The unit risk calculated from the oral studies therefore, should be used for both oral exposure and route-to-route extrapolation for the dermal route.

4.3.3 Human studies

Information on the (dose-response) association between nitrosamine exposure and risk of cancer is mainly provided by two types of exposure routes, i.e. occupational exposure through inhalation and exposure in the diet.

Occupational studies

Although at that time no epidemiological data were available, IARC concluded that there was sufficient evidence for a carcinogenic effect of NDMA in many experimental animal species

and that N-nitrosodimethylamine should be regarded for practical purposes as if it were carcinogenic to humans (Group 2A) [IARC, 1972b;IARC, 1978b].
At present, some epidemiological data are available. Available studies include those among workers occupationally exposed to nitrosamines, such as in the rubber industry and automobile workers exposed to metal working fluids (Cocco et al., 1994; Cocco et al., 1998; Li and Yu, 2002; Straif et al., 2000; Sullivan et al., 1998) (Table A9.21).
Although all the studies summarized in the table have addressed nitrosamine exposure based on job title and/or work area/department of the workers included in the study, the exposure assessment differed in the level of detail and quantification. The studies by Cocco et al. (1994/1998) found increased risks for stomach cancer for workers exposed to nitrosamine according to a Job Exposure Matrix. A statistically significant, but slightly increased risk was only observed in the very large proportional mortality study based on US death certificates between 1984 and 1996 (Cocco et al., 1998). Exposure to nitrosamines was not quantified in both studies. Sullivan et al. (1998) investigated in detail the increased risk from oesophageal cancer that was observed in a previous study among a huge cohort of workers in the automobile industry. In this study, cumulative exposure to some types of metal working fluids in combination with specific tasks was associated with an increased risk of cancer. Measurement of exposure to nitrosamines, arising from working with metal working fluids, was included in the study but level of exposure was not quantified. Risk of oesophageal cancer was 3.7 times higher for every 5 years of exposure to nitrosamines. Straif et al. (2000) conducted a study among rubber workers employed between 1950 and 1981 in Germany. Semi-quantitative exposure assessment of the nitrosamines NDMA and NMOR was based on specific work areas of the workers, combined with expert assessment of the exposure levels in each work area and period. Statistically significant, substantially increased risks were observed for oesophagus
(RR= 9.1, 2.1-38.8) and lip/oral/pharynx (RR= 5.1, 1.2-20.6) cancer mortality and for total cancer mortality
(RR = 1.4, 1.0-1.8) among workers having worked 10 or more years in areas with exposure to more than 15 $\mu g/m^3$ NDMA or NMOR, compared to workers exposed to levels lower than 2.5 $\mu g/m^3$ and less than 0.5 years to higher levels. Relative risks were adjusted for co-exposures in this study, but not for smoking and alcohol consumption, both risk factors for upper gastrointestinal tract cancers. The study by Li and Yu (2002) investigated risk of lung cancer among rubber workers, but was not sufficiently specific with respect to nitrosamine exposure.
The available evidence on occupational exposure to nitrosamines and risk of cancer is most convincing for upper gastrointestinal tract cancers (Straif et al., 2000; Sullivan et al., 1998). A limitation is that in both studies, smoking and alcohol consumption, important risk factors for upper gastrointestinal tract cancer, were not controlled for. In both studies, however, internal comparisons were made, i.e. risk among highly exposed workers were compared to risks among low-exposed workers in the same plants; it is therefore not very likely that differences in smoking and alcohol habits entirely explain the increased risk, but some influence can not be excluded. Furthermore, it is striking but not implausible that, while occupational exposure is mainly by inhalation, upper gastrointestinal tract cancer appears to be increased. This phenomenon is also seen for smoking.

Dietary studies
Two cohort and five case-control studies were identified that investigated exposure to nitrosamines in the diet and risk of several types of cancer (Larsson et al., 2006; Ward et al., 2000; Knekt et al., 1999; De Stefani et al., 1998; Wilkens et al., 1996; Pobel et al., 1995; LaVecchia et al., 1995) (Table A9.22).
All studies measured habitual dietary intake by a food frequency questionnaire or diet history and nitrosamine contents of the foods were calculated using published tables or values, sometimes specific for the country of the study (Pobel et al., 1995; Larsson, 2006). The major contributors to NDMA intake in all studies were cured meats and beer. Most studies used only NDMA content of the foods. Most studies, with exception of Larsson et al. (1996), did not specify the actual intake of NDMA expressed in µg/day across the quintiles included in the analysis, although they presented a mean intake in the population. Most studies controlled for confounding due to smoking (except Pober et al., 1995) and other potential (dietary) confounders.
Five of the studies, including the two cohort studies, investigated the risk of stomach cancer in relation to NDMA intake. The three case-control studies and the Swedish cohort study observed a statistically significant positive association between quantiles of NDMA intake and risk of stomach cancer. The Finnish cohort study did not.
Other cancer outcomes, nasopharyngeal, colorectal, head & neck, and urinary tract, were investigated in one study each. Wilkens et al. (1996), who studied urinary tract cancer, did not include beer consumption in the calculation of NDMA intake. For this reason, this study is not considered suitable for our purpose. For head & neck cancer, investigated in the Finnish cohort study, no association with NDMA intake was observed. Nasopharyngeal cancer in Taiwan was associated with NDMA intake when subjects had been exposed at very young age. Colorectal cancer was associated with NDMA intake in the Finnish cohort study. Considering the accumulated and very consistent evidence from virtually all cohort studies that consumption of cured meat increases the risk of colorectal cancer (Norat et al., 2002; Sandhu et al., 2001), colorectal cancer may also be considered as a relevant adverse health effect of nitrosamine intake, besides stomach cancer. As the results for nasopharyngeal cancer were based on one study only, it first needs consistent confirmation to consider it as relevant adverse health effect.

Calculation of unit risk
The only occupational study allowing some quantification of the dose-response association is the study by Straif et al. The authors, however, did not present an average exposure level or duration in the high exposure group. Based on the midpoints of the exposure ranges of the work areas included in the high exposure group, we assume an unweighted average exposure of 55 µg/m^3 NDMA and 119 µg/m^3 NDMA+NMOR; the latter estimate is more uncertain since exposure to NMOR was substantial in one work area only. Assuming furthermore an average exposure duration of 25 years in the high exposure group and 15 years exposure to 1.6 µg/m^3 in the low exposure group, the following unit relative risks were calculated (Table A9.20).

Table A9.20. Relative risk per µg/m^3.yr exposure as worker to NDMA (Straif et al., 2000)

Cancer type	RR	RR per µg/m^3.yr
All cancer	1.4	1.0002
Lip/oral/pharynx	5.1	1.0012
Oesophageal	9.1	1.0016

For the dietary studies, most of the authors did not present quantified nitrosamine intake for each quintile or a continuous intake variable. Only the study by Larsson et al. presented median exposure across quintiles. We therefore took this study to calculate the unit risk of stomach cancer for NDMA (Larsson et al., 2006). From this study it can be derived that the difference in intake between quintile 5 and 1 of 0.26 µg/day NDMA is associated with a relative risk of stomach cancer of 2 (95% CI 1.1 – 3.6). This intake corresponds with an intake of 4.3 ng/kg bw/day NDMA, assuming a body weight of 60 kg. The unit relative risk per ng/kg bw/day, assuming lifetime exposure, is therefore 1.175 (95% CI 1.02 – 1.35), according to the log-linear model. We arrived at the same unit relative risk if a linear or log-linear model was fitted to all five data points. For colorectal cancer, specific data to calculate a unit risk are lacking, therefore we assume the same figure as for stomach cancer.

Table A9.21. Overview of epidemiological studies on occupational exposure to nitrosamines and risk of cancer

First author, publication year	Cancer site	Design	N cohort or cases/controls	Exposure assessment	Contrast	Adjustment for confounders	RR	95% Confidence interval
Cocco et al., 1994	stomach	case-control	640/959	JEM; not quantified	Occupational exposure to nitrosamines for 21+ years	Smoking, dietary	>1	not significant
Sullivan et al., 1998	oesophagus	nested case-control	53/46384	JEM (specific); not quantified	Duration of exposure (per 5 yrs) to nitrosamines in metalworking fluids lagged 20 yrs among automobile manufacturers	Co-exposures	3.7	1.2-11.1
Cocco et al., 1999	stomach	PM	41957	JEM; not quantified	workplace exposure to nitrosamines		1.06	1.01-1.11
Straif et al., 2000	all cancers	cohort	8933	Semi-quantitative, based on specific work areas + expert assessment; NDMA, NMOR	High (≥15 μg/m^3, ≥ 10 yrs) vs Low (<2.5 μg/m^3 and < 0.5 yrs high)	Co-exposures	1.4	1.0-1.8
	oesophagus	cohort	8933	idem	idem		9.1	2.1-38.8
	lip/oral cavity /pharynx	cohort	8933	idem	idem		5.1	1.2-20.6
Li andYu, 2002	lung	case-cohort	1598	Not specific for nitrosamines	For 30-45 exposure-years in curing department of rubber plant	smoking	3.8	1.4-9.9

Table A9.22. Overview of epidemiological studies on dietary exposure to nitrosamines and risk of cancer

First author, publication year	**Country**	**Cancer site**	**Design**	**N cohort or cases/controls**	**Exposure assessment**	**Contrast**	**Adjustment for confounders**	**RR**	**95% Confidence interval**
Larsson et al., 2006	Sweden 1987-1990	Stomach	Cohort; 18 yr follow-up	156/61433	FFQ; quantified (*NDMA* table, Osterdahl, 1988)	NDMA quintile 5 vs quintile 1; 0.277 vs 0.017 µg/day	Smoking, other	2.0	1.1-3.6
Ward et al., 2000	Taiwan ?	nasopharyngeal	case-control	375/327	Adult & retrospective childhood diet; *NDMA* table (published values);	NDMA quartile 4 vs 1: Diet age 10 Diet age 3 Weaning diet	?	 2.2 2.6 3.9	 0.8-5.6 1.0-7.0 1.4-10.4
Knekt et al., 1999	Finland 1967-1972	Colorectal	Cohort; 24 yr follow-up	73/9985	Dietary history; *NDMA* table (published values); mean 0.05 µg/day + 0.07 from beer	NDMA quartile 4 vs 1; not quantified	Smoking, other	2.1	1.0-4.3
		head & neck		48/9985					No ass.
		Stomach		68/9985					No ass.
De Stefani et al., 1998	Uruguay 1993-1996	Stomach	case-control	340/698	?	NDMA ?	?	3.6	2.4-5.5
Wilkens et al., 1996	Hawaii 1979-1986	urinary tract	case-control	261/261 population	Diet history, designed for *nitrosamines*; quantified (Canadian databank, 1984); mean 0.03 (m), 0.02 (f) µg/day excluding beer	Nitrosamines tertile 3 vs 1 (excluding beer); not quantified	Smoking, dietary, occupational	3	P trend =0.01 (among Japanese, but not Caucasian men)
Pobel et al.,	France	stomach	case-	92/128	Dietary history;	NDMA tertile 2 vs	Several, not	4.1	0.9-18.3

First author, publication year	Country	Cancer site	Design	N cohort or cases/controls	Exposure assessment	Contrast	Adjustment for confounders	RR	95% Confidence interval
1995	1985-1988		control	hospital	*NDMA* table (published values); Median = 0.23 µg/day P75 = 0.29 µg/day, P25 = 0.19 µg/day	Tertile 3 vs 1 (not quantified)	smoking	7	1.8-26.5
LaVecchia et al., 1995	Italy 1985-1993	Stomach	case-control	746/2053 hospital	FFQ; ?	NDMA tertile 3 vs 1		1.4	1.1-1.7

5. Current risk assessment

Integrated into the specific sections of the next chapter.

6. Calculation of Public Health Gain

6.1 Decrease of exposure

Legislation on exposure to nitrosamines has focused on three types of consumer products: exposure through teats and soothers, through balloons, and through the use of cosmetics.

Table A9.23 shows the change in exposure due to different exposure sources. There is a large reduction in exposure through cosmetics, and to a lesser extent through rubber teats and soothers. The exposure (and reduction) through balloons is negligible despite a higher concentration of NA, which is due to the short duration of oral contact and the low weight of the mouth piece of the balloon. If there are other rubber toys with relatively high contamination of nitrosamines, the true exposure through toys can be much higher than suggested by this case.

Table A9.23. Exposure to nitrosamines through different sources.

		Exposure (ng/kg bw/day)			
Exposure source	**Sub population**	**before**	**after**	**absolute reduction**	**% reduction**
Teats/ soothers	0-6 months	8.0	0.39	7.6	95
	6-12 months	1.68	0.07	1.6	96
	1-2 years	1.1	0.05	1.0	96
	2-4 years	0.30	0.02	0.29	95
Balloons	0-6 months	0	0	-	-
	6-12 months	0	0	-	-
	1-2 years	0	0	-	-
	2-4 (3-4) years	$0.97*10^{-3}$	$0.94*10^{-3}$	$0.03*10^{-3}$	3
All cosmetics	0-6 months	65	8.7	56	87
	6-12 months	42	5.6	36	87
	1-2 years	35	4.7	30	87
	2-4 years	27	3.6	24	87
	Adults	5.3	1.2	4.1	78
All products	0-6 months	73	9.1	64	87
	6-12 months	43	5.7	38	87
	1-2 years	36	4.7	31	87
	2-4 years	27	3.6	24	87
	adult men	5.3	1.2	4.1	78
	adult women	5.3	1.2	4.1	78
Weighted life time average exposure*		7.0	1.4	5.6	80

* exposure of children > 4 assumed to be the same as adults

Table A9.24. Backgound exposure of adults

	Exposure (ng/kg bw/day)
Food	5
Smoking	15
Household gloves	1
Total	≈ 20

The largest absolute decrease in exposure (in units per kg bw per day) is expected to be found among children, especially by the reduction in exposure through cosmetics. For adults, the reduction is much smaller. For them, exposure through three sources of background exposure is estimated to be higher than exposure through cosmetics (see also Table A9.24). However, since the background exposure through food (by reduction in food) and through smoking (reduction in smoking) is at present lower as has been suggested by the calculations, the relative contibution of the legislative measures to reduction of nitrosamine exposure is higher than suggested by Tables A9.23 and A9.24.

6.2 Increase Margin of exposure

Nitrosamines such as NDMA are genotoxic carcinogens, and therefore considered to present a linear relationship between exposure and cancer incidence. Consequently, the decrease in incidences can be estimated.

6.3 Decrease of incidence of effect and derivation of DALYs

6.3.1 Based on animal studies

Calculations are based on the unit risk for NDMA of 1.5×10^{-3} (μg/kg bw/d)-1 (see section 4.1.3.2), derived from oral animal studies, as the exposures considered here only occur through the dermal and oral route. Exposure has been quantified in terms of total nitrosamines. NDMA is one of the most potent nitrosamine carcinogens, and the assumption that the entire calculated nitrosamine exposure will consist of NDMA, will overestimate the health risk of this exposure if all nitrosamines are measured in the products and consequently in this case the health gain of exposure reducing measures will also be overestimated.

In general, it is assumed that children are more sensitive to toxic effects than adults. However, a search in the on-line PubMed database (www.pubmed.gov) did not reveal any information describing, let alone quantifying, a higher sensitivity to the toxic effects of nitrosamines. Therefore, possible higher sensitivity of children to nitrosamine toxicity was not taken into account by increasing the unit risk for this age group.
Acute, high exposure to carcinogens may cause a greater incidence of cancer than can be expected based on linear extrapolation of dose rate over time (Bos et al., 2004; Verhagen et al., 1994). Children receive a higher nitrosamine exposure than adults, which may yield the impression they receive an acute peak exposure. However, their exposure is more long term in nature as it is a consequence of a daily feeding and/or soothing routine. Furthermore, exposure is at least a factor 30 lower than the lowest dose used in the long term animal study and can therefore hardly be defined as ‘high exposure’, even when taking into account exposure has been averaged over the total age group. Therefore no correction of the unit risk is introduced for acute peak exposure.

The number of cases per year attributed to exposure to nitrosamines from consumer products before and after the measures is calculated according to the following formula:
[Excess Lifetime Risk per unit of exposure] * [Exposure] * [Population size]) / [Life expectancy in years].
The number of cases due to exposure before the measure amounts to: [1.5*10-3] * [7.0*10-3] * [16*106] / 75 = 2.2 and after the measure to: [1.5*10-3] * [1.4*10-3] * [16*106] / 75 = 0.4, resulting in a reduction of 1.8 cases per year attributed to the measures. This number corresponds to 1.8*8 = 14 DALYs per year. Clearly, the degree of uncertainty in this number is high.

6.3.2 Based on epidemiological studies

Although risk estimates can be derived from dietary as well as occupational epidemiological studies, we base our risk estimates on one dietary epidemiological. This choice was based on several considerations, such as availability of quantitative exposure data, adjustment for confounding by other risk factors for cancers, and comparability of exposure routes. The unit relative risk (RR) per ng/kg bw/d NDMA calculated in 4.1.3.3 was 1.175 (95% CI 1.02 – 1.35). The decrease in exposure, averaged for all age groups, was 7.0 – 1.4 = 5.6 ng/kg bw/day NDMA. As stomach and colorectal cancer were the cancers affected by NDMA exposure, the decrease in exposure is calculated for these two cancers only. We assume that, due to the long incubation period of cancer, the effect of the nitrosamine exposure situation (from consumer products) before the measures is still included in the total current incidence of these cancers in the Netherlands. The calculation of the estimated number of cases and corresponding DALYs to be prevented by the measures is presented in Table A9.25. The table includes calculation of the number of cases for the 95% confidence limits of the RR estimates from the original study (Larsson et al., 2006) to take into account the statistical uncertainty attached to the RR estimate derived from the epidemiological study. Furthermore, in the lower part of the table, we calculated the number of cases for a scenario in which we assumed that some residual confounding was present in the RR estimate observed in the study. We assumed that the RR would be 1.5 instead of 2 for comparing the highest with the lowest quintile of NDMA intake.
In the scenario without residual confounding, the number of cancer cases potentially prevented ranged from 1068 to 9250 (corresponding to 8500 to 74000 DALYs). In the scenario assuming some residual confounding, the number of prevented cases ranged from 0 to 8184, corresponding to 0 to 65000 DALYs.

Table A9.25 Number of cases and DALYs potentially prevented by measures to reduce nitrosamine exposure from consumer products

		Unit RR (per ng/kg bw/d)	Reduction of exposure (ng/kg bw/d)	RR associated with reduction of exposure[1]	Number of prevented stomach cancer cases per year[2]	Number of prevented colorectal cancer cases per year[2]	Total DALYs[3]
Scenario without residual confounding	Mean	1.175	5.6	0.41	1167	5886	56424
	Lower CL	1.02	5.6	0.90	206	1039	9959
	Upper CL	1.35	5.6	0.19	1597	8054	77207
Scenario with residual confounding	Mean	1.09	5.6	0.62	751	3789	36322
	Lower CL	0.96	5.6	1.26	0	0	0
	Upper CL	1.26	5.6	0.27	1424	7185	68872

1 calculated according the log-linear model as RR = exp[ln{1.175}*(-5.6)] = 0.41
2 calculated as: Total number of current cases per year (i.e. situation before measures) – Total number of cases after measures = N – RR(N) = N (1-RR); Numbers for stomach and colorectal cancer were 1962 and 9898 cases respectively in 2003.
3 i.e. 8 DALY per incident cancer case

6.4 Derivation of DALYs

Since health gain is based on carcinogenic effects, the average number of 8 DALYs per case has been taken for the calculations. Derivation of this number is described in the main report.

7 Discussion

When evaluating the exposure to nitrosamines through consumer products, we see a decrease in exposure between the 1980's en 2000 of 87% for children and 78% for adults. In comparison to background exposure through food and cigarette smoking, average changes in exposure are large for children but limited for adults when using food exposure data of the eighties. However, since the nineteen eighties exposure through the food has decreased considerably and the relative change in exposure will thus be larger. The exposure through cigarette smoking is difficult to evaluate; other literature sources estimate the relative contribution of smoking much lower although the absolute exposure estimated in that publication is of the same magnitude (Tricker, 1997). Since active smoking has decreased in the past years the background exposure through this route will be decreased too.

Nitrosamines are a complex group of substances to evaluate in terms of change in exposure and health effects. In order to estimate the health effects, valid information should be available on aspects of exposure and toxicology. Often data has been taken from sources of which the validity for the case under study is not known. There are several sources of uncertainties that affect the validity of the effect estimates. They will be discussed briefly below and an expert judgement will be given on the overall potential error for the total Risk Assessment caused by the different sources of uncertainty. If the error is small, the uncertainty is in the order of magnitude of up to a few factors. If the error is large, the uncertainty can be in the order of magnitude of a factor 100 or more.

7.1 Target population

For the evaluated exposure sources, the population at risk will be relatively accurate, and the error is thought to be low.

7.2 Exposure

7.2.1 Exposure sources

Exposure is widespread through the use and exposure to rubber and other products. We considered dermal exposure to nitrosamine-containing rubber products not to contribute significantly to the total internal dose of nitrosamines, although information on this subject is lacking. To get a feeling of the potential effect, exposure through use of household gloves has been estimated. The exposure was about 20% of exposure through other consumer products. It is possible that not all important sources have been evaluated, and that the assumption of the role of dermal contact is not correct. It is estimated that the effect is low to, at most, moderate on the overall RA.

7.2.2 Different nitrosamines and nitrosatable compounds

There is a large number of nitrosamines. For only a limited number of these substances exposure values are known specifically. Different substances have very different carcinogenic potential (see: toxicity). In this report we could not account for these differences between substances. Estimates have been made on the assumption that exposure is to NDMA, whereas at least in several cases the specified exposures were to other nitrosamines, such as NDMA, NDBzA for bottle teats and soothers after the measures, and a.o. NMPABAO and NDELA for cosmetics. Because of the relatively high toxicity of NDMA (see Table A9.19), this may lead to an overestimation of health effects. On the other hand, it has been assumed that all nitrosamines in the products were evaluated, whereas in most cases it is not known whether this assumption was justifiable. This may cause underestimation, of unknown size.

Further, precise information on conversion of nitrosatable compounds to nitrosamines is lacking. For estimating the total exposure to nitrosamines, it is assumed that 1% of the nitrosatable substances will be converted to nitrosamines (Van Leeuwen et al., 2003). It is not known whether this percentage is valid.
Overall, we judge this source of potential error for the overall risk assessment as (very) large.

7.2.3 Exposure frequency, duration and amount used

For use of rubber bottle teats, the potential error in frequency and duration is considered to be low, whereas this is thought to be moderate for the other sources of exposure. For several sources information has been taken form RIVM fact sheets (Bremmer and Van Veen, 2000/2002 and Bremmer et al., 2002), in which exposure information is generally given for

estimation of a reasonable worst case situation. For children, no data are given in the fact sheet and hence the error in input variable may be larger than for adults.
Since it was estimated that the use of cosmetics is a major source of overall exposure, the total error is considered to be moderate.

7.2.4 Exposure levels

As far as possible, Dutch data on exposure levels have been used. Data originate generally from one source and from a restricted number of samples, with unknown representativeness. Although we believe that the order of magnitude of contamination used for most of the sources is in line with data from other countries, the abundance of different cosmetic products and brands, the lack of insight in the representativeness of tested products, the error in the mean exposure levels is considered potentially to be moderate. Also, no details are given on the analytical methods.
For calculating daily oral exposure, we assumed that leaching rate is constant during the total 'lifetime' of evaluated products, and represents true leaching 'in vivo'. These assumptions may result in an over- as well as underestimation of the actual leaching rate.
In several cases not all the relevant data have been published on exposure average and variation in exposure. The estimates for the mean exposure, used in the risk assessment, can be affected most likely by several factors. Probabilistic modelling can describe and limit some of these uncertainties.
Overall, the effect of the uncertainty in exposure levels on the overall risk assessment is considered to be moderate to high.

7.2.5 Bioavailability

For most substances only part of the external exposure will result in relevant internal exposure. No correction has been made for uptake after oral exposure (and after inhalation exposure for smoking as background exposure).
The variation in uptake through the skin can be quite large. Various experimental data have been used to estimate the skin penetration. The effect of uncertainties in these data is considered to be low, or at most moderate.

7.3 Toxicity and Risk Assessment

7.3.1 Animal data

One problem in the available data is the lack of consistent unit risk values for all nitrosamines[3] consumers may be exposed to. Therefore, NDMA has been used to represent all nitrosamines, because of ubiquitous exposure to this compound. However, it is a relatively potent carcinogen and variation in potency among nitrosamines is large, spanning a range of 4 to 5 orders of magnitude. Consequently, the choice for NDMA as a representative nitrosamine will probably lead to an overestimation of health gains obtained from exposure reducing measures, as stated above. This overestimate may be substantial, and be several orders of magnitudes

[3] In 2007 DECOS will publish (draft) report with unit risk estimates for nearly 20 occupationally relevant nitrosamines.

The uncertainty surrounding the dose response analysis of the oral NDMA cancer data used is low, due to the availability of a large number of data spanning many relatively low doses. However, this is not a measure of the uncertainty of the unit risk when applied to humans, as the uncertainty of the extrapolation from animal to human was not taken into account nor the uncertainty associated with fitting a multistage model to the dose–response data. In general, the multistage model is considered to be a conservative approach, which overestimates the carcinogenic risk provoked by the animal exposure. Overall the uncertainty surrounding the unit cancer risk in humans cannot be quantified, but it may be several orders of magnitude.

7.3.2 Epidemiologic data

The available evidence from epidemiologic studies showing that nitrosamine exposure may cause several types of cancer is quite consistent, although not yet established as proven. Evidence available from occupationally exposed populations (workers in the rubber industry and workers exposed to metal working fluids) as well as the general population exposed through the diet (nitrosamines from mainly cured meat and beer), both support an increased risk of several cancers. Although a weight-of-evidence approach is preferable, we based our risk estimates on one dietary epidemiological study only. This choice was based on several considerations, such as availability of quantitative exposure data and adjustment for confounding by other risk factors for cancers. Also, the exposure routes in the occupational studies (mostly through inhalation) were not directly comparable to the exposure routes of consumer products. However, the choice for one study implies more uncertainty in the resulting risk estimates than is warranted for the body of available evidence.
Although the evidence across the available epidemiological studies on dietary intake of nitrosamines (mostly assessed as NDMA) is consistent with relative risks of 1.4 or more between high and low exposed groups (quantiles) in the population, we can not exclude some residual confounding due to other, unmeasured or unknown risk factors for the relevant cancers. We conducted a sensitivity analysis, assuming a relative risk to be attenuated to 1.5 instead of 2 as observed in the underlying study. Consequently, we concluded that the reduction in DALYs due to reduction in nitrosamine exposure from consumer products lies between 0 and 77000 DALY. However, incorporating all available data should reduce the range of uncertainty.
Based on the epidemiological evidence, we considered the stomach and colorectum the major targets of nitrosamine exposure. Whether this is justified needs to be confirmed in further studies.

7.3.3 Comparison animal and epidemiological data

Compared to the DALY estimate derived from animal studies, the potential DALY reduction based on epidemiological data is quite large. The difference might be due to several reasons:

- A difference in sensitivity between humans and rats. Considering the relative consistency of the epidemiological studies, this argument merits serious attention and more research should be conducted to confirm the association between oral nitrosamine exposure in humans and risk of several types of cancer.
- In epidemiologic studies, the effect measure is a Relative Risk (RR), which is transportable from the study population to the target population of the risk assessment. The RR multiplies the background risk of the relevant cancer in the target population. If

the background risk and the RR are high, the resulting risk is also high. The effect measure derived from animal studies is usually an Excess (or additional) Lifetime Risk. This measure adds to the risk in the target population. Therefore, the background risk of cancer in the target population does not influence the risk estimate based on animal studies.

- Considering the uncertainty in both estimates, the observed large difference between estimates based on animal and epidemiological data might in reality be smaller.

In this case, we used the average DALY of 8 per average cancer case as used for all cancers in general. It is not unlikely that the average loss of life years per cancer case through premature death will be higher than ca. 8 years as children are the highest exposed age group and thus the health effects. However, no data are available that may afford the quantification of this age effect.

7.4 Summary

Overall, there are a great many uncertainties in exposure levels, dose-response relationships and hence in related heath effects and associated heath gain. The potentially largest source of restricted validity in the estimated health gain is thought to be the variation in specific nitrosamines and the related lack of specific exposure and specific toxicity data. Estimations based on animal and human epidemiological data yielded very different results, for which, within the scope of this case, no reason could be given with certainty. These, also potentially for other substances, large differences should be taken into account when evaluating measures in terms of health gain.
It should be noted that the validity of exposure data might differ considerably for the period before and after the measures. Since this might be the case, the estimated health gain might be invalid. The results of this case should therefore be interpreted with the largest caution.

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Appendix 10 Case report Toluene

Susan Peters, Liesbeth Preller, Gerwin Schaafsma, Dinant Kroese (TNO).

1. Introduction

This case addresses the influence of legislation on exposure to toluene from consumer non-food products in the Dutch general population. Toluene is present in various consumer products, including paints, adhesives, varnishes, and inks for pens. It has been chosen because of the potential reproductive toxicological effects. Especially the ‘do-it-yourself’ population and hobbyists are exposure groups of concern.

2. Background information

2.1 C, M. R, or S legislation

The classification of toluene with regard to human health effects is as follows (EU-RAR, 2003):

- Repr.Cat.3; R63 Possible risk of harm to the unborn child;
- Xn; R48/20-65 Harmful: danger of serious damage to health by prolonged exposure through inhalation. May cause lung damage if swallowed;
- Xi; R38 Irritating to skin;
- R67 Vapours may cause drowsiness and dizziness.

Following the EU Directive 76/769, toluene may not be placed on the market or used as a substance or constituent of preparations in a concentration equal to or higher than 0.1% by mass in adhesives and spray paints intended for sale to the general public. This amendment to the Directive became active in 2005 (European Union, 2005).

Since 1995 the Dutch law requires gas filling stations which deliver over 500 m^3 gasoline a year, to have gas pumps which contain control equipment for the vapour recovery system, which prevents gasoline vapour from escaping to the air (Besluit tankstations milieubeheer, 1995).

Table A10.1. Dutch and European legislation.

Product	Limits	Year of enforcement	
Adhesives	Maximum concentration by mass of 0.1%	2005	EU Directive 2005/59/EC
Spraying paints	Maximum concentration by mass of 0.1%	2005	EU Directive 2005/59/EC
Gasoline	Vapour recovery system obligatory	1995	‘Besluit tankstations milieubeheer’

The Dutch limit value for occupational exposure (MAC-value) is 150 mg/m^3 (8hr TWA). At present, no limit value exists for short term exposure yet. However, a short term limit value of 384 mg/m^3 (15 min TWA) has been suggested by the sub commission MAC-values, based on indicative values of the European Commission (Directive 2006/15/EU).

2.2 General information

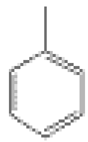
2.2.1 Substance information

Toluene is a clear, colourless liquid with an aromatic odour. It is a natural constituent of crude oil and is produced from petroleum refining and coke-oven operations. At room temperature, toluene is both volatile and flammable. Because toluene is lipid soluble, it has a moderate tendency to bioaccumulate in the food chain (ATSDR, 2001).

Commercial toluene is mainly (80%) used as an intermediate in the production of other chemicals. Approximately 20% of commercial toluene is used as a solvent carrier in paints, thinners, adhesives, inks and finally as a processing aid (extraction solvent) in the production of pharmaceutical and other chemical products (EU-RAR, 2003).

Synonyms for toluene (CAS No 108-88-3) include methylbenzene, phenyl methane, toluol, methyl benzol and methacide.

Molecular formula: C_7H_8



2.2.2 Exposure sources and routes

Toluene is present in many consumer products, including household aerosols, paints, varnishes, adhesives, glues, and inks for pens (EU-RAR, 2003).

Table A10.2. Potential sources of exposure to toluene for consumers, both adults and children (based on expert judgement).

	Exposure routes			**Target population Consumer**	
	Inhalation	**Dermal**	**Oral**	**Children**	**Adults**
Glue/adhesives	x	x			x
Paint	x	x			x
Paint thinner	x	x			x
Nail polish	x	x		x	x
Correction fluid	x				x
Ink from pens	x	x	(x)	x	x
Printing ink	x			x	
Car polish	x	x			x
Cleaning agent		x		x	x
Rust inhibitor	x	x			x
Gasoline	x				x
Cigarette smoke - passive	x			x	x
Cigarette smoke - active	x				x

Besides consumer exposure, occupational exposure can be relatively high for a number of jobs. Exposure to toluene is possible in industries where toluene and gasoline is produced. Toluene is also used as a chemical agent or as ingredient in many products or preparations used occupationally, like polymer, paint, lacquer and varnishes, pulp, paper and board, textile processing, and chemical industry (EU-RAR, 2003). However, occupational exposure is beyond the scope of this study.

2.2.3 Selection of exposure scenarios

The relevant data reported in the Risk Assessment Report (EU-RAR, 2003) were used and where applicable completed with additional published data and/or adapted to the Dutch consumer situation. According to the legislation in the Netherlands, the following exposure scenarios are chosen:
Glue used for modelling to scale
Spray painting applied by hobbyists
Filling gasoline at self service gas stations

Although carpet gluing might be a potential risk (EU-RAR, 2003), this scenario is not taken into account since the frequency is assumed to be very low among consumers.

Further, background exposure through indoor air contamination and cigarette smoking is evaluated.

3. Description of exposure

3.1 General

To make the exposure assessment for the selected scenarios the following defaults are used:

Inhalation rate:	20 m^3/day
Consumer body weight:	70 kg
(Hobby) room size:	20 m^3

Toluene is absorbed rapidly via inhalation and the amount absorbed depends on pulmonary ventilation. For both inhalation and dermal exposure, 100% absorption is assumed (EU-RAR, 2003).

In the RAR several exposure levels were calculated. In this case report, various exposure scenarios were computed mostly based on calculations from the RAR. However, since the RAR is usually based on reasonable worst case exposure scenarios, estimates have been made for average exposure for use in this case, to obtain a more realistic estimate for general exposure reduction and health gain.

3.2 Glue used for modelling to scale

The gluing scenario is estimated for hobbyists (e.g. modelling to scale aeroplanes or ships). Rastogi (1993) investigated twenty-six glue products for non-occupational use, of which twenty-two contained toluene. The percentages are presented in Table A10.3. A maximum of 28.5% was found in super glues (liquid cement for plastic) used for modelling to scale.

Almost 70% of the glues for hobbyists already contain less than 0.1% toluene, even before enforcement of the legislation. Assumed is that the remaining glues (31.8%) will be used by one third of the hobbyists, with an average concentration of about 15% (median percentage of group with highest levels).

Table A10.3. Toluene in glues for hobby use (Rastogi, 1993)

Percent range	**Number of products**
0 – 0.042	9 (40.9%)
0.043 – 0.05	6 (27.3%)
1.0 – 28.5	7 (31.8%)
Total	22 (100%)

According to APA (1998, in: EU-RAR, 2003), the amount used for this type of glues will be 0.5 g per event. This amount seems realistic for a hobbyist modelling to scale. Skin is assumed to be exposed to approximately 0.5% of the used glue, based on information on paint (Bremmer and Van Veen, 1999) and all toluene is assumed to be available for absorption (EU-RAR, 2003).
The dermal exposure to toluene is then:
500 mg glue * 15% * 0.5% * 1/(70 kg bw) = 0.005 mg/kg bw per event.

The remaining toluene in glue is then available for inhalation exposure. It is assumed that the room is slightly ventilated and that 100% of the glue evaporates. The air concentration toluene in the room than will be:
(500-2.5) mg glue * 15% * 1/(20 m^3 room volume) = 3.75 mg/m^3
An exposure time of (30 min use + 180 min stay after use) 210 min/day (US EPA, 1987) is chosen. The exposure by inhalation is then:
3.75 mg/m^3 * 1/(70 kg bw) * 20 m^3/day inhaled volume * 210 min/event * 1/(1,440 min/day) = 0.16 mg/kg bw per event = 160 μg/kg bw per event.

The total toluene exposure in this scenario will be 0.16 mg/kg bw per event (= 160 μg/kg bw per event), for those assumed 1/3 of the hobbyists using glue with toluene > 0.1%. Other glue users will be exposed to less than 0.1/15 * 0.16 = 1.10 μg/kg bw per event. The average exposure among all 5000 hobbyists will then be 54 μg/kg bw per event, whereas the average exposure concentration over all 5000 hobbyists will be 1.3 mg/m^3 during gluing.

According to the EU Directive 76/769 for toluene, the concentration by mass in adhesives available for consumers is restricted at 0.1%. Assuming that after 2005 all glues used by hobbyists contain 0.1% toluene in stead of 15%, with similar remaining conditions, the exposure per will decrease with 99.3%. The total toluene exposure for all hobbyists after establishment of the EU Directive will be 0.1/15 * 0.16 = 1.10 μg/kg bw per event, with an average exposure concentration of 0.025 mg/m^3.

An average frequency of one event per week is assumed. In The Netherlands, the plastic modelling society has 1,000 members (IPMS, 2006). The actual number of persons performing scale modelling will be much higher. The number of people exposed to the toluene levels calculated above due to gluing with scale modelling is therefore assumed to be about 5,000 in the Netherlands.

As two-third of the hobbyists was already assumed to be using glue with less than 0.1% toluene, the exposure will not decrease for them after enforcement of the directive. The calculated reduction will only be counting for 1,750 of the hobbyists.

3.3 Spray painting

The spray painting scenario is estimated for hobbyists (e.g. modelling to scale aeroplanes or ships). Many toluene containing spray paints are not available for consumers. A Dutch study however found five products, containing 5 to 20% toluene, which were meant for consumers. Besides, professional products which can be interesting for consumers (due to volume, price, and application features) are relatively easy to obtain by consumers (KvW Noord, 2003).

According to APA (1998, in: EU-RAR, 2003), the amount of paint used will be 100 g per event. This amount seems realistic for a hobbyist modelling to scale. The toluene concentration is chosen to be 12.5% in this calculation as average concentration of the paints containing toluene.
The skin is assumed to be exposed to approximately 0.5% of the used paint (Bremmer and Van Veen, 1999) and all toluene is considered to be available for absorption. The dermal exposure on a painting event is then:
100,000 mg * 12.5% * 0.5% * 1/(70 kg bw) = 0.9 mg/kg bw per event.

The toluene in the remaining paint is available for inhalation exposure.
It is assumed that the room is not ventilated and that 100% of the toluene in paint evaporates. The air concentration toluene then will be:
(100,000 -500) mg paint * 12.5% * 1/(20 m^3 room volume) = 620 mg/m^3.
An exposure period similar to gluing of (30 min use + 180 min stay after use) 210 min/day is used. The exposure is then:
620 mg/m^3 * 1/(70 kg bw) * 20 m^3/day inhaled volume * 210 min/event * 1/(1,440 min/day) = 26 mg/kg bw per event.

The total toluene exposure in this scenario will be 27 mg/kg bw per event.

According to the EU Directive 76/769 for toluene, the concentration by mass in spraying paints available for consumers is restricted at 0.1%. Assuming that after 2005 spraying paints used by hobbyists contain 0.1% toluene in stead of 12.5%, with similar remaining conditions, the exposure per event will be 0.1/12.5* 27 = 0.22 mg/kg bw per event, after establishment of the EU directive.

An average frequency of one event per week is assumed. In the Netherlands, the plastic modelling society has 1,000 members (IPMS, 2006). The actual number of persons performing scale modelling will be much higher. The number of people exposed to the toluene levels calculated above due to gluing during modelling to scale is therefore assumed to be about 5,000 in The Netherlands.

3.4 Filling gasoline at self service gas stations

Some data are available for exposure during filling gasoline at self service gas stations. On average, gasoline contains 5% to 7% toluene by weight (ATSDR, 2001), but it may have up to 35% toluene (MSDS gasoline unleaded, 2003). Full-shift inhalation exposure measurements (in 1993 to 1998) to toluene on 451 service station attendants in Europe show a range of 0.012 to 2.8 mg/m^3 with an arithmetic mean of 0.51 mg/m^3, when there was no vapour recovery system (CONCAWE, 2000). Toluene exposure from diesel and LPG is assumed to be negligible.

In the Netherlands, 81% of the passenger cars use gasoline as a fuel. In 2004 that were 5,892,000 cars. It is assumed that most cars have one main driver, who also usually does the refuelling. This makes a population at risk of about 6 million people in the Netherlands. Together they used 5,547 million litres gasoline that year. (BOVAG, 2005) This makes an average of 941 litres per car. Assuming an average gasoline volume of 35 litres for one tank event, the total tank events for a car owner comes down at 27 events per year.

The exposure period is usually only the time it takes to fill the gasoline tank. A standard gasoline pump has a speed of 40-50 l/min. To fill a tank of 35 litres, it takes about one minute. With a concentration of 0.51 mg/m^3 (= 510 µg/m^3) and an exposure period of 1 min/event, the inhalation exposure per event is assumed to be:
510 µg/m^3 * 20 m^3 * 1 min/event * 1/(1,440 min/day) * 1/(70 kg bw) = 0.10 µg/kg bw/event.
With an assumed frequency of 27 events per year, the exposure per day will be:
0.10 µg/kg bw/event * 27 events/year * 1/(365 days/year) = 0.0073 µg/kg bw/day.
The toluene air concentration at pumps with a vapour recovery system should be 75% lower; 128 µg/m^3. This will also lead to a 75% reduction in exposure; 0.025 µg/kg bw/event and 0.002 µg/kg bw/day.

Dermal exposure during filling of gasoline at self service gas stations is considered negligible (EU-RAR, 2003).

3.5 Background exposure

The most likely pathway by which people may be exposed to toluene is by breathing contaminated air. Toluene concentrations in the outdoor air are highest in areas of heavy traffic, near gasoline filling stations, and near refineries. Toluene is short-lived in ambient air because of its reactivity with other air pollutants (ATSDR, 2000).

The concentrations of toluene in outdoor air have been found to be quite low in remote areas, but levels of 1.3-6.6 ppb (1 ppb = 3.8 µg/m^3) are common in suburban and urban areas. Indoor air concentrations are often several times higher (averaging 8 ppb; 30.4 µg/m^3) than outside air (ATSDR, 2001). Since most people spend a large amount of the day indoors, about 90% of their time (Van Andel et al., 2002), indoor air levels are likely to be the dominant source. Based on an assumed typical indoor air concentration of 30 µg/m^3 with an inhaled volume of
20 m^3/day, non-smokers will be exposed to about 0.6 mg of toluene a day. Which corresponds with 9 µg/kg bw per day for a person of 70 kg. Smokers absorb about 80-100 µg of toluene per cigarette (ATSDR, 2001). So if one smokes 20 cigarettes per day, another

2 mg of toluene is added to the daily exposure (29 µg/kg bw per day for a person of 70 kg).

An overview of exposure through different sources is given section 6, Table A10.4.

4. Description of toxicology

Introduction
The toxicology of toluene has been studied extensively. The present evaluation is based on the evaluation of toluene under Council Regulation (EEC) 793/93 on the Control and Evaluation of the Risks of Existing Substances which was finalised in 2003 (EU-RAR, 2003). For each toxicological endpoint it was checked whether in the toxicological profile of toluene published by the Agency for Toxic Substances and Disease Registry (ATSDR, 2000) additional relevant quantitative information was specified.

Toxicokinetics (EU-RAR, 2003)
Toluene is absorbed rapidly via inhalation (assumption 100%) and the amount absorbed depends on pulmonary ventilation. Absorption from the gastrointestinal tract seems to be high. Dermal uptake after skin exposure to liquid toluene occurs to a limited degree. Dermal exposure to toluene vapours is not likely to be an important route.
Toluene distributes widely throughout the body with the highest concentrations in fat. Toluene readily passes the placenta and is excreted in human breast milk. Toluene biotransformation occurs by oxidation in the liver. The major metabolite is benzoic acid, which is linked to glycine, resulting in the formation of hippuric acid.
Toluene is mainly eliminated via urine, as hippuric acid, while a small part is exhaled unchanged via the lungs.

Additional data on toxicokinetics from ATSDR (2000)
In both humans and rats, up to about 75–80% of toluene that is absorbed can be accounted for by urinary excretion of the principal metabolite, hippuric acid (Lof et al., 1993; Ogata, 1984; Tardif et al., 1998, cited in ATSDR, 2000). Excretion of minor metabolites including S-benzyl mercapturic acid, S-*p*-tolulyl mercapturic acid, and conjugates of *ortho*- and *para*-cresol account for less than 5% of absorbed toluene. Excretion of nonmetabolized toluene in exhaled air can represent from 7 to 20% of absorbed toluene (Carlsson, 1982; Leung and Paustenbach, 1988; Lof et al., 1993, cited in ATSRD, 2000).

Analyses of kinetic data for toluene concentrations in blood, exhaled breath, or adipose tissue following inhalation exposure of humans (Leung and Paustenbach, 1988; Lof et al., 1993; Pellizzari et al., 1992; Pierce et al., 1996, 1999, cited in ATSRD, 2000) and rats (Rees et al., 1985, cited in ATSDR, 2000) indicate that most absorbed toluene is rapidly eliminated from the body and that a smaller portion (that which gets into adipose tissues) is slowly eliminated. Using three-phase exponential mathematical models to describe curves of human blood concentration as a function of time up to 3–5 hours after 2-hour exposures to 100 or 53 ppm toluene (410 and 210 mg/m^3, respectively), calculated half-lives (the time to decrease the amount in the phase by one-half) were 1.5 and 3 minutes for the initial phase, 26 and 40 minutes for the second phase, and 3.7 and 12.3 hours for the final phase (Lof et al., 1993; Sato et al., 1974, cited in ATSDR, 2000).

Acute toxicity (EU-RAR, 2003)
In humans experimentally exposed to toluene, concentrations of 75 ppm (285 mg/m^3) and above caused headache, dizziness, and feeling of intoxication, irritation and sleepiness.
A NOAEC of 40 ppm (150 mg/m^3) for these effects has been identified. Furthermore, toluene causes impaired neuropsychological function in humans from levels of 75 ppm (285 mg/m^3).

Regarding animals, an LC50 of 28,100 mg/m^3/4 hours (rats), an oral LD50 of 5.58 g/kg bw (rats) and a dermal LD50 of 12.4 g/kg bw (rabbits) have been reported.

Irritation (EU-RAR, 2003)
Toluene has been shown to be irritating to the skin of rabbits, mice, and guinea pigs. Furthermore, it is well known that toluene has a degreasing effect on the skin of humans. Liquid toluene is irritating to eyes in animals, while toluene vapours in concentrations at and above 75 ppm causes complaints of eye irritation in humans. A NOAEC of 40 ppm (150 mg/m^3) for eye irritation has been identified.
Animal studies suggest that toluene can cause irritation to the respiratory tract, though at very high concentrations.

Sensitisation (EU-RAR, 2003)
The results of a guinea pig maximisation test indicate that toluene is not a skin sensitiser. It is unlikely that toluene is a respiratory allergen.

Repeated dose toxicity (EU-RAR, 2003)
General toxicity
In the rat a NOAEL for general systemic toxicity of 625 mg/kg/day for repeated oral exposure was identified in a 90-day study. At higher levels (1,250 mg/kg and above) neurone necrosis and organ weight increases were found. In a similar 90-day mouse study effects (liver enlargement and one death) were found at 1,250 mg/kg.
A NOAEC for general systemic toxicity of 625 ppm (2,344 mg/m^3) for repeated exposure via inhalation (not reported whether exposure was 'nose-only' or 'whole body') was identified in a 15-week study with rats. At the higher exposure levels (from 1,250 ppm (4,688 mg/m^3)) a decrease in leukocyte count in females, and relative organ weight increases (kidney, liver, brain, heart, lung and testes) were found. In a two-year rat study a NOAEC of 300 ppm (1,125 mg/m^3) was found, this was the highest dose level tested (not reported whether exposure was 'nose-only' or 'whole body'). In another two-year rat study, the lowest dose tested, 600 ppm ((2,280 mg/m^3) was a LOAEC for increased occurrence of nasal toxicity (i.e., erosion of the olfactory epithelium and degeneration of the respiratory epithelium (males and females); inflammation of the nasal mucosa and respiratory metaplasia of the olfactory epithelium (females only)) and forestomach ulcers in males (not reported whether exposure was 'nose-only' or 'whole body').
For the dermal route, no data on repeated dose toxicity were found.

Neurotoxicity
Repeated exposure to toluene via inhalation has been shown to affect the central nervous system and the inner ear. These endpoints were not part of the studies investigating general toxicity, but are toxicologically important.

Long-term high-level exposure to toluene (abuse) via inhalation has caused serious damage to the brain including severe neurological abnormalities and brain atrophy. As these effects are not associated with normal use of toluene, they are not further specified.

Long-term exposure to volatile solvents at exposure levels possible in occupational settings may lead to organic brain syndrome (i.e., mental dysfunction (as delirium or senile dementia) resulting chiefly from physical changes in brain structure and characterized especially by impaired cognition). Two studies show an increased prevalence in toluene-exposed workers compared with the control group. In both studies the length of employment was high, while only recent exposure data were well documented. Exposure during the years preceding the investigation was not well described. Therefore, LOAECS and NOAECS can not be determined for organic brain syndrome, since well-documented exposure information covering a considerable proportion of the entire period of employment would be necessary.

In animals several effects on the central nervous system have been found. Neuronal cell necrosis in the dentate gyrus and Ammons horn of the hippocampus was seen in both male and female rats that received 1,250 or 2,500 mg/kg in a 90-day study. Also necrosis and/or mineralization were present in the granular layer of the cerebellar cortex. A reduced number of neurones in the hippocampus and a reduced hippocampal weight in rats exposed to 1,500 ppm (5,625 mg/m^3) of toluene via inhalation for 6 months were found.
In very young rats exposed to toluene via inhalation on postnatal day 1-28, a reduced volume of certain hippocampal structures was found at 100 and 500 ppm (380 and 1,900 mg/m^3). Changes in brain neurochemistry in rats have been described. Effects were found at an exposure level of 80 ppm (300 mg/m^3) after only 3 days of exposure. Long-term exposure has been shown to cause effects on brain neurochemistry at 500 ppm (1,900 mg/m^3) still present six months after the last exposure, indicating possible irreversible changes.

Occupational exposure to toluene at high concentrations may increase the risk of developing mild high-frequency hearing loss. However, the studies showing this effect are not appropriate for determining a LOAEC or NOAEC.

The ototoxicity of toluene in the rat is well documented by behavioural, electrophysiological, and morphological techniques. Impaired hearing function in the rat has been demonstrated at exposure concentration levels of 1,000 ppm (3,750 mg/m^3) for as little as 2 weeks.
A 16-week NOAEC of 700 ppm (2,625 mg/m^3) has been reported.

Additional data on repeated dose toxicity from ATSDR (2000)
Neurotoxicity
In the toxicological profile of toluene of the ATSDR (2000) additional relevant references were described. One of these references (Zavalic et al., 1998a, cited in ATSRD, 2000) was used by the ATSDR to calculate a chronic inhalation Minimal Risk Level (MRL).
Studies of occupationally exposed workers indicated that chronic exposure to average concentrations as low as 30–130 ppm toluene damages hearing and colour vision presumably involving, at least in part, effects on neurological components of these systems (Abbate et al. 1993; Morata et al., 1997; Zavalic et al., 1998a, 1988b, 1988c, all cited in ATSDR, 2000). Hearing loss has also been reported in laboratory animals exposed to 700–1,500 ppm toluene (Campo et al., 1997; Johnson and Canlon, 1994; Lataye and Campo, 1997; Pryor et al., 1984b all cited in ATSDR (2000).

Low-level occupational exposure to an average of 97 ppm toluene for 12–14 years had an apparent effect on hearing in 40 rotogravure workers when brainstem auditory evoked potential (BAEP) results were compared to a group of 40 workers who were of comparable age but were not exposed to toluene (Abbate et al., 1993 cited in ATSDR (2000)). Workers were carefully screened to eliminate slight hearing abnormalities or exposure to other chemicals. Two series of stimuli were used, one with 11 repetitions/second and one with 90 repetitions/second. In both cases the intensity was 80 dB/nHL. Mean latencies were significantly higher for the exposed group than the control group for each BAEP wave evaluated (I, III, and V). Discernment mean values for the exposed and control groups were distributed homogeneously with very little overlap of exposed and control responses for both the 11-repetition and 90-repetition cycles. Wave I showed the most pronounced increase in latency. According to the authors, the effects on Wave I could be due to either a change in the membrane of the peripheral receptor, a modification of the structure of the junction, or a change in the stimulus transduction mechanism.

Zavalic et al. (1998a, cited in ATSDR, 2000) examined colour vision in 83 controls, 41 shoemakers, and 32 printers exposed respectively to geometric mean toluene concentrations of 0, 35, or 156 ppm. Toluene exposure was estimated by measuring toluene levels in the air and in the blood of workers, and by measuring the amount of hippuric acid and orthocresol in their urine at the end of the work shift. The technology, ventilation, and types of workplaces included in the study had not changed in the preceding 30 years. Colour confusion was significantly higher in printers compared with both shoemakers and controls. Colour confusion index was increased in shoemakers compared with controls, but the difference was not significant (Zavalic et al. 1998a, cited in ATSDR, 2000). Regression analysis established a significant correlation between colour confusion as a dependent and alcohol intake and age as independent variables for the control group. Age- and alcohol-adjusted colour confusion index was significantly increased in printers compared with shoemakers and controls, and in shoemakers compared with controls. After age and alcohol adjustments, individual colour confusion indices were significantly correlated with individual exposure estimates (air, blood, or urine) in printers, but in shoemakers, the correlation was not statistically significant. The significantly increased colour confusion index for the shoemakers in this study was assessed as a less-serious adverse effect and a LOAEL of 35 ppm was established.

Mutagenicity (EU-RAR, 2003)
Toluene is considered to be non-genotoxic.

Carcinogenicity (EU-RAR, 2003)
Toluene was not considered to be carcinogenic to rats or mice after long term respiratory exposure.
Toluene has been evaluated by IARC in 1989 and 1999. Overall, IARC classified toluene in group 3 (The agent is not classifiable as to its carcinogenicity to humans).

Toxicity for reproduction (EU-RAR, 2003)
Effects on fertility
Toluene does not have clear effects on fertility in rats. However, in male rats exposed to 2,000 ppm (7,500 mg/m^3) a significantly reduced sperm count (approximately 20-25%) was

found with a NOAEC of 600 ppm (2,250 mg/m^3). In humans no study of adequate quality has been found.

Developmental toxicity
Developmental toxicity of toluene has mainly been studied in rats. Lower foetal and birth weight was found in offspring of dams exposed to inhalation concentrations around 1,000 ppm (3,750 mg/m^3). The NOAECs for lower birth weight were around 600 ppm (2,250 mg/m^3).
Long-lasting developmental neurotoxicity (impairment of learning ability) has been demonstrated in offspring exposed pre-natally or pre- and post-natally to 1,200 ppm (4,560 mg/m^3).

Rates of late spontaneous abortions were determined using a reproductive questionnaire in 55 women with 105 pregnancies exposed to toluene (mean 88 ppm, range 50-150 ppm), 31 women (68 pregnancies) working in the same factory in departments where little or no exposure to toluene occurred (0-25 ppm), and an external community control group of 190 working class women with 444 pregnancies (Ng et al., 1992b, cited in ATSRD, 2000). Significantly higher rates for late spontaneous abortions defined as pregnancy loss between weeks 12 to 28 were noted in the toluene exposed women compared with those in the internal and external control groups (12.9% vs. 2.9-4.5%). This study suggests an increased risk of late spontaneous abortions associated with exposure to toluene at levels around 88 ppm (range 50-150 ppm).
Furthermore, case studies on high-level toluene exposure of pregnant women (sniffing) provide evidence of developmental toxicity (physical and neurological abnormalities) in humans.

5. Critical NOAELs for current risk assessment

Critical effects of toluene which are taken into account in the risk assessment
Adverse effects on the nervous system are the critical effects of concern from acute and chronic exposure to toluene. In this risk assessment short-term and long-term exposure to toluene are considered separately. Acute exposure is associated with reversible neurological symptoms progressing from fatigue, headaches, and decreased manual dexterity to narcosis with increasing exposure levels. Furthermore, eye irritation is observed at the same levels at which effects on the nervous system were reported in humans. Results from studies of groups of occupationally exposed workers suggest that chronic exposure to toluene at lower exposure levels (from about 50 to 200 ppm) can produce subtle changes in neurological functions including cognitive and neuromuscular performance, hearing, and colour discrimination. Supporting data come from studies of toluene-exposed animals showing changes in behaviour, hearing loss, and subtle changes in brain structure, electrophysiology, and levels of neurotransmitters.
Case reports of birth defects in children of mothers who abused toluene during pregnancy suggest that exposure to high levels of toluene may be toxic to the developing foetus. Results from animal studies indicate that toluene is not a teratogenic agent, but can provoke lower birth weight, delayed postnatal development and behavioural effects.

Acute inhalation toxicity
Based on the available data, a human NOAEC of 40 ppm (150 mg/m^3) toluene has been established for headache, dizziness, feeling of intoxication, irritation and sleepiness.

Acute dermal toxicity
The available data show that toluene has a low toxic potency after acute dermal exposure in animals.

Repeated dose inhalation toxicity
In accordance with the derivation of the chronic minimal risk level for inhalation exposure by the ATSDR (ATSDR 2000), the study of Zavalic et al (1988) (cited in ATSDR (2000)) is used for the derivation of a derived no effect level. In this study a LOAEC of 35 ppm was established for alcohol-and age-adjusted colour vision impairment.

Repeated dose dermal exposure
No data are available on repeated dose dermal toxicity of toluene.

Toxicity for reproduction
Developmental toxicity
Inhalation exposure
In humans, limited data indicate an increased risk for spontaneous abortions at dose levels around 88 ppm (330 mg/m^3).

In animals (rats), 600 ppm (2250 mg/m^3) was a NOAEC for lower birth weight. In another study, long-lasting developmental neurotoxicity study (impairment of learning ability) has been demonstrated in offspring exposed prenatally or pre- and postnatally to 1,200 ppm (4,560 mg/m^3).

Dermal exposure
No data are available on repeated dose dermal toxicity of toluene.

6. Calculation of Public Health Gain

6.1 Decrease of exposure

Legislation on exposure to toluene has focused on different types of consumer products: adhesives, spray paints and gasoline.

As only few measured data are available for toluene in consumer products, especially after establishment of legislation, it is difficult to estimate the effect of the intervention. Hypothetically, based on levels given by legislation, the reductions in toluene exposure will be as shown in Table A10.4. They are only relevant for adults, as children do not use the glue and spray painting described, and only adults refuel their cars. Except for background exposure, all exposures are short term exposures, merely restricted to the duration of the event and some time afterwards.

Table A10.4. Exposures before and after legislative measures

Exposure source	**Exposure**		**Legislation**	**Reduction (%)**
	Before	**after**		
Glue used for modelling to scale	160 µg/kg bw/event 1.3 mg/m³ (average whole population) 3.75 mg/m³ (highly exposed population)	1.10 µg/kg bw/event 0.025 mg/m³	EU directive 2005/59/EC	99
Spray painting modelling to scale	27000 µg/kg bw/event 620 mg/m³ during event	220 µg/kg bw/event 5 mg/m³ during event	EU directive 2005/59/EC	99
Gasoline filling	0.10 µg/kg bw/event 0.51 mg/m³ during event	0.025 µg/kg bw/event 0.13 mg/m³ during event	'Besluit tankstations milieubeheer'	75
Background exposure	9 µg/kg bw per day 0.03 mg/m³ 29 µg/kg bw per day		Non-smokers Smokers	

6.2 Increase Margin of Safety

The margin of safety (MOS) approach is another method to describe the effect of the decrease in exposure. Generally, a reference MOS describes the margin which is allowed between human exposure and the dose at which no adverse affects are observed in animals or humans. When the MOS is too low, efforts should be made to reduce the exposure until the desired MOS is reached.
In Table A10.5 the MOS approach using the exposure levels of toluene before and after the reduction is presented.

Glue used for modelling to scale
Toluene exposure occurs only once (210 minutes) a week.
Spray painting for modelling to scale
Toluene exposure occurs only once (210 minutes) a week.
Gasoline filling
Toluene exposure occurs only 27 events (1 minute/event) per year.
Based on the available toxicokinetic data on toluene (rapid elimination within few days, no accumulation occurs), only acute exposure is assumed for above mentioned scenarios. Therefore, the MOS approach is performed using data on acute toxicity. The repeated dose inhalation toxicity data and the data on toxicity for reproduction are not taken into consideration as repeated exposure is not expected based on the exposure scenarios.

For all scenarios only inhalation exposure is taken into account, because:
- the contribution of the dermal exposure in the different exposure scenarios to the total systemic dose is very low (see section 2.2.2 and 2.2.3);
- the assumption that all toluene on the skin is available for absorption (see section 2.2.2 and 2.2.3) is rather conservative (in the RAR it is concluded: 'dermal uptake after skin exposure to liquid toluene occurs to a limited degree. Dermal exposure to toluene vapours is not likely to be an important route');
- the limited available data show a low toxic potency for dermal exposure.

Acute inhalation exposure
Based on the available data, a human NOAEC of 40 ppm (150 mg/m^3) toluene has been established for headache, dizziness, feeling of intoxication, irritation and sleepiness.
It should be noted that the exposure duration in the different scenarios (scenario 1 and 2: 210 minutes/event and scenario 3: 1 minute/event) differ from the exposure duration from which the NOAEL was taken (6 hours). Based on the available data, it is not possible to conclude whether the effects are concentration or dose dependent. In the approach it is assumed that the effects are concentration related and therefore no correction for exposure duration was made.

Comparison of the acute inhalation NOAEC with the estimated exposure levels is presented in Table A10.5 as MOS values. The MOS values are evaluated by comparison with the reference MOS.
The reference MOS is 10 (the study was performed with students, an assessment factor of 10 for intraspecies differences covering the whole human population including the young and elderly human subpopulation is considered sufficient).
Application of the MOS approach shows that for the exposure scenario 'Spray painting for modelling to scale' the reduction in exposure level was sufficient to remove the concern for acute inhalation toxicity. For the other scenarios, the exposure values before the reduction were already of no concern.

Table A10.5. Margin of Safety before and after reduction in exposure levels (acute exposure)

Exposure scenario	**Exposure mg/m^3**		**MOS[1]**		**Concern**	
	before	**after**	**before**	**after**	**before**	**after**
Glue used for modelling to scale	3.75	0.025	40	5714	no	no
Spray painting for modelling to scale	620	5	0.24	30	yes	no
Gasoline filling	0.51	0.13	294	1172	no	no

[1] MOS: NOAEC of 150 mg/m^3 divided by exposure (mg/m^3)

6.3 Decrease in incidence of effect

Regarding acute exposure, for all the exposure scenarios (except 'Spray painting for modelling to scale'), the toluene exposure before and after reduction are both below the derived no effect levels (see Table A10.5). Therefore, for these scenarios (except 'Spray

painting for modelling to scale'), the decrease in consumer exposure to toluene is not considered related to a decrease in the incidence of adverse effects.
The reduction in exposure for the scenario 'Spray painting for modelling to scale' resulted in a 'no concern exposure level' for acute exposure. For a quantification of the decrease in incidence of effect related to this reduction in exposure the original study report is needed as from the data specified in the RAR no dose response curve can be derived.

6.4 Derivation of DALY

As specified in section 6.3, no dose response curve for acute toxic effects can be derived based on the available data. Therefore, the incidence of people who suffer from acute toxicity after toluene exposure at the exposure concentration of 620 mg/m^3 (exposure concentration for the scenario 'Spray painting for modelling to scale' before reduction in exposure) cannot be specified.
In the derivation of the DALY it is assumed that the whole target population experiences acute effects before the reduction in exposure and that no effects would occur after the reduction in exposure.

In general, a DALY is calculated as follows:
target population * disability weight * duration disability.

DALY before reduction in exposure (acute toxicity)
As specified in section 2.2.3, the number of people exposed to the toluene in this scenario in the Netherlands is 5000. It is assumed that the whole target population experiences acute effects.
For the disability weight, no data was available for the effects on which the acute inhalation NOAEC (headache, dizziness, feeling of intoxication, irritation and sleepiness) was established. Therefore, the disability weight was estimated using known disability weights (see Melse et al., 2000). The disability weight of visual impairments was taken (0.1). Using the EuroQol method the disability weight is considered 0.083-0.17, this figure is in the same order of magnitude as 0.1 (for details see a report by VTV (in Dutch) (1997)). Therefore, 0.1 is used as disability weight.
Regarding the duration of the disability, it is assumed that the effects are reversible and are present for about 4 hours. As the target population is exposed once a week, the duration of the disability amounts to: 4/(24*7).
Based on these data and assumptions the DALY is calculated to be:

5000 * 0.1 * {4/(24*7)} = 12 DALYs per year

DALY after reduction in exposure (acute toxicity)
It is assumed that no effects would occur after the reduction in exposure. Therefore, the target population is 0 which results in a DALY of 0.

7. Discussion and conclusion

7.1 Target population

For both gluing and spray painting it is difficult to obtain accurate information on the population at risk. It is possible that the population at risk is largely underestimated. According to the Nederlandse Vereniging van Modelbouwers NVM (Dutch Association of Modelling to Scale Hobbyists) the number of hobbyist in the Netherlands may be several 10 thousands. Besides, only two selected scenarios (gluing and spray painting by modelling to scale hobbyists) have been evaluated. Since it is not known to which extent these scenarios are responsible for use of toluene containing glues and spray paints, no conclusion can be drawn on the potential error in the estimated population at risk.
For gas filling, the data on number of cars using gasoline are based on Dutch survey information. The error in the estimated population at risk will be small.

7.2 Exposure

For both gluing and spray painting exposure has been estimated based on only few observations on content in products. For gluing it has been based on international data, for spray painting on Dutch data. It is not known to which extent these data are representative for all products used in the Netherlands for these purposes. Limited representativeness might potentially be responsible for a moderate error (> 10), caused by non representativeness of concentrations as well as on percentage of products with levels > 0.1 %, being the products in which the concentration should have been lowered. Also, it has been assumed that the use of products is distributed equally over the studied glues. True use of products may be totally different, inducing additional error.
Concentration levels have been estimated based on a very simple model with estimated amounts used, room size, and assumed absence of ventilation. It is unknown to what extent this model deviates form true exposure levels. The error in (average) exposure during application could be relatively large (factor 10-100).

Reduction of exposure and related health gain has been estimated based on the assumption that all products will comply with new legislation. No information is available to corroborate this assumption. Also, people might use professional products, with different legislation.

For refuelling gasoline, concentration levels based on true exposure measurements have been used for assessments. Measurements were done for full shift service station attendants. Their average daily exposure is potentially much lower than the peak exposure experienced during a very short time of actual filling a tank. The highest measured value for attendants was 2.8 mg/m^3, much lower than the critical effect level. Besides, exposure during filling lasts only a very limited time (1 to few minutes). To cause critical health effects, toluene has to reach the brain. It is doubtful whether a short duration with potentially moderate exposure levels could be responsible for relevant health effects.

Since the critical effect depends on concentration and not on total dose, errors in frequency of use do not affect the effect estimate.

Exposure may occur simultaneously through different sources, included ones which have not been studied. Concentration levels may add up to over a level at which health effects occur. This effect has not been taken into account.

7.3 Toxicology

The study which was used for acute inhalation toxicity was a well controlled human volunteer study. There are no indications for uncertainties in this study.

For the exposure scenarios 'Glue used for modelling to scale', 'Spray painting for modelling to scale' and 'Gasoline filling' only acute exposure is assumed based on the available toxicokinetic data on toluene (rapid elimination within few days, no accumulation occurs). The effects which may occur are considered reversible. It should be noted however that no data is available on the long-term consequences of the occurrence of acute effects each week.

No data is available on the relationship between acute exposure to toluene and the occurrence of reproduction effects.

7.3.1 Risk assessment

For a quantification of the effect of policy measures, background exposure levels should also be taken into consideration. The concentrations of toluene in outdoor air have been found to be quite low in remote areas, but levels of 1.3-6.6 ppb (1 ppb ≈ 4 µg/m^3) are common in suburban and urban areas. Indoor air concentrations are often several times higher (averaging 8 ppb; 30.4 µg/m^3) than outside air (ATSDR, 2001).
These background exposure levels are relatively low compared to the exposure levels in the three specified scenarios. Therefore the impact of the background exposure is considered small. It should be noted that smokers may be exposed to higher background levels of toluene.

Decrease in incidence of effect
The reduction in exposure after the measure for the scenario 'Spray painting for modelling to scale' resulted in a 'no concern exposure level' for acute exposure using the MOS approach. For a quantification of the decrease in incidence of effect related to this reduction in exposure, a dose response curve is needed. As a dose response curve could not be derived from the available data, the original study report is needed.

Derivation of DALY
Based on the available data no dose response curve and no incidences of acute human health effects as a consequence of exposure to toluene can be derived. The absence of such information may cause uncertainties in deriving the DALY. In this case, it is assumed that all exposed people are affected before the reduction in exposure and that after the reduction in exposure no effect would occur. This approach will result in an overestimation of the DALY. The disability and duration scores are also points of discussion. The disability weight for headache, dizziness, feeling of intoxication, irritation and sleepiness was assumed to be comparable to the disability weight of visual impairments (0.1). This figure is in the same order of magnitude as the disability weight calculated using the EuroQol method (0.083-0.17)

(for details see a report by VTV (in Dutch) (1997)). The duration for these effects is assumed to be 4 hours (i.e., the effects are assumed to be reversible).

Overall, the health gain due to regulations on toluene in glue (for modelling to scale), paint for spraying (for modelling to scale) and on vapour recovery systems was estimated to be 12 DALYs per year. This is only due to potential acute health effects such as headache, dizziness, and feeling of intoxication, irritation and sleepiness when spray painting before the regulations. No reproduction toxicological effects due to toluene exposure during evaluated scenarios are expected to occur before as well as after the measures. The validity of the DALY-estimates is restricted mostly because of the lack of representative exposure data, data on the target population, toxicological data for scenarios similar to the evaluated ones, and the potentially experienced health effect and related choice of weight for the DALY calculations.

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Appendix 11 Case report Volatile Organic Compounds

Wouter ter Burg (SIR-RIVM)
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1. Introduction

Volatile organic compounds (VOCs) are chemicals with high vapour pressures causing them to evaporate easily from all kinds of materials. There is a large number of VOCs. They can be released from numerous sources, such as environmental (natural) sources, industrial sources, traffic, and several consumer products.
There has been concern about the release of VOCs into the environment, because these compounds are known to form ozone in the troposphere and may have adverse health effects in humans. In order to decrease emissions of VOCs into the environment a Council Directive 1999/13/EC came into force in 1999 (EC, 1999). The implementation affected the use of organic solvents in certain industrial activities and installations. In the attempt to reduce VOC emissions even further, the use of VOCs in paints and varnishes also became the focus of regulators. VOCs in paints were increasingly suspected to cause toxicological effects. The causal relationship between the use of paints containing high amounts of VOCs and the development of chronic toxic encephalopathy (CTE) was established, the biologic mechanism remaining unknown (Baars et al., 2005). While in fact, for most uses of VOCs there are proper alternatives available which are to a lesser extent or non-toxic. To protect workers against the toxic effects from VOCs, legislation on worker environments the (Ministry of Social Affairs and Employment (2000) states that solvent based paints should no longer be used indoors professionally, except for specific paint tasks. This law was made effective January 1st 2001.
An EU wide legislation of the restriction of the use of VOCs in paints and varnishes was amended to reduce VOC emissions and to protect human health (EC, 2004). This restriction implies the substitution of organic solvent rich products with products that contain no or low amounts of VOCs wherever possible. This implication does not discriminate between the professional paints and paints meant for the consumer market. Paints and varnishes used in the Do-It-Yourself (DIY) sector will therefore also have lower VOC levels then before. Subsequently, consumers will be less exposed to VOCs from paints, previously known to contain high amounts of VOCs.

2. Background information on Volatile Organic Compounds

2.1 General information

2.1.1 Definition of volatile organic compound

The definition of an organic compound is that any compound must contain at least a carbon element and one or more hydrogen, oxygen, sulphur, phosphorus, silicon, nitrogen or a halogen atom. Exceptions are carbon oxides, inorganic carbonates and bicarbonates. Further, a volatile organic compound is an organic compound having a boiling point of ≤ 250 °C measured at a standard pressure of 101.3 kPa.
There are hundreds of compounds which fit the definition of a VOC.

2.1.2 Volatile organic compound legislation

The amended legislation affects consumer exposure to VOCs from paints via two pathways. In the first place, the Council Directive aims at lowering emissions of VOCs from paints by reducing the VOC content. As a consequence, available paints for consumers will contain less VOC due to the Council Directive. Secondly, Dutch legislation prescribes the use of water based (WB) paints indoors for workers instead of the higher VOC containing solvent based (SB) paints. This replacement of paint by another sort of paint may also be observed for consumer use, as WB paints will become more available in DIY markets. This led to the question what the health benefit would be if the measure intended for workers also applied to consumers (regarded to as the *alternative measure*, described in scenario 2b). Indirectly, both measures may affect the consumer exposure to VOCs from paint. A more detailed description of legislation concerning VOC is given below.

Legislation concerning VOCs is mainly focused on the reduction of emissions into the environment. VOCs released into air can react with nitrogen oxide which then forms the toxic compound ozone in the troposphere (lower atmosphere). Ozone can be toxic for the environment, animals, and humans.
This has been translated into Council Directive 1999/13/EC, which covers VOC emissions from stationary commercial and industrial sources, thereby complementing Directive 94/63/EC on VOC emissions from petrol storage depots and its distribution (Scadplus, 2006). Council Directive 1999/13/EG also states that substances likely to have serious effects on human health must be replaced wherever possible (EC, 1999). The substances of interest are carcinogenic, mutagenic, and toxic to reproduction (CMR) chemicals. Furthermore, Council Directive 2001/81/EC on national ceilings for emissions of pollutants also include VOCs. Member states have to comply with this Directive and targeted a number of different categories to achieve a decrease in emission of VOCs (EC, 2004).
Following the investments of reducing the emission of VOCs a new Council Directive was formulated to limit the emissions of organic solvents from paints, varnishes, and vehicle refinishing products, another prominent source of VOC emission. Council Directive 2004/42/CE states under section 1, paragraph 1: "The purpose of the Directive is to limit the total content of VOCs in certain paints and varnishes and vehicle refinishing products in order to prevent or reduce air pollution resulting from the contribution of VOCs to the formation of tropospheric ozone".
In Annex I of the Directive, the scope of the Directive is described wherein a list of products is provided which are to be replaced with products containing less VOCs. The products concerned are paints, varnishes, coatings, stains, primers, fillers, putty, cleaners and removers. Aerosols are not considered in the Directive (EC, 2004). Annex II describes the maximum levels of VOC in above mentioned products from January 1st 2007 (phase I) and from January 1st 2010 (phase II). The Directive was implemented in the Dutch legislation November 28th 2005: Besluit organische oplosmiddelen in verven en vernissen Wet milieugevaarlijke stoffen (Wms).
Next to efforts to reduce emission rates, effort was made to reduce the exposure to VOCs in the working environment. Workers are no longer allowed to use solvent based paints for indoor painting tasks, except for specific painting tasks. The Dutch legislation was made effective January 1st 2001.
In addition, many individual VOCs are regarded in legislation as hazardous chemicals, but a description of this kind of legislation is beyond the scope of this case study.

Table A11.1. Legislation concerning VOC in paint.

Legislation	Year effective	Consequence for consumer
Vervangingsplicht	2001	Intended for workers; use of SB paint indoors forbidden. Measure is extrapolated to consumers; full shift from use of SB to WB paint (indoor use). **Note**: Fictive measure for consumers
Council Directive 2004/42/CE		
- phase I - phase II	2007 2010	Reduction of VOC content in WB and SB paint to be achieved in two phases. Spray painting not considered

3. Exposure to volatile organic compounds

3.1 Background exposure to VOC

People can be exposed to VOCs by inhalation and dermal contact from many different sources. Because the large diversity in VOCs and their widespread use it is likely to be exposed to VOCs on a daily basis. Several sources can be distinguished such as industrial sources where VOCs are emitted into the air or into waste water; traffic where VOCs are formed during combustion processes; and the environment as some VOCs are occurring naturally. An important source of VOC exposure indoors is tobacco smoke (Payne-Sturges et al., 2004).

In addition to environmental/industrial sources, consumer products may also be an important source of exposure to VOCs. VOCs are commonly found in several household, automotive, and DIY products. The function in these products is mainly as solvent, thinner, propellant or degreaser. Some examples of DIY products containing VOCs are paints, varnishes, glues, sealants, fillers, removers, and chipboard (see case study formaldehyde). However, VOCs may also be present in trace amounts in some other (non-)food consumer products as a result of production processes.

3.2 Description of exposure to VOCs from paint

3.2.1 Target population

The selected population for this case is the DIY population. Consumers that will be affected by this measure are individuals who conduct paintjobs themselves. The largest paint producer in Sweden stated that approximately 80% of the paint tasks in dwellings are conducted by professionals (Wieslander et al., 19971/b) and 20% by inhabitants. In the Netherlands, 31% of the produced paint is sold in the DIY sector, according to Vereniging Verf en Drukinktfabrikanten (VVVF; a Dutch society for Paint and Printing Ink industries, 2003). With respect to refinishing of vehicles, it is not expected that this particular task is conducted by consumers.

According to Statistics Netherlands (CBS) approximately 25% of the Dutch population spends 1 to 4 hours per week on DIY tasks. Reasonably, it can be assumed that subjects perform a painting task at least once per year. This provides a target population of 25% of the total population of 16 million; 4 million.

3.2.2 Exposure to VOC from paints

VOCs are used in paints mainly as solvents. Their functions are to reduce viscosity and to disperse the other constituents of the formulation. This makes paint manageable during application. After paint is applied a large fraction of these VOCs will evaporate from the surface thereby hardening the paint. This evaporation of solvents is generally a rapid process (depending on vapour pressure), which can result in high peak exposures during application. Inhalatory exposure is therefore considered the most important route of exposure to VOCs. Next to inhalation exposure, dermal exposure can occur due to spills (Hansen et al, 1997). Oral exposure is not expected to play an important role in exposure assessment.

In this case study, three scenarios will be described, i.e. (1) the scenario before the measures and two scenarios (2a, 2b) after the measures. Scenario 2a will describe the use of paints after both measures; i.e. after the duty to substitute for employees and after the Council Directive 2004/42/CE is made effective. Scenario 2b encompasses the duty to replace SB paint by WB paint for consumers as well (see also Table A11.4). Over time the measures resulted in two noticeable consequences: the content of VOC was significantly reduced and toxic VOCs were replaced by lesser toxic VOCs. These consequences will be described in scenarios after the measures, by using information on paint usage (regarding specifically VOCs) and paint composition.

Shift in use of paint

The shift in use of paint in the Dutch situation can be best described by the sales number percentages of solvent rich and solvent lacking paints in the DIY market sector. The sales percentages before the measure can be compared to the sales percentages after the measure. In a letter from the Vereniging Verf en Drukinktfabrikanten (VVVF; a Dutch society for Paint and Printing Ink industries) sales percentages were provided for the years 1995 and 1996 (VVVF, 1996). These sales percentages for solvent rich paints/lacquers/stains were 77% and 73% in the year 1995 and 1996, respectively. The sales percentages for solvent lacking paints/lacquers/stains were 22% and 26% in the year 1995 and 1996, respectively. Regarding these numbers, it can be concluded that the ratio between solvent rich and 'solvent lacking' before the measure was 3:1 (rounded to 75% versus 25%). Note: solvent lacking paint is regarded as water based paint.
Due to legislation and recent developments the ratio changed after the measure. Table A11.2 shows more detailed information on paints and their VOC average from the DIY market (VVF, 2002/2004). Data from 2002 and 2004 are lined up for comparison. In Table A11.2 stains were separated from paints and lacquers. It is difficult to assign stains to either solvent rich or solvent lacking group, because their average VOC content lies on the boundary of being either solvent rich or solvent lacking (this is not the case in 2004). No adjustments for stains were made to compare the figures for lacquers and paints with the figures before the measure. From the data in the table below, a ratio between solvent rich and solvent lacking after the measure was derived: 2:3 (rounded to 40% versus 60%).

Table A11.2.Sales numbers of stains, lacquers, and paint in 2002 and 2004. Data from VVVF statistics 2002 and statistics 2004

DIY product	Sales (tons) In 2002/2004		Subtotal (%) In 2002/2004		VOC in sales (tons) In 2002/2004		Average VOC content in sales (%) In 2002/2004	
Stains	1800	1337	-	-	495	293	28%	22%
Lacquers, paint								
Solvent rich	6200	6243	37%	47%	1984	2124	32%	34%
Solvent lacking	10500	6820	63%	53%	2205	707	21%	10%
Wall paint								
Solvent rich	300	268	1%	1%	102	81	34%	30%
Solvent lacking	42700	40546	99%	99%	384	306	1%	1%

A third scenario (2b) will be regarded in this case study. This scenario describes the situation when the alternative measure is made effective. In this third scenario the ratio of SB paint and WB paint for indoor use is set at 0:1.

Overall decrease in VOC contents in paint

1) The change in use of paint (switch from SB paint to WB paint) is thought to decrease the overall VOC percentage in paints, because due to the shift relatively more low-VOC containing products will be used.

2) The observed decline in VOC content may also be caused by the decrease in VOC content in either solvent rich or solvent lacking paints. Regarding Table A11.2 it seems that the reduction of VOCs in solvent lacking paints is responsible for this decline where a decrease in VOC content from 21% to 10% was observed during two years (from 2002 to 2004).

The sales numbers and percentages of VOC content are presented in Table A11.3. A slight decrease in total VOC can be observed over the years, declining from 10% to 5%. Bear in mind that all paints (SB paints and WB paints) are taken into account.

Table A11.3.Data from VVVF; statistics 2002 and statistics 2004. Data focused on DIY market.

Year	**Sales (tons)**	**VOC in sales (tons)**	**VOC in paint/paint related sales (%)**
1995	59500	6000	10
1996	63400	6300	10
1997	69808	6242	9
1998	83451	6049	7
1999	83922	5757	7
2000	86566	6702	8
2001	75822	6063	8
2002	75050	5434	7
2003	70120	4697	7
2004	68824	3754	5

1995-1996 vanuit briefrapport,;1997-1998 vanuit statistieken 2002; 1999-2004 vanuit statistieken 2004

Based on the data above it can be concluded that the exposure to VOC has declined over the years, when assuming that sales numbers are indicative for use numbers. However, basing the health benefit solely on the reduction of VOCs may lead to false conclusions since the toxicity of the individual VOCs are not considered.

Short summary on paint usage
The implemented measure of substitution SB paint with WB paint and the intended measure of reducing the VOC content in all paints are taken together to describe the health risk reduction. Although the substitution law was not implemented for the DIY market sector it did however affect the market supplies of both SB and WB paints. Indirectly, consumer exposure is affected by the measure. For this reason it was decided to estimate the health risk reduction of both measures combined.
This resulted in three scenarios which are described above and briefly in Table A11.3. The data in the table (Table A11.4) are used as followed: VOC contents (or weight fraction of product) will be used in paragraph 3.2.3 in order to model the exposure to VOC from paint. The use percentages are used to determine the population which uses either SB or WB paint in a certain time period (see section 5). It was assumed that the use percentage of SB paint (75%, scenario 1) resembles the part of the population which uses SB paint (75% of 4 million equals 3 million). This assumption is crude, however necessary to reflect paint usage on a population level.

Table A11.4. Summary of paint usage and VOC content per scenario

	Scenario 1	**Scenario 2a**	**Scenario 2b**
Time point (year)	**Before measures (-2001)**	**After measures (2010-)**	**After alternative measure**
Percentage use SB paint	75 %	40%	0%
Percentage use WB paint	25%	60%	100%
VOC content SB paint	40%	10%	NA
VOC content WB paint	10%	3%	3%

VOC composition SB paint
SB paints contain organic solvents in concentrations typically ranging from 30% to 70% (Fortmann et al., 1998; ATSDR, 1995; IPCS, 1996); product information). Solvents that may be used in these paints are aromatic solvents like benzene (although it is hardly used anymore), xylene, toluene and/or naphtha; aliphatic hydrocarbons; and mixtures of aliphatic and aromatic hydrocarbons: e.g. white spirit, also known as Stoddard solvent. Note that a solvent mixture, such as white spirit (in Dutch: ‘terpentine’), may contain all above mentioned compounds. The composition of white spirit will most likely differ per batch and thus it is difficult to provide a clear overview of the constituents of white spirit. In Table A11.5, a general composition of white spirit is provided, which may indicate that compounds such as xylene and naphthene, often shown separately on safety data sheets, originate from the solvent mixture.

In the present exposure assessment for SB paints it was decided to regard white spirit as the sole organic solvent (mixture), instead of regarding VOCs, present in white spirit, separately. Because toxicological data on white spirit is available (ATSDR, 1995; IPCS, 1996), risk characterisation of exposure to white spirit in SB paint is possible.
The main advantage of this approach is that no separate exposure estimates have to be made for the individual constituents, but only for white spirit which can be compared to its toxicological profile. Further, the toxicological mechanisms and endpoints must be common, in order to 'add up' their health effects, which is not completely elucidated. The disadvantage of this approach is that during the modelling of exposure, white spirit is regarded as one compound while it actually consists of approximately one hundred compounds. The ATSDR document on white spirit provides averaged (or median) chemical characteristics like molecular weight and vapour pressure, but using these numbers may underestimate or overestimate the exposure to individual compounds as their chemical characteristics may differ significantly.

For exposure assessment and risk assessment it is thus assumed that only white spirit is used as organic solvent in SB paint. Further, it is assumed that the VOC composition of SB paint before and after the measure remained the same; only the VOC content may be reduced due to the upcoming measure. For many paints the VOC content at this moment is already below the maximum limit of phase I (40% VOC content for most interior paints in 2007) stated in the Council Directive 2004/42/CE. Data on average VOC contents of SB paints in the years 2002 and 2004 even show a slight increase for the DIY market sector (based on sales numbers and the percentage VOC in the sales).
The maximum limit of VOC content after the second phase (January 1st 2010) is significantly lower in contrast to the VOC content of present SB paint and varnishes. Because no specific product is regarded here, the 'average' maximum limit (this differs per specific product) is set at 10% VOC content. For the current exposure assessment this implies that before the measure the content of VOC is set at 40% and after the second phase 10% (summarized in Table A11.4).

Table A11.5. General composition of white spirit (ATSDR, 1995) that is used in paints.

Component	**Ranges of concentrations**	**Example of specific white spirit** (Shell (2005)
Aromatic hydrocarbons corresponding nearly exclusively to benzenic hydrocarbons: traces of toluene, xylenes, ethylbenzene, trimethylbenzenes, methylethylbenzenes, propylbenzene	1 to 20%	13% (by volume)
Paraffinic hydrocarbons: from C_8 to C_{12}	40 to 60%	60% (by weight)
Naphtenes: from C_9 to C_{12}	Generally 30% (can go up to 70%)	25% (by weight)

VOC composition WB paint

Water replaces organic solvents and is therefore the main solvent present in this type of paint. But still, water-based paints contain a certain amount of VOCs. In general, these organic solvents are alcohols, glycols, and glycol ethers (Wolkoff, 2003) and sometimes trace amounts of white spirit (Van Faassen and Borm, 1991). Water-based paints typically contain VOCs in amounts ranging from 6% to 12% (Bremmer and Van Veen, 1999).

Different types of water-based paint exist: water borne wall paints, water borne emulsion paints (binding agent is alkyd), and water borne dispersion paints (binding agent is acrylate). There are also lacquers which are water borne (binding agent is polyurethane). The organic solvent content may differ between these types of WB paints where the wall paint generally contains 1-2% VOC while polyurethane lacquers may reach levels of 12% VOC.

From literature (Van Faassen and Borm, 1991; Sparks et al., 19991/b; Chang et al., 1999) and paint producers' data sheets, three VOCs substances and their concentration ranges in water-based paints are selected (Table A11.6). Ethylene glycol, propylene glycol, and 2-(2-butoxyethoxy)ethanol are thought to represent glycols and glycol ethers based on their occurrence and concentration in WB paints.

Table A11.6. Selected compounds to represent VOCs in WB paints.

Component (solvent)	**CAS Number**	**Range of concentration**
Ethylene glycol	107-21-1	0 to 10%
Propylene glycol	57-55-6	0 to 10%
2-(2-butoxyethoxy)ethanol (=DEGBE)	112-34-5	0 to 10%

It is difficult to assess which compounds are used in combination and, if they actually are used in a combination, what their respective ratios are. According to van Faassen and Borm (1991) propylene glycol scored the highest prevalence number amongst WB construction paints followed by DEGBE. The maximum concentrations in percentage of weight for ethylene glycol, propylene glycol, and DEGBE were 7.9%, 7,9%, and 5%, respectively (Van Faassen and Borm, 1991). However, from these numbers no general VOC composition of WB paint can be made.

Paint producers' data sheets listed a range of concentration of 0 to 10% for these compounds when present in WB paint. Furthermore, as stated previously, the typical range of organic solvents in water-based paints is from 6 to 12% (National Pollutant Inventory, 1999; Bremmer and Van Veen, 1999). As a reasonable realistic concentration, it is assumed that water-based paints contain about 10% of organic solvents. Hence, 10% VOC content in WB paint is considered before the measure of reducing the VOC contents in paint.

Identical to the SB paints, the WB paints used today already comply with the intended maximum VOC concentration (phase I) listed in Annex II of Council Directive 2004/42/CE. In phase II the maximum VOC concentration for most indoor WB paints is 3%. This value will be used to determine the exposure to VOCs from WB paints after the measure. Again it is assumed that the VOC composition after the measure does not change, merely the VOC content changes.

3.2.3 Results

Several methods are possible to determine the exposure to VOCs from paint. Measurement data from either occupational or experimental settings are useful to determine the acute exposure from paints. Professional painting can be compared with consumer painting where differences in time and amount used can be expected. It is reasonable to assume that peak levels will be in the same range for professional or consumer painters. Furthermore, the same environment is regarded, whereas in experimental settings the environment is controlled by the experimenter. It was decided to use a second method: modelling of the exposure. The advantage is that a scenario for consumers can be described and focused on the type of VOC one is interested in.
Available information on exposure levels of VOCs will be compared with results obtained from modelling exposure. For this reason, it is important to have information on paint usage, VOC content and composition of these different paints to describe the exposure to VOCs. These aspects will be discussed in the section below.

The exposure was estimated using ConsExpo. In order to estimate the exposure, a description of the painting scenario is required. Detailed information, such as product amount used, surface area treated, room in which the task is performed, user habits, and more are needed to estimate the exposure. This kind of information required to estimate the exposure (or even variation in exposure) is not available. An attempt to estimate the average exposure to VOC from paint would lead to a point estimate with an unknown variation and uncertainty.
For this reason, the Paint fact sheet (Bremmer and Van Veen, 1999) is advised to describe the scenario in which a subject is painting. This scenario, which describes a realistic worst case scenario for painting a large surface, is used for all exposure estimates. The parameters in the Paint fact sheet are set in a way that they reflect the 25th or 75th percentile (depends on what leads to higher exposure levels). Inserting the parameters will 'add' up these estimates to a worse case (Bremmer and Van Veen, 1999). However, uncertainty remains at what percentile the realistic worst case point estimate will arrive.
The underlying assumption is that identical painting tasks are performed indoors with either SB and WB paints before and after the measures. Both the exposure via inhalation (often regarded as the most important when painting) and the dermal route are treated similar for both types of paint. This implies that the viscosity of both SB and WB are in the same range, which is not unthinkable for indoor use of paints. Thus, only the parameters related to the type of paint or component are different. By using identical painting scenarios in all three scenarios the results are comparable, since the difference in exposure is caused by the difference in products.

The non-product specific parameters for the painting scenario were as followed:

- Room volume: 20 m^3
- Ventilation rate: 0.6 h^{-1}
- Release area: 10 m^2
- Applied amount: 1 kg
- Application duration: 133 minute
- Exposure duration: 146 minute
- Use frequency: 1/year
- Dermal exposure area: 61 cm^2
- Dermal product amount 0.9 g

Product-specific parameters (regarding water based versus solvent based paint, it does not regard specific substances) for the painting scenario were:

- Molecular weight matrix SB: 450 g/mol
- Molecular weight matrix WB: 45 g/mol

In addition chemical characteristics of compounds are required to estimate the exposure to these compounds. These characteristics are listed in Table A11.7.

Table A11.7. Chemical characteristics of selected compounds.

	SB paint	**WB paint**		
	White spirit	**Ethylene Glycol**	**Propylene glycol**	**DEGBE**
CAS Number	64742-48-9	107-21-1	57-55-6	112-34-5
Molecular weight (g/mol)	150	62.1	76.1	162
Vapour pressure (Pascal)	600	8	9.3	3
Kow (10Log)	5.7	-1.36	-0.92	0.91

The data above was inserted in ConsExpo, where for inhalation the *exposure to vapour: evaporation* was used and for dermal contact *instant application*. For more detailed information on formulas used in ConsExpo the reader is referred to Delmaar et al. (2005). As shown in Table A11.8 there is a significant difference in air concentrations between white spirit from SB paint and the other VOCs from the WB paints. Differences in terms of air concentration between SB paint and WB paint were expected, because the higher VOC content and vapour pressure of the compounds in SB paints. As a result WB paints have lower emissions of VOCs than SB paints. In literature emissions were found to be about 100 times higher for SB paints in contrast to WB paint (Hansen et al., 1987; Chang et al., 1999; Norback et al., 1995).

Table A11.8. Estimated exposures from SB paint and WB paint using ConsExpo in a realistic worst case. All values are in mg/m³ (inhalation exposure) or in mg/kg (dermal exposure). Before describes scenario 1, and after describes scenario 2a.

	SB paint		WB paint					
	White spirit		Ethylene glycol		Propylene glycol		DEGBE	
Scenario	1	2a	1	2a; 2b	1	2a; 2b	1	2a; 2b
Mean event concentration	5,880	1,420	10.2	3.01	11.9	3.47	3.82	1.09
Concentration day of exposure	596	144	1.04	0.305	1.21	0.351	0.387	0.11
Year average concentration	1.63	0.395	0.003	0.001	0.003	0.001	0.001	0.0003
Dermal external dose (mg/kg)	4.8	1.2	1.2	0.36	1.2	0.36	1.2	0.36

Exposure estimates for individual compounds in WB paint is based on assumption that the specific compound is the main VOC used.

Exposure to white spirit from SB paint

The high air concentration estimated for white spirit before the measure was reported once in literature. Fortmann and colleagues (1998) measured a peak concentration of 10,000 mg/m^3 TVOC in a small chamber emission test with an air exchange rate of 0.5 per hour in a 53 l test chamber. TVOC peak emissions of three alkyd paints each applied on a different pine board previously coated with a primer: each of the three is comprised between 5,000 and 7,000 mg/m^3 in the first 2 hours (measured in environmental chambers tests). These measurements do not reflect exposures in practice.

Personal exposure measurements during indoor painting in Finland resulted in white spirit concentrations ranging from 150 to 1,800 mg/m^3 in 1980. In 1985 in Norway, breathing zone measurements showed similar exposure levels (450 to 840 mg/m^3) as reported by Varsa in 1989 (Norbäck et al., 1995; Wieslander et al., 1997b; original reference: Varsa, 1989 in Norwegian). In Scandinavia during 1974-1991 TVOC levels of 475-1,490 mg/m^3 with an average of 660 mg/m^3 was observed for several SB paints for indoor use.

In a study by Wieslander et al. (1997b) where house painters were observed the majority used WB paint and to a lesser extent SB paint. During the study exposure measurements were taken during which an average exposure estimate of 57 mg/m^3 TVOC was found with a range 1 to 380 mg/m^3 TVOC. The authors stated that the average contribution to TVOC from SB and WB paint was 97% and 3%, respectively. Painters who used SB paints predominantly were exposed to a range of 100 to 380 mg/m^3 TVOC.

Exposure levels in occupational settings were in the range of 33 to 6140 mg/m^3 white spirit (IPCS, 1996). It was noted in that white spirit vapour may not contain identical proportions of constituents as observed in its liquid form. This is caused by different vapour pressures of the individual components. This possible occurring difference is not accounted for in exposure assessment of white spirit.

Exposure to selected organic solvents from WB paint

Estimated exposures using ConsExpo for WB paint showed similar results among the glycol ethers. The lower exposure levels estimated for DEGBE were expected, because of its lower vapour pressure (see Table A11.8). The air concentrations found for the WB paints in literature generally agrees with the modelled exposures. Hansen et al., (1987) measured air concentrations in work areas (15 workplaces) for DEGBE and propylene glycol and found ranges of 4 to 5 mg/m^3 and 2 to 70 mg/m^3, respectively. The vapours were measured by personal sampling. Work areas and paint jobs differed significantly from each other, which makes comparisons more complex. Wieslander et al. (1997) estimated a TVOC concentration ranging from 1 to 3 mg/m^3 for 50 painters exposed solely to WB paint. Norbäck et al. (1995) measured an average TVOC exposure from WB paint of 4 mg/m^3. Results of the study for some individual VOCs are listed in Table A11.9. Sparks et al. (1999b) found similar results in two experiments. A surface of 10 m^2 (in the front corner bedroom, EPA IAQ test house) was painted with WB latex paint. Details on air exchange rate and room volume are unknown. Exposure levels ranging from 0.1 to 10 mg/m^3 were found, where ethylene glycol was found with highest exposure levels followed by propylene glycol and DEGBE. Experiments with WB latex paint in test chambers (53 l) provided exposure levels up to 120 mg/m^3 TVOC (Sparks et al., 1999a).

Table A11.9. Exposure (µg/m^3) to selected polar or high boiling point compounds during indoor application of water-based paints, Phase II (N=20) (personal sampling in the breathing zone of the painter) (Norbäck et al., 1995)

Compound	AM	GM (GSD) [a]	Maximum value
Propylene glycol	2630	350 (20.2)	12700
DEGBE	820	18 (14.2)	8060
DEGEE	204	7 (4.5)	3980
EGBE	59	8 (4.2)	730
DPGME	185	9 (5.5)	3800
Texanol	164	18 (7.0)	1680
TXIB	13	10 (2.1)	40

a: 1-h mean exposure during painting with WB paint

The modelled exposure is based on a worst case scenario. Nevertheless, data from literature found for WB paint seem to agree with the modelled data. For SB paint this is not the case, although high exposure levels have been observed in occupational settings. These acute peak exposures can also be expected for consumers. Reported exposure levels displayed an average exposure of approximately 660 mg/m^3 during paint tasks. Although the setting during which the TVOC was measured is often unclear, this value is useful in risk characterisation for white spirit. Because the measure is not effective yet, there is no data for after the measure on the average exposure. Therefore, the average value before the measure (660 mg/m^3) is divided by four, since the VOC content is reduced four-fold, which is regarded the only impact factor for change in exposure. This provides an average exposure estimate after the measure of 165 mg/m^3.

In combination with the toxicity (see section 4) of ethylene glycol and similar exposure levels amongst the WB paint VOC constituents the estimated exposure for ethylene glycol is chosen for risk characterisation.

It was decided to use the modelled data (in combination with reported data for white spirit) bearing in mind that the marginal error for SB paint may be larger than for WB paint.

Table A11.10. Exposure estimates that will be used for characterising the risk

	Exposure estimate (mg/m^3)		
	Scenario 1	**Scenario 2a**	**Remark**
White spirit in SB paint	660 5,880	165 1,420	Average (from literature) Worst case (ConsExpo)
Ethylene glycol in WB paint	10	3	Worst case (ConsExpo)

4. Description of toxicity

4.1 Health effects of VOCs in paints

The description of toxicity for the VOCs in this chapter is derived from the ATSDR documents on Stoddart Solvent (= white spirit) (1995), Ethylene glycol and Propylene glycol (ATSDR, 1997), the Environmental Health Criteria on White Spirit (IPCS, 1996), and the EU RAR on DEGBE (EU-RAR, 1999). Descriptions of studies were as cited from these sources.

4.1.1 Acute health effects of VOC

Acute effects from exposure to VOC reported are nose and throat irritation and adverse Central Nervous System (CNS) effects, i.e. headaches, fatigue, nausea, drowsiness, dexterity problems, narcosis (unconsciousness) and even death. VOCs are generally small molecules which enables the molecules to pass the blood-brain barrier, where they can elicit CNS depression. In the past, studies have been conducted to observe the health effects from painting activities. The toxicological effects related to exposure to paint were generally neurotoxicological effects (CNS depression) and eye and skin irritation. These neurotoxicological effects were ascribed to the VOCs present in the paint. The eye and skin irritations observed were ascribed to the binders and/or filling agents, e.g. latex paints, present in the paint. Nevertheless, some VOCs were also related to irritation effects observed amongst painters (Carpenter, 1975, as cited by IPCS, 1996). Skin sensitisation and skin irritation is found in both WB paint as in SB paint (Terwoert et al., 2002).
When these VOCs are inhaled by humans in mixture the toxic effect, in this case CNS depression can be the result of the exposure to all the present VOCs. Up until now, the toxic mechanism is still to be elucidated. Therefore, it is assumed that CNS depression is caused by the cumulative exposure to VOCs present in paint.

4.1.2 Chronic health effects of VOC

The chronic health effect from exposure to VOC in relation to painting tasks is chronic toxic encephalopathy (CTE), also referred to as chronic painters' syndrome. This disease is found amongst painters which are exposed to high VOC concentrations almost every day for prolonged periods of time (at least a few years). Clinical health effects of CTE are divided in stages of the disease. Manifestations of the disease (different stages taken together) are depressions, fatigue, CNS depression, loss of interest, impaired psychomotor function, memory loss, loss of intellectual abilities, and personality changes (IPCS, 1996). This toxic effect, however, is not relevant for consumers as they are not exposed to high concentrations of VOC for prolonged periods of time.

Some VOCs have been reported to be carcinogenic, e.g. benzene is a well known carcinogen. It goes beyond the scope of this case study to provide an overview of carcinogenic VOCs.

4.2 Toxicity of VOC in SB paint

4.2.1 White spirit

White spirit as a mixture is not studied extensively for its toxicity. In addition, the composition of white spirit may differ between batches and brands making it difficult to obtain a general toxicology profile. The composition of white spirit is therefore often given with ranges. White spirit is in fact a mixture of VOCs. The most critical acute effects observed in humans after exposure to white spirit were irritation and CNS depression. Carpenter (1975, as cited by IPCS, 1996) exposed six volunteers to 140, 850, and 2,700 mg/m^3 white spirit for 15 minutes. At the highest dose group all volunteers reported eye irritation and lacrimation, and two of the volunteers reported slight dizziness. In studies by Hastings et al. (1984, as cited by IPCS, 1996), and Stokholm and Cohr (1979, as cited by IPCS, 1996) irritation effects were observed at concentrations of 600 mg/m^3 white spirit for durations of either 30 minutes or seven hours. The latter study also reported increased headaches amongst the exposed group of house painters at 600 mg/m^3.
Gamberale et al. (1975, as cited by IPCS, 1996)) did not observe neurobehavioural effects in 14 volunteers up to levels of 2,500 mg/m^3 white spirit for duration of 30 minutes. Significant effects were observed at 4,000 mg/m^3 white spirit for 50 minutes; impaired performance for perceptual speed and short-term memory.
The correlation between white spirit and carcinogenicity has been studied in several epidemiological studies. Increased risks for developing cancer (lung, kidney, prostate, and hodgekin's lymphoma) amongst painters, metal machinists, construction workers, and dry cleaners have been observed. However the studies did not adequately demonstrate causal relationships between exposure to white spirit and cancer development.

For risk characterisation data obtained from human volunteer studies will be used. Irritations were observed at 600 mg/m^3 during a 30 minute and 7 hour exposure. Irritation effects are not correlated with time, therefore 600 mg/m^3 is used as a reference value for irritation effects. At the same exposure level headaches were also observed. For this reason, 600 mg/m^3 is also used as a reference value for CNS depression despite of contradictions from other studies. Because it is unknown what the threshold is for elicitation of either irritation or CNS effects, it was assumed that below 600 mg/m^3 no effects will occur in humans. The total health is possibly underestimated by this assumption. Slight dizziness was observed at a concentration of 2,700 mg/m^3 during 15 minute exposure. It is expected that being exposed for a longer duration to the same concentration will lead to more intensive effects and thus 2,700 mg/m^3 is regarded to reference value for dizziness. The toxicological reference value for impaired functionality was set at 4,000 mg/m^3 based on findings by Gamberale et al. (1975, as cited by IPCS, 1996).

4.3 Toxicity of VOC in WB paint

4.3.1 Ethylene glycol and propylene glycol

There is a general agreement that ethylene glycol is more toxic than propylene glycol regarding systemic effects and neurological effects (ATSDR, 1997). On the other hand,

dermal exposure studies with ethylene glycol are rare, where propylene glycol was studied extensively in human volunteers for its irritation and sensitisation potential.
Wills et al. (1974, as cited in ATSDR, 1997)) exposed a group of volunteers (n=22) for 20-22 hours per day for 4 weeks to an average concentration of 7-19 ppm (= 18-48 mg/m^3). Slight headaches and backaches were observed amongst the volunteers. No other neurological effects were observed. No neurological studies concerning inhalation exposure were located for propylene glycol.
In the same study by Wills upper respiratory tract irritation was observed after 15 minutes inhalation exposure to 55 ppm (140 mg/m^3). A concentration of 79 ppm (201 mg/m^3) was not tolerated for more than one minute.
Propylene glycol was tested on skin of human volunteers in several studies. Propylene glycol proved to have slight irritation properties and is a skin sensitizer. Clinically, propylene glycol caused erythema with oedema in patients. In general, the larger part of contact dermatitis (= clinical effect) is the result of irritation rather than sensitisation. In a study by Kinnunen and Hannuksela (1989, as cited in ATSDR, 1997) acute dermal exposure to 0.2 to 22.8 mg/cm^2 propylene glycol resulted in skin oedema and erythema in 3.8% of the 823 patients tested. In other studies positive results were close to 15% when tested during skin patch tests with varying dilutions. The lowest exposure level during which irritation effects were observed in humans was 18 mg/m^3 during a 4-week study, exposure 20-22-hours per day. In comparison to a painting task where the exposure duration is much lower the estimated exposure does not reach 18 mg/m^3. No neurological studies with propylene glycol exposure in humans are known to us.

4.3.2 DEGBE

The acute toxicity of DEGBE was considered low. The oral and dermal LD_{50} were higher than 2,400 mg/kg bw. The substance was considered 'not-toxic' by inhalation, partly because of the low vapour concentrations that are generated during use of the substance. No lethality was observed when rats were exposed to the maximum attainable vapour concentration (120 mg/m^3) in this study for 7 hours (EU-RAR, 1999). It was noted, however, that a definitive conclusion based on available data was not permitted. Further the substance was found not to be an irritant, corrosive, or a skin sensitizer upon acute exposure.
In repeated dose studies the major target organs were the liver and lungs. Generally, in the lungs more local effects were observed, while increased relative liver weights and fatty change were observed in the liver. The spleen and kidney were other target organs of DEGBE (EU-RAR, 1999). The lowest NOAEL was 39 mg/m^3 in a subacute inhalation study in rats based on increased relative liver weights observed at higher dose groups. The lowest NOAEL in a repeated dose study was 94 mg/m^3. No human data was available.
Because the substance was not considered toxic by inhalation and conclusion ii was drawn in the EU RAR on DEGBE (1999), no toxicological reference value was derived for DEGBE.

5. Current risk assessment

For painting with SB paint the assumption was made that VOC present in SB paint is consistent of white spirit only. Currently, there is no existing risk assessment report for white spirit. Therefore it was decided to compare the reference values derived for several health

endpoints with the estimated and reported exposure levels. Although, only limited data is available for white spirit and contradictions have been reported, it is still useful in risk characterisation since the effects were observed in humans.
The average exposure to white spirit from the use of paint was reported to be 660 mg/m^3 white spirit (Wieslander et al., 1997b). From modelling the exposure an air concentration of 5,880 mg/m^3 white spirit was estimated in a worst case setting, remaining uncertain at which percentile the worst case estimate arrived. The toxicological reference values were 600 mg/m^3 (irritation/headache), 2,700 mg/m^3 (dizziness), and 4,000 mg/m^3 (impairment functionality) for white spirit.

For painting with WB paint estimations were made with the underlying assumption that either ethylene glycol, propylene glycol, or DEGBE is the sole VOC in WB paint. Ethylene glycol was selected, because of its toxicological profile. However, estimated exposure concentrations remained below concentrations at which health effects were observed in humans for ethylene glycol. In the risk assessment report for DEGBE, prepared by the Netherlands, a conclusion ii was drawn meaning that there is no need for risk reduction measures for consumers when painting with latex paint. A maximum concentration of 5% was taken into account in the assessment based on data from industry (EU-RAR, 1999). Dermal exposure to VOCs from WB paint can lead to irritation and sensitising effects in humans. Propylene glycol is known to be an irritant or sensitizer in human patch tests. Individuals who are previously sensitized are more prone to develop health effects. However, it is not possible to provide quantitative data on the amount of subjects suffering from irritation/sensitisation effects during painting tasks with WB paint. Furthermore, a threshold value for these effects can not be derived from the available data. Therefore, no risk characterisation was made for possible skin effects as the result of exposure to WB paint. One must take into consideration that some constituents of WB paint may cause adverse effects on the skin. For risk characterisation, therefore, only the health effects ‘caused’ by the exposure to white spirit from the use of SB paint is described.

Scenario 1 (before)
The average exposure was 660 mg/m^3 for white spirit. The distribution of the exposure is unknown; therefore it is assumed that the average exposure is also the median exposure. Thus, half of the subjects painting with SB paint will have higher exposure levels. In addition, to characterize the risk for subjects (population based) exposed to higher concentrations a distribution of the exposure is required. Assumptions are made for the percentage of subjects that are expected to be exposed to certain levels. It is assumed that 50% of the population is exposed to concentrations above 600 mg/m^3 of which 10% will be exposed to concentrations of and higher than 2,700 mg/m^3, and of which 1% (of subjects using SB paint) are higher exposed than 4,000 mg/m^3 (see Table A11.11 for the simplified population distribution linked to health effect due to exposure to VOCs from painting). No lethality is expected from exposure to white spirit during painting tasks. Furthermore it is assumed (as worst case) that all subjects exposed to a certain concentration will suffer from the corresponding health effect at that concentration until a higher cut-off point is reached.

Scenario 2a (after)
In this scenario it was stated that the VOC content would decrease in both SB paint and WB paint. Next to the decreased VOC concentration, a shift in use from SB paint to WB paint was assumed. Thus, the number of subjects using SB paint will be decreased.

The measure is not yet effective, thus no measured data exists. Predictions on the exposure can be made based on the modelled exposure. Here, only the VOC content of the SB paint was adjusted (from 40% to 10%) which provided an estimate of 1,420 mg/m^3 after the measure. As mentioned before, this is a worst case estimate. On average the exposure will be lower as well. Since it is assumed that individuals behave similarly the decrease in exposure is parallel to the decrease in VOC content. An average exposure to white spirit after the measure is calculated to be 165 mg/m^3 (see section 3.2.3). Compared to the toxicity of white spirit it can be expected that a small part of the population will still be exposed to levels higher than 600 mg/m^3. Because no data is available 15% (of subjects using SB paint) are assumed (personal judgment) (see also Table A11.11).
Based on the worst case estimate of 1,420 g/m^3 for white spirit no dizziness or impairment of functionality is expected.

Scenario 2b (after, complete shift to WB paint)
Because WB paints are not considered to be of any risk, no calculations will be made. Nonetheless, it should be considered that possible effects on the skin cannot be excluded.

Table A11.11. Overview of population with health effects based on the use of SB paint in the total population of 4 million subjects.

	Population with health effects (absolute number / % of total population)					
	Irritation/headache		**Dizziness**		**Impairment functionality**	
	Absolute	%	Absolute	%	Absolute	%
Scenario 1 75% SB	1,200,000	30	270,000	6.75	30,000	0.75
Scenario 2a 40% SB	240,000	6.0	0	0	0	0
Scenario 2b 0% SB	0	0	0	0	0	0

Impairment of functionality means significant affected perceptual speed and short term memory loss.

6. Calculation of public health gain

6.1 Decrease in exposure

The decrease in exposure to VOCs from paint will be caused by the decrease of VOC content in SB and WB paint and by the shift in use of type of paint. Because the milestones of the measure are to be reached in the near future, effects from the measure cannot be measured yet. However, over a number of years a reduction of VOC content was observed; 5% reduction was found already before the measures (see section 3.2.2). To provide insight on the decrease of exposure to more specific VOCs from paints a model was applied which estimated the exposure before the measure and after the measure in worst case situations. The exposure to VOCs from paint will decline, when manufacturers will follow legislation.

Roughly, it is estimated that the TVOC exposure will drop 4-fold, because painting with SB paint was considered responsible for the major part of the exposure.
It should be considered that exposure to WB paints and its constituents (VOC and other) will increase (on a population level) due to the measures.

6.2 Increase of Margin of Safety

The margin of safety (MOS) will increase when the exposure drops. When the exposure might drop 4-fold; the MOS will increase 4-fold. The MOS for the use of SB paint will not be high in either situation, but this also depends one the choice of starting point for calculating the MOS. Logically, the MOS will be higher when the average exposure rather than the worst case estimate is considered.
For the use of WB paint, the MOS is considered sufficiently high as no health effects in humans are expected at these concentration levels.

6.3 Decrease in incidence of effect

In the scenario after the measure (scenario 2 and 3) the incidence in effect is likely to decrease based on the estimated exposures and user tendency towards WB paint. Irritation effects and CNS depression (headaches, dizziness, and impairment of functionality) will decrease in the population. This is partly visualised in Table A11.11.
One must bear in mind that exposure to WB paints and its constituents (VOC and other) will increase due to the measures. It is expected that VOC exposure from WB paints will not result in health effects. But, possible other health effects resulting from constituents other than VOCs are not taken into account.

6.4 Derivation of DALYs

Chronic health effects from exposure to VOCs from the use of paint were not expected, because the chronic exposure is not high enough for consumers. Hence, the health effects related to exposure to VOC from paint are all acute effects, not lasting more than a day. The headache and irritation will disappear upon ceasing the activity, which lasts for approximately two hours. Dizziness is expected to linger somewhat longer than a headache, but will lighten up upon ceasing the activity and thus four hours is assumed. The impairment of functionality is considered more severe than the other health effects and affects the short-term memory. The duration is set at one day. The severity and duration of the health effects were based on personal judgment.
The severities of these acute health effects can be determined by using the EuroQol method (described in main document). An overview of the health effects and belonging details is provided in Table A11.12.

Table A11.12 Overview of expected health effects with associated disability weight, duration of the disability, and the EuroQol score.

Health effect	**Disability weight**[a]	**Duration of disability (years)**	**EuroQol score**
Irritation / headache	0.08	0.08 / 365	111211
Dizziness	0.17	0.17 / 365	212111
Impairment of functionality	0.58	1 / 365	223222

[a] The disability weight is determined by the EuroQol score. To avoid confusion; the fact that the disability weights for irritation/headache and dizziness resemble the figures in the duration column is based on coincidence.

Scenario 1:
The DALY was derived by multiplication of the number of affected subjects (see Table A11.11), disability weight, and the duration of the health effects. The DALYs for the different health effects are then added together to obtain the total amount of DALYs estimated before the measure is made effective.

Number of subjects (1,200,000) * irritation / headache (0.08) * duration (0.08 / 365) = 21 DALYs.
Number of subjects (270,000) * dizziness (0.17) * duration (0.17 / 365) = 21 DALYs.
Number of subjects (30,000) * impairment of functionality (0.58) * duration (1 / 365) = 48 DALYs.

The total amount of DALY before the measure was estimated at: 90 DALYs per year.

Scenario 2a:
Number of subjects (240,000) * irritation / headache (0.08) * duration (0.08 / 365) = 4 DALYs per year, which is the total amount of DALYs.

Scenario 2b:
No DALYs can be calculated, because no health effects are assumed to occur.

A health benefit of 86 DALYs per year could be calculated when the intended measure would become effective and manufacturers live up to legislation. In the third scenario where only WB paints are used, the health benefit would be 90 DALYs per year.

7. Discussion

7.1 Uncertainties and assumptions

7.1.1 Exposure assessment

As there are several types of paint it was decided to group these types of paint and discriminate only between SB paints and WB paints. The next step was to come up with a general composition of SB and WB paint. Obtaining this kind of data is troublesome, because

manufacturers are not keen on providing such detailed information about their products. In the case composition data was found, one has to realise that the diversity of used VOCs in paint is very large and that other VOCs of interest may be overlooked. A simplified methodology was chosen where single compounds or a known chemical mixture was selected as the sole VOC constituent. Regarding the most toxic single compound (as was the case for WB paint; ethylene glycol) resembles a worst case scenario, but provides more certainty about the risk characterisation. Likely, in reality the risk will not be higher than estimated in this case study.
The selection of white spirit as sole VOC constituent in SB paint may have resulted in under- or overestimations of the exposure. As stated previously, the liquid phase of white spirit can differ significantly from the vapour phase, because of the range of vapour pressure of the compounds. After modelling the exposure (in a worst case scenario) with the characteristics of the mixture it seemed that the exposure was overestimated as data from literature generally showed lower concentrations. In literature, however, the circumstances during which the exposure was measured are not always stated, making it difficult to compare the results.
An exposure distribution on a population level was made artificially by combining results from modelling and data from literature (see section 3.2.3 and section 5). Hence, the uncertainty of the exposure assessment is very large. However, providing a quantitative estimate of the uncertainty is not possible.

7.1.2 Toxicity

White spirit as a mixture is not studied extensively for its toxicity. In addition, the composition of white spirit may differ between batches and brands making it difficult to obtain a general toxicology profile. The composition of white spirit is therefore often given with ranges. Nevertheless, in the ATSDR document and EHC document on white spirit toxicity data was available. More importantly, data concerning exposure to human volunteers was present (though limited) making it possible to use for risk characterisation without the need for extrapolations. However, no dose response relationship of the effect of white spirit could be obtained. A few data points were selected to sketch the dose response of white spirit in humans, but a no effect level was lacking. Hence, the basis for risk characterisation of white spirit is weak.
For the VOCs used in WB paint it was chosen not to provide a full overview of the toxicity, but data from risk assessment reports from the existing chemicals program were used. Conclusions of risk assessment report that were adopted stated no risk for consumers. Discussion remains on the fact that possible skin effects from the use of WB paints can not be excluded. Quantification of possible health effects on the skin was not possible.

7.1.3 Derivation of the DALY

Underlying assumptions and uncertainties surrounding the exposure assessment and toxicology, which is the basis for risk characterisation, will indefinitely lead to a more uncertain DALY value. Logically, because the number of subjects estimated to suffer from health effects due to painting with SB paints was based on risk characterisation. In addition, the use of paints in the population was based on use percentages of SB and WB paints. These percentages in their turn were based on sales numbers. The assumption that use of paints reflects its use in the population was necessary for risk characterisation to indicate the number of subjects affected by exposure to VOCs from paints. On the other hand, linking sales numbers to use of paints in a population introduces uncertainty, because it is unknown

how this assumption reflects reality. Due to a high initial target population the number of subjects affected is estimated to be high and thus heavily influences the DALY estimate. Uncertainty of the DALY also originates from the approach to calculate the DALY. The descriptions of health affects are based on personal judgment on duration, but implicitly also on severity when using the EuroQol method. The approach used is very crude and introduces uncertainty to the estimate DALY.
Because worst case assumptions were made in both exposure assessment and risk characterisation, it can be concluded with reasonable certainty that the number of DALYs calculated for scenario 1 will not be much higher in reality. This implicitly means that the health gain from the measure (in future) for consumers will not be higher than the estimated 90 DALYs. However, overall the DALY estimate is highly uncertain.

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Appendix 11.1

Determination of the EuroQol score was executed according to six dimensions, which varied in severity over three levels. The dimensions were: mobility, self care, daily activities, pains and other complaints, anxiety/depressions, and cognition. These dimensions describe the functional state of health of a certain individual with a certain disability. A score of 1 equals full health. A EuroQol score of 111111 will consequently result in a disability weight of 0. A score of 2 equals to a disability weight of 0.0833. A EuroQol score of 222222 will result in a disability weight of 0.5 (since all dimensions were scored as being half). A EuroQol score of 333333 will result in a disability weight of near 1. For details see a report by VTV (in dutch) (1997) and an overview of the table is given below.

For the AEGL levels EuroQol scores were determined:

- Irritation / headache: 111211 corresponding to a disability weight of 0.083
- Dizziness (moderate to severe): 212111 corresponding to a disability weight of 0.17
- Impairment of functionality: 223222 corresponding to a disability weight of 0.58

Table A7.6 EQ-6. Dimensions with their 3 levels (no problem, some problems, many problems).

Dimension	Level	Score
mobility	No problems in walking about.	1
	Some problems in walking about.	2
	Confined to bed.	3
self care	No problems with washing or dressing self.	1
	Some problems with washing or dressing self.	2
	Unable to wash or dress self.	3
usual activities	No problems with usual activities (e.g. work, study, housework, family or leisure activities).	1
	Some problems with usual activities.	2
	Unable to perform usual activities.	3
pain / discomfort	No pain or discomfort.	1
	Moderate pain or discomfort.	2
	Extreme pain of discomfort.	3
anxiety / depression	Not anxious or depressed.	1
	Moderately anxious or depressed.	2
	Extremely anxious or depressed.	3
cognition	No problems with cognitive functioning (e.g. memory, concentration, coherence, IQ)	1
	Some problems with cognitive functioning	2
	Extreme problems with cognitive functioning	3

EuroQol (6 Dimensies) (EQ-6D). For more details see a report by VTV (in Dutch) (Van der Maas and Kramers, 1997) and Hoeymans et al., 2005a.

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