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Exploration of aggregate exposure to compounds present in food

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Summary

This report describes the result of a study into the exposure to harmful compounds via more than one source / route (so-called aggregate exposure) in relation to the relevance of extending dietary exposure assessments as performed using the Monte Carlo Risk Assessment (MCRA) programme with other sources than diet (and drinking water) or other routes. An overview is given of relevant groups of compounds for which aggregate exposure may be relevant, and of models available to calculate aggregate exposure, including NORMTOX and several American models. Also relevant stakeholders of aggregate exposure are identified. From this overview the following conclusions were drawn:

- For some harmful compounds present in food exposure via other sources is or may be relevant. The group of compounds that seem to be most relevant at the moment, in view of stakeholder needs and models available, are the pesticides. This agrees well with the expertise within RIKILT.
- In view of the developments in the field of risk assessment, more advanced modelling of exposure (cumulative exposure, risk-benefit issues, integrating exposure and effect modelling), the development of a methodology to assess aggregate exposure would a desired step forward.
- Models are available to estimate aggregate exposure. These include models assessing the exposure using a person- or population-orientated approach. Depending on the goal of the assessment, the time frame of the exposure assessment and the required accuracy of the resulting estimation a choice of the model can be made.
- In long-term population-orientated models correlations between exposure routes are not addressed. For specific patterns this may however be relevant. It is therefore important that the impact of correlations between exposure routes on long-term exposure is studied further.
- Data availability regarding the exposure via different routes is minimal. This is true for all compounds addressed in the report. Generation of data to perform aggregate exposure assessments will therefore be as important as aggregate model development.
- We recommend that models developed in food and environmental sciences should be made compatible. A first step along this pathway has been taken in May 2007 by initiating cooperation between NORMTOX and MCRA regarding the aggregate exposure to lead. This project may identify other options for modelling aggregate exposure, including pesticides.
- To stimulate aggregate exposure modelling within the Netherlands it is recommended to start a joint activity of RIKILT and the Radboud University Nijmegen towards the Dutch Ministries of Agriculture, Nature Management and Food Quality (LNV), of Health, Welfare and Sports (VWS) and of Housing, Spatial Planning and the Environment (VROM) to stress the importance of aggregate model development and its added value for policy making.
- Cooperation between the EU-projects NoMiracle (all sources except food) and SAFE FOODS (only food) would be a big step forward in aggregate model development within Europe. It is therefore recommended that the coordinators and responsible scientists involved in both EU Projects should discuss future possibilities within Europe with DG Research and DG Sanco.

Overall, we conclude that aggregate exposure is important for several compounds and that aggregate model development following both a person- and population-orientated approach should be advanced both in the Netherlands and Europe following the recommendations mentioned above.

Contents

1 Introduction

Humans can be exposed to toxic compounds via multiple routes (ingestion, inhalation and dermal absorption) from multiple sources, such as food, air, and non-dietary sources (e.g. water, soil, consumer products). The source and route most important will differ per compound, as well as the number of routes and / or sources. This type of exposure was named, during an ILSI workshop, **aggregate exposure.** The procedure to assess this type of exposure was defined as:

> *The process for developing an estimate of the extent of exposure of a defined population to a given chemical by all relevant routes and from all relevant sources* (ILSI 1998).

In this definition aggregate exposure is defined as exposure to a given chemical. However, aggregate exposure can also involve exposure to more than one compound, e.g. to compounds with the same mechanism of action, or maybe in risk-risk / risk-benefit tradeoffs.

In this project aggregate exposure is studied in relation to the relevance of extending the dietary exposure assessments as performed using the Monte Carlo Risk Assessment (MCRA) programme with other sources than diet (and drinking water) or other routes. The underlying report focuses therefore only on those harmful compounds for which exposure via at least food occurs.

The following issues will be addressed:

- Description of groups of harmful compounds for which aggregate exposure may be relevant
- Which models, including data, are available to model aggregate exposure?
- Which stakeholders can be identified for which aggregate exposure assessments may be relevant?

2 Relevant groups of compounds

In the literature numerous studies are available which describe aggregate exposure to chemicals present in food. The most predominant are the studies looking at aggregate exposure to pesticides (Buck et al. 2001, Clayton et al. 2003, Lu et al. 2004, Morgan et al. 2005, Moschandreas et al. 2001, Pang et al. 2002). Other compounds reported are for example heavy metals (Carrington et al. 1996, Pang et al. 2001, Trasande et al. 2006), dioxins (Baars et al. 2004, Glorennec et al. 2005, JECFA 2002, Lee et al. 2005), PCBs (Baars et al. 2004) and brominated flame retardants (BFRs; (Jones-Otazo et al. 2005)). Exposure sources identified, other than food (and drinking water), are dust (e.g. BFRs, pesticides), hand-to-mouth behaviour (pesticides), air (e.g. dioxins, pesticides, heavy metals) and skin (e.g. pesticides).

Modelling exposure via other routes may become of interest if also a substantial proportion of the compound reaches the population via these routes. Below different groups of compounds for which aggregate exposure may be of interest are described. This list is not intended to be exhaustive, but tries to include the most relevant and important compounds.

2.1 Pesticides

Pesticides are, primarily in the U.S., the subject of aggregate exposure estimations for the general public. The interest in the U.S. for aggregate exposure to pesticides is due to the passage of the Food Quality Protection Act (FQPA) in 1996, which required that risk assessments of pesticide exposure should also address aggregate risks from all potential sources and routes of exposure (Shurdut et al. 1998). For pesticides, aggregate exposure becomes important for those chemicals with many home uses, such as insect control, lawn and garden treatments, home food production and pet treatment. In the U.S., residential use of pesticides is rather wide-spread. Two of the most widely used pesticides are chlorpyrifos and diazinon (Moschandreas et al. 2001). A national survey conducted by the U.S. Environmental Protection Agency (EPA) in 1979 (EPA 1979) revealed that 90% of U.S. households used pesticides: 83.7% of the households used them inside the house, 21.4% in the garden, and 28.7% on the lawn. In another study of residential use of pesticides in 238 Missouri families, nearly all (97.8%) used pesticides at least once a year and two-thirds used pesticides more than five times per year (Davis et al. 1992). Important other sources of exposure to pesticides may be soil / dust ingestion, inhalation of indoor- and outdoor air / dust and hand-to-mouth behaviour.

The different studies performed in the U.S. show that the dietary intake of pesticides is the main, continuous source of exposure. The exposure via the other sources will be more intermittent, due to the seasonality of pesticide use (application during the growing season). The importance of these other sources for a certain (sub)population will depend on the circumstances. For example, living in an agricultural environment results in higher exposure levels compared to a non-agricultural environment. A recent small study among homes of 13 children living either in the Seattle metropolitan area or in the agricultural region of Washington state showed that residential contamination of pesticides tended to be more prevalent in agricultural families and that the exposure in the non-agricultural groups was mainly caused by exposure through the diet (Lu et al. 2004). Another study demonstrated that relatives of farmers (children and spouses) are more exposed to pesticides than persons of non-farm households (Curwin et al. 2007). This was primarily due to take-home contamination; pesticides can be tracked into

farm homes on the clothing and shoes of farmers. Also whether the household has an allotment in which vegetables are grown and pesticides are applied will determine the relevance of other sources of exposure than diet (Lu et al. 2006).

Aggregate exposure to pesticides, including diet, in the general public in Europe does not seem to be an issue, in view of the publications in the literature and on the web. Also when setting Maximum Residue Limits (MRLs) for (new) pesticides, only the exposure through the diet is considered. However there is an example of a compound that has been evaluated recently by the Netherlands for which aggregate exposure was relevant, namely carvone (personal communication). Carvone is a substance that naturally occurs in oil of citrus fruit peel and which is among others used as a flavouring agent in toothpaste, perfumes and soaps (Svendsen et al. 2004). However, carvone is also used to prevent premature sprouting of potatoes during storage. A preliminary, worst-case assessment showed that use of carvone as an anti-sprouting agent was no problem but adding up the exposure via toothpaste indicated a possible health problem (personal communication). In Europe, aggregate exposure to pesticides seems currently predominantly an issue in the field of operator exposure (Hamey 2001, Machera et al. 2003, Machera et al. 2002, Van der Jagt et al. 2004). In the authorisation process of pesticides in the EU, according to Common Acceptance Directive 91/414/EEC (EC 1991) exposure via different routes / pathways is included to evaluate the safety of the operator applying the compound.

2.2 Dioxins, PCBs and furans

The major source of human exposure to polychlorinated biphenyls (PCBs), dioxins and furans is through the diet, which accounts for > 90% of their exposure (Huwe 2002). The main products being meats, fish and dairy products. A study performed by the EPA in 2003 and reported in a draft document still under discussion (EPA 2003), demonstrated that 99% of the exposure to dioxins, furans and dioxin-like PCBs was via food. The resulting 1% was due to ingestion of soil, dermal contact with soil and via water. Contamination of food with these compounds is primarily caused by deposition of emissions of various sources (e.g. waste incineration, production of chemicals, metal industry) and a subsequent accumulation in the food chain in which these compounds are particularly associated with fat (Huwe 2002). Reduction of these emissions is therefore seen as the major route of exposure reduction.

Levels of dioxins and dioxin-like compounds in water and air are generally very low and are therefore of very low relevancy (EPA 2003). Highest levels of these compounds in other sources than food products are found in soils, sediment and breast milk. Exposure other than dietary may therefore become important for certain subpopulations. A very clear subpopulation is young children playing outside and ingesting contaminated soil, and households that grow their own vegetables on contaminated soils. Also young infants that are breast-fed may have higher exposure levels. However, in this last case, it is generally accepted that the beneficial characteristics of breast milk outweigh the possible detrimental effect of a short period of higher dioxin exposure. Furthermore, during the main period of breast-feeding (first 6 months) the sole source of dioxin exposure will be breast milk. The consumption of other ‘foods’ that may contain dioxins during this period is either absent or negligible, so it is not likely that substantial aggregate exposure will occur via the diet in this subpopulation.

It is generally known that the levels of dioxins and dioxin-like compounds are decreasing in the environment, resulting in lower levels in food and also in other media and lower exposure levels (Huwe

2002). In the Netherlands the intake of dioxins decreased on average with 50% between 1990 and 1998/1999 and 60% for PCBs. This decrease in intake was mainly due to lower levels of dioxins in foods rather than changes in food consumption (EU-SCOOP 2000).

2.3 Acrylamide

Acrylamide (AA), a renowned compound, was detected in 2002 to be present in high concentrations in heat treated food products rich in carbohydrates (Tareke et al. 2002), which has led to worldwide concern due to its probable carcinogenic effects. The main sources of exposure to AA via the Dutch diet are fried potato products (including crisps) (Boon et al. 2005). However, AA may also be present in other media, including cosmetics, drinking water, and cigarette smoke. Exposure through cosmetics is mainly relevant for workers in the cosmetic industry. Water on the other hand may be relevant for the general public if the water has been purified with polyacrylamide flocculants. In the Netherlands however, other purification methods are used[1], resulting in the absence of AA in water. The only other relevant source is exposure via cigarette smoke, which is potentially relevant for smokers and people who come in contact with cigarette smoke (e.g. spouses / children of smoking relatives). A study of Smith et al. (2002) estimated that the intake of AA was about 1-2 µg per cigarette. This level of intake can result in a substantial contribution of cigarette smoke to the overall AA intake compared to the average daily dietary AA intake of 0.5 µg per kg body weight (Dybing et al. 2005, Konings et al. 2003, Svensson et al. 2003).

Exposure to AA via other routes than food and cigarette smoke is primarily occupational. AA is a chemical used in the production of polyacrylamides, which have a great many uses, including paper and pulp processing, the treatment of water and waste and in the processing of minerals (Bull et al. 2005). During manufacture, exposure may occur to AA vapour of the 50% aqueous solution used to make polyacrylamides. AA can also sublime and absorption may be via inhalation or dermal contact (Bull et al. 2005, Jones et al. 2006). Also laboratory personnel working in biomedical laboratories using either crystalline or commercially available solutions of AA to make polyacrylamide gels, are exposed to AA via other routes than food (Pantusa et al. 2002).

2.4 Heavy metals

Heavy metals are individual metals and metal compounds that negatively affect people's health. These compounds include arsenic, cadmium, lead, mercury, selenium, copper and zinc. In very small amounts, many of these metals are necessary to support life. However, in larger amounts, they become toxic. They may build up in biological systems and become a significant health hazard. Heavy metals are well-known compounds to which people can be exposed via more than just diet and water. Known sources are soil and air. It is outside the scope of this project to examine all heavy metals in relation to their sources of exposure. I restrict myself here to a couple examples.

A ‘hot’ heavy metal is **cadmium**, present in high levels in soil of ‘De Kempen’ (together with zinc), an area in the south of the Netherlands[2]. Main exposure routes there are inhalation of circulating dust (both

[1] www.vewin.nl

[2] www2.vwa.nl/CDL/files/1/1004/12326%20Beoordeling_Malpiebeemden_totaal.pdf

in- and outdoor), drinking of contaminated well water and consumption of vegetables grown on contaminated soil[3]. For children also consumption of contaminated soil, via hand-to-mouth behaviour, is a relevant exposure route. However, for the general population not living on contaminated soils it is widely recognised that dietary ingestion of cadmium is the main pathway of cadmium intake (WHO 2004).

Lead exposure can occur via the air (dust particles containing lead), consumption of water or vegetables and hand-to-mouth behaviour of children playing outside. In the years 1980-90 it was recognised that lead was harmful for the environment and human health. The use of lead was therefore prohibited in petrol and in piping for drinking water, which resulted in a substantial decrease of lead exposure, as demonstrated in a recent study in Rotterdam (Peeters 2006). The exposure to lead is normally monitored by taking blood samples, because of uncertainty about bioavailability of lead from dust/soil and estimations of hand-to-mouth behaviour of children.

Another example is **mercury**. Mercury is a metal that occurs naturally in small amounts in the environment. People are most commonly exposed to mercury either through breathing mercury vapours or eating foods contaminated with mercury or mercury compounds. One of the most common, and most toxic, mercury compounds is methylmercury, which can be present in soil, water and seafood. The main source of exposure in the general public to methylmercury is via the consumption of fish and shellfish, which have a natural tendency to concentrate mercury in their bodies (Wheatley & Paradis 1995, WHO 2000). For young infants also human milk may be an important source (Grandjean et al. 1994). Levels of mercury in outdoor air are negligible (WHO 2000).

2.5 Flame retardants

Polybrominated diphenyl ethers (PBDEs), also known as brominated flame retardants (BFRs), are anthropogenic chemicals that are added to a wide variety of consumer/commercial products (e.g. plastics, polyurethane foam, textiles) to improve their fire resistance. Unlike several of the ‘classical’ persistent organic pollutants such as PCBs, dioxins and furans, whose levels have been decreasing markedly during the last 20 years, levels of BFRs have increased starting early 1970 (Alaee et al. 2003, Alaee & Wenning 2002).

The exposure to BFRs in humans can occur via the ingestion of food, house dust and soil, and via the inhalation of (indoor) air. As for dioxins and PCBs, food products of animal origin with a high fat content are the major contributors to dietary exposure (De Mul et al. 2005). The ingestion of house dust can contribute significantly to the exposure as shown in a study by Jones-Otaza et al. (2005) within the Canadian population. However, the concentrations of BFRs in house dust of European origin are far less than in American and Canadian homes. As demonstrated by De Winter-Sorkina et al. (2006), a daily exposure of 1.2 – 3.1 ng may be calculated for adults and (maximally) 12.4 ng for toddlers within Europe. Compared to a life-long exposure in the Netherlands via food of about 121 ng/ day for a person of 70 kg (De Mul et al. 2005), the exposure to BFRs via soil/dust ingestion seems to be only a minor route of exposure (De Winter-Sorkina et al. 2006). Furthermore, the absorption of BFRs originating from house dust is expected to be far less than from food, although more research is needed to clarify

[3] www.milieu-en-gezondheid.be/nieuwsbrief/nieuwsbrief%203/metalen.htm

the level of absorption of BFRs from soil/dust relative to food. Intake from air is negligible compared to food and dust / soil (Jones-Otazo et al. 2005).

2.6 Phthalic acids

Phthalic acid esters (phthalates) are used as plasticizers in numerous consumer products. These compounds are not chemically bound to these products and are therefore released into the air or leach from products. The presence of phthalates in food is due to emissions of phthalates from the various sources of its production / use / disposal or they may migrate from processing equipment (e.g. gloves, tubes and pots) or the packaging (including imprints and adhesives) into the food. A study conducted by Wormuth et al. (2006) demonstrated that of eight frequently used phthalic acid esters, for two food was the dominating source of exposure (DiBP and DEHP). For the other six esters other sources, such as application and incidental ingestion of personal care products, toys mouthed by toddlers, dust, plastic gloves, were most important.

3 Models of aggregate exposure

Within the Monte Carlo Risk Assessment programme (De Boer & Van der Voet 2006), an internet based probabilistic programme developed by RIKILT and Biometris, the dietary exposure to a compound or multiple compounds via all foods that may contain the compound of interest can be estimated. In these assessments all the different foods that may contain the compound and which can be consumed during an arbitrary day by an individual are considered. To avoid unrealistic combinations of food consumption patterns and amounts consumed, daily individual food patterns are used to assess these types of exposures. In a way, this can be seen as a form of aggregate exposure. Instead of looking at different routes, different foods are addressed. Extrapolating this to aggregate exposure via different routes / sources, it is important when performing these assessments to study individual exposure route / pathway combinations that are likely to occur. For acute exposure assessments, these patterns can be deduced from consumption and behaviour surveys which generally cover 2-7 days of an individual's life. This data can subsequently be used in a person-oriented modelling approach that simulates the exposure of a particular individual. For chronic exposure assessment, reliable estimation of long-term exposure patterns is problematic because consumption and behaviour surveys generally cover a limited number of days. Therefore, a population-based approach is often followed in which the exposure distributions of different routes are randomly combined. This approach has the disadvantage that the correlation structure between the different exposure routes is generally lost, but it produces a relatively reliable estimate of the exposure per route. Which of the approaches, person- or population-oriented, should be used in a particular situation depends on the goal of the assessment and data availability. For chronic assessments, a population-based approach will often be the only option because of a lack of reliable long-term data on exposure patterns. For acute assessment, the assessor may choose between population- or person-oriented approaches. For screening purposes, a population-based approach may suffice, but if reliable exposure pattern data are available a person-oriented approach will always provide more realistic results.

In a recent paper by Fryer et al. (2006) an overview is given of different human exposure models currently employed for health risk assessments, including aggregate exposure models. The only aggregate models that have been developed so far for the general public and which are person-orientated are those that estimate aggregate exposure to pesticides. Aggregate exposure calculations to other compounds, mostly environmental chemicals but also phtalates, are performed using point estimates of exposure per route, which are then summed up to get an overall exposure estimate. Models that follow this approach are e.g. CalTOX[4], SUS model (Lijzen et al. 2003), and EUSES (Vermeire et al. 1997). For a general description of these models, see (Fryer et al. 2004). Another model that follows this approach but produces probabilistic exposure distributions is the NORMTOX model, developed by the Department of Environmental Science of the Radboud University Nijmegen (Brouwer et al. 2007, Ragas & Huijbregts 1998). This model will be addressed in Section 3.1. In Section 3.2, we will describe three person-orientated models to estimate aggregate exposure, which follow the approach of MCRA when addressing acute dietary exposure. Shortly also operator models (Section 3.3) and exposure to consumer products (Section 3.4) will be addressed.

[4] eetd.lbl.gov/IED/ERA/caltox/index.html

3.1 NORMTOX: an aggregate population model for estimating exposure to environmental compounds in the general public

There are different models available to estimate the aggregate exposure to environmental contaminants (but also other compounds). One of these models is the NORMTOX model (Ragas & Huijbregts 1998). NORMTOX predicts the lifetime averaged daily exposure to substances. The model consists of several mathematical equations and parameters, which together describe the oral and inhalatory intake of a substance through multiple environmental media, i.e. food, air, soil, drinking and surface water (Figure 1). There is no distinction between men and women, and predictions are on a bodyweight basis. The model is implemented in Microsoft Excel, which uses Crystal Ball (Decisioneering Inc.) as an add-in to define statistical distributions for the input parameters and run Monte Carlo simulations.

The model was originally developed to test the coherence of Dutch environmental quality objectives (EQOs). A set of EQOs is called coherent if simultaneous exposure to different environmental media which are all polluted up to their respective EQOs, does not result in exceeding the acceptable or tolerable daily intake (ADI or TDI). Ragas & Huijbregts (1998) tested the coherence of the Dutch EQOs for benzene, lead and lindane and found that these EQOs were coherent, partly incoherent and completely incoherent, respectively. In a follow-up study, Brouwer et al. (2007) tested the coherence of Dutch EQOs for 54 substances, mainly pesticides, with an updated version of the NORMTOX model. The aim of this study was not only to test the coherence, but also to separate uncertainty from interindividual variability in the exposure predictions. First, ANOVA was used to calculate interindividual variability in input parameters. Second, nested Monte Carlo simulation was used to propagate uncertainty and interindividual variability separately. Output distributions specified the population fraction at risk, due to a particular exposure, and the reliability of this risk. From the case

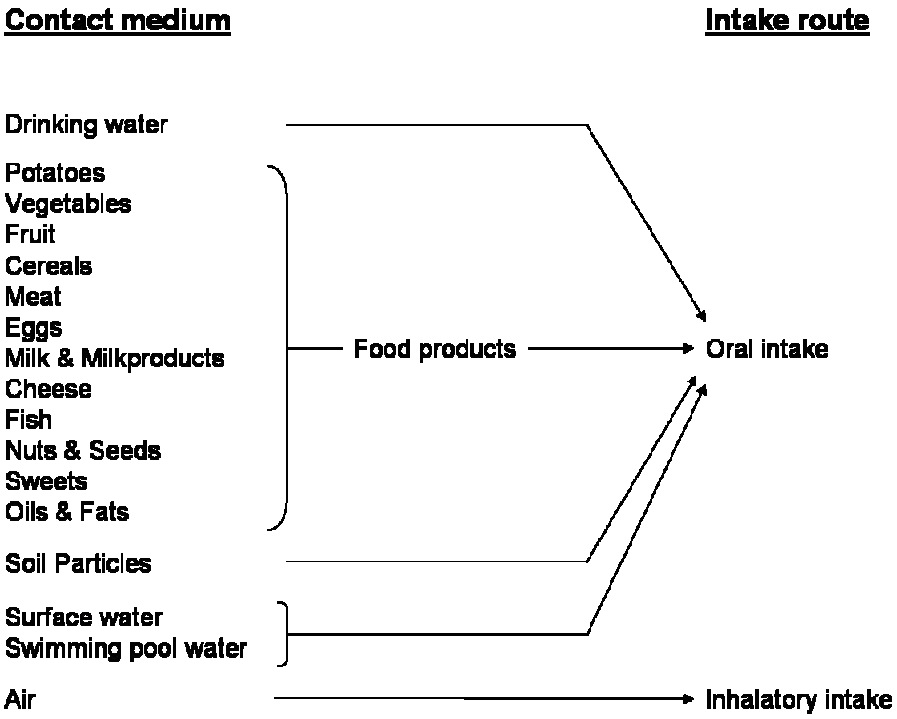

Figure 1. The NORMTOX model.

study it was concluded that the variance in the exposure predictions is mostly caused by interindividual variability instead of true uncertainty.

The main strengths of the NORMTOX model are that it predicts aggregate exposure for the Dutch population and that uncertainty and interindividual variability can be quantified separately. It is also a very flexible model because it has been implemented in Microsoft Excel. The main disadvantages are the fact that it does not predict acute exposure and that correlations between exposure routes are ignored due to the population-oriented approach followed.

3.2 Aggregate person-orientated models for pesticide exposure in the general public

As indicated earlier aggregate models have been developed which address exposure to pesticides via different sources / routes in the general public within U.S. Below the three aggregate models within this field currently available are discussed in relation to their characteristics and data input needs. For this, information was derived from a report by Fryer et al. (2004). In this report a thorough discussion is given of models available to model human dietary exposure.

3.2.1 LifeLine™[5]

LifeLine™ is an exposure model that estimates aggregate exposure using the probabilistic approach. Sources of exposure included in the model are diet, soil, grass, drinking water, indoor surfaces and in- and outdoor air. The routes included are ingestion, inhalation and dermal contact. Where pesticides have a common mechanism of action, cumulative assessments can be performed for multiple compounds. LifeLine™ is designed to predict exposures of pesticides only, but the dietary components of the model are also applicable for a broader range of chemicals. Exposure periods that can be addressed by the model range from 1 day up to an entire lifetime. A maximum is set at 85 years due to lack of robust data for older individuals (Figure 2).

As summarised by Fryer et al. (2004), the strengths of LifeLine™ are among others that it can address aggregate and cumulative exposure and that it assesses exposure durations from a single day to a lifetime. A major limitation however of the model is that it is designed to be applicable for the U.S. population, and therefore contains many U.S. databases and assumptions. Because of this, it will require considerable modification to be applicable for European situations. The way in which exposure is estimated over a lifetime, using data of different individuals at different ages and in different environments, will require intensive data input and very likely many assumptions, which may result in exposure estimates with a high degree of uncertainty. Also the model is not able to deal with variability in residue levels within a composite sample, the unit in which residue levels are analysed in Europe.

3.2.2 Calendex™[6]

Calendex™ is another probabilistic model, developed by Exponent, which estimates human exposure to chemical residues in foods and home-based chemical treatments via different sources / routes. It is a calendar-based system, which entails that for each day of the year the model combines exposure distributions with the probability that an exposure to a given compound could occur as a result of a

[5] www.thelifelinegroup.org/

[6] www.exponent.com/practices/foodchemical/calendex.html

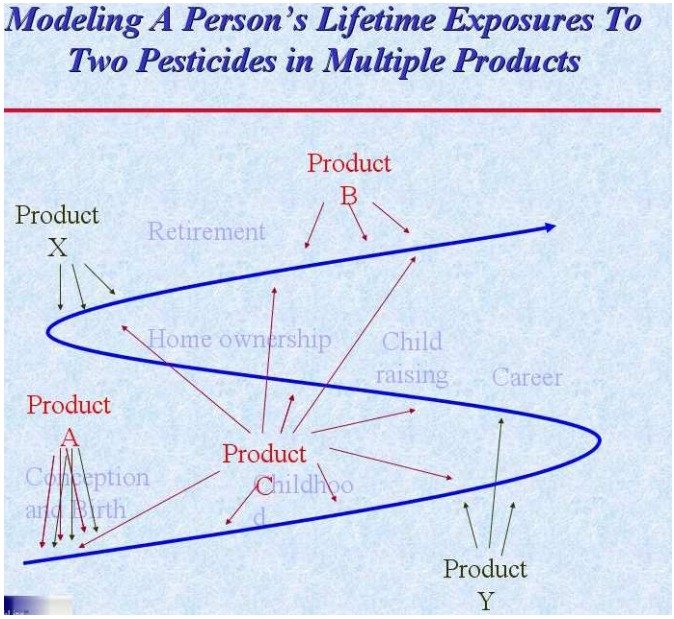

Figure 2. LifeLine™

previous or concurrent application of a product containing that compound. The model takes into account the probability that exposures to more than one product may occur on a single day.

Calendex™ links with DEEM™ and has been licensed to EPA, USDA and Health Canada. DEEM™ stands for Dietary Exposure Evaluation Model and is a model that was developed to assess pesticide exposure through the diet using the probabilistic approach. Of this model there is both a U.S. version used by EPA and a UK version, which differ regarding the food consumption database behind the programme. This model shows large similarities with MCRA.

The strength of Calendex™ is that it can assess single-serving dietary exposures through the use of a decompositing algorithm, as implemented in DEEM™. However, as with LifeLine™, also this model is based on U.S. specific databases, some of which cannot be adjusted in the model to be representative for conditions in other countries. Furthermore it requires an extensive array of input parameters (e.g. timing / frequency of pesticide use, inhalation rates, dermal absorption rates, etc.). Furthermore, this model cannot assess exposures lasting longer than a year, as can be performed with MCRA.

3.2.3 CARES®[7]

Another aggregate model is CARES®, which stands for Cumulative and Aggregate Risk Evaluation System. This model was originally an industry effort to create an aggregate and cumulative risk assessment model, but is now managed by the ILSI Research Foundation. CARES® allows risk assessors to estimate exposure to a single pesticide occurring via ingestion, dermal, and inhalation routes from food, drinking water, and residential sources, as well as cumulative exposure. The program and its source code are publicly available at no charge.

[7] cares.ilsi.org/About+Us/

CARES® is able to perform acute, intermediate and chronic exposure assessments – from a single day to an entire year. Exposures longer than a year, as can be performed with MCRA, are not possible. The strength of CARES® compared with the other two models is that the source code is freely available. The model has been specifically designed to be transparent, reproducible and flexible. Its limitations are however that it cannot address exposures for periods longer than a year, it needs intensive data requirement (as the other models), and that it contains data and default values specifically for U.S. situations. As LifeLine™, the model is not able to deal with variability in residue levels within a composite sample.

3.2.4 Input data

All the three aggregate models described above contain food consumption data from the U.S. and have as such limited use for estimations of exposure outside the US. If used for assessments outside U.S. (e.g. Europe), it is necessary to obtain similar data for the regions of interest. Furthermore, all models are specifically developed for assessing the exposure to pesticides and may therefore be of limited use for assessing the exposure to other chemicals, but they definitely show that these approaches are possible. ILSI Research Foundation examines for example at the moment the potential of CARES® for application to other types of assessments, such as nutrient intake analysis.

As described above all three aggregate models ask for intensive data needs. Data availability is therefore a very important issue when using these models. You can build a very complicated model, but if the data you need to put into the model is not available or scarce and surrounded by much uncertainty, the model will not work. Data needed for these models include among others (except those related to the dietary component of exposure, including tap water):

- Data on residential pesticide use, reflecting both the misuses and the proper uses of pesticides by the general public.
- Data on levels of pesticides in soil, (carpet) dust, (out- and indoor) air, lawn, and surface areas indoor
- Data on oral inhalation and dermal absorption rates
- Data on hand-to-mouth behaviour
- Data on activity patterns of individuals, especially with regard to the co-occurrence of exposure-related activities
- Data on residential characteristics that may influence residential pesticide exposure, e.g. use of carpet and carpet area in the house, presence of garden / allotment / pets

For some of these data inputs, information can be obtained from so-called ‘Exposure Factor Handbooks’. These handbooks contain (standard) figures for all kinds of exposure factors, i.e. the variables that describe contact with exposure media, including physiological, dietary, and behavioural factors. Examples of variables are housing conditions, hand-to-mouth behaviour, and time spend in different parts of the house (microenvironments). For Europe such a ‘handbook’ has been established within the ExpoFacts project (Vuori et al. 2006). Within this project a Finnish research group (National Public Health Institute (KTL)) has collected European exposure factor data in one centrally available, freely accessible site on the Internet: the ExpoFacts database[8]. This database contains data from 30 European countries, including the Netherlands. It clearly presents the present availability of European exposure factors data, but inherently also the restrictions of such a database. For the Netherlands at

[8] www.ktl.fi/expofacts/

least, data presented are rather old and only available at summary statistical levels. No data at the level of an individual are available. Furthermore most of the data is limited or incomplete and has a large margin of uncertainty connected to it.

Data on residential use of pesticides (including frequency of use, duration of use, amount used, what is used and percentage of the population applying a certain pesticide) are missing at both international and national level within Europe. For the Netherlands (and very likely also for other EU countries) the only information about pesticide use can be obtained from pesticide sale figures at retail level. These sale figures indicate that in 2004 about 80 ton of active ingredient has been purchased by consumers (Vijftigschild 2006). Most of these pesticides (80%) were herbicides (65 ton), of which more than 40% was ferrosulfate and almost 25% glyfosaat. Ferrosufate is used to prevent moss growth and glyfosaat is used to resist weeds. The sale of pesticides to consumers is however very small compared to the total sales. When expressed in the amount of active ingredient bought by consumers in 2004 this amounts to less than 1% of the total sale. Two studies have looked at some other parameters of residential pesticide use (such as frequency and amount used) but focused only on a limited number of consumers that actually used pesticides (Baas 2000, Weegels 1997). These studies have therefore very restricted value.

3.3 Aggregate models for pesticide exposure in relation to operator exposure

As opposed to aggregate exposure to pesticides in the general population, this type of exposure is an issue in Europe when related to operator exposure. For this type of exposure several models are in use including POEM (Predictive Operator Exposure Model). POEM looks at exposure via different routes during the application of pesticides. Routes included are inhalation and dermal contact. However, POEM is a very conservative model using many default upper bound values, resulting in one possible upper-bound exposure level for a certain application of a compound. The model can therefore best been seen as first screening tool for risk assessment. Furthermore, POEM has a limited scope, as it is designed to predict exposure levels experienced by operators preparing and applying pesticides in the UK under UK conditions. A European version of the POEM model (EUROPOEM) is currently in development. EUROPOEM is heavily based on the approach and methodology adopted by POEM, but will also include worker re-entry exposures and bystander exposures.

Another operator exposure model, presented at the AgChem Forum Conference of 3 -4 October 2005, is the Agricultural Handlers Exposure Database (AHED™). AHED™ is a huge database containing data on all kinds of variables relevant for operator exposure including among others worker information (e.g. age, height, weight), application information (e.g. crop height, application equipment), mixing information, product information, personal protection equipment, head / face / neck sample data, glove / hand sample data, and inhalation sample data. The model can address 12 different exposure scenario's including open-pour and closed-system mixer/loaders, orchard sprayer, groundboom, hand spray and aerial applicators, and liquid, granular, dry flowable and wettable formulations. Using this information, exposures can be calculated via dermal contact and inhalation. Exposure levels per route and individual can be exported from the database to excel.

None of the operator models available contain a dietary component. The reason for this is very likely that the exposure via the actual application of pesticides is much higher compared to other sources also relevant for the general population, predominantly diet (Curwin et al. 2005, Denovan et al. 2000). It is

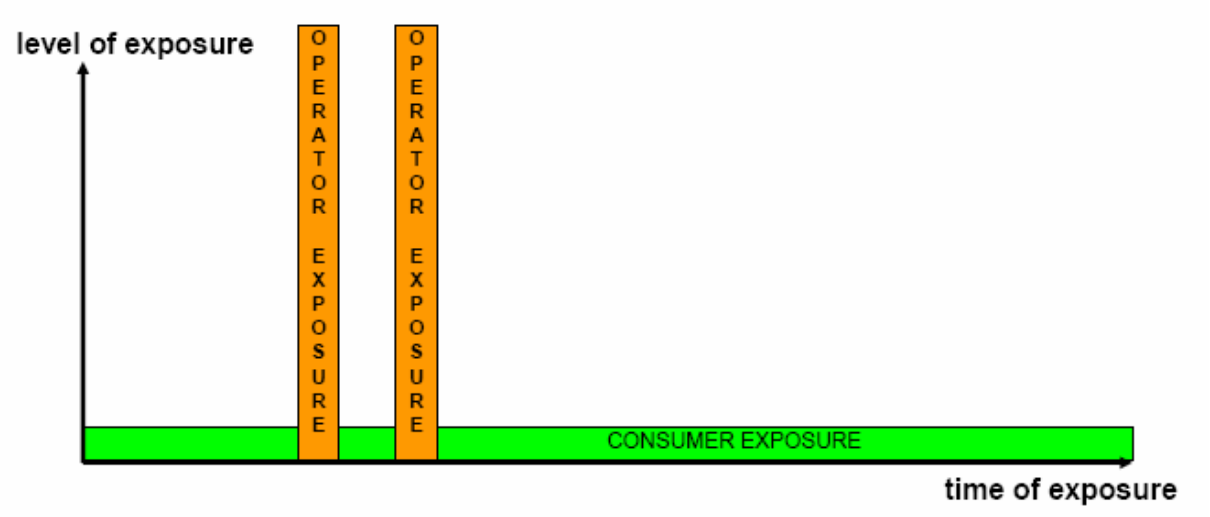

Figure 3. Operator exposure vs. consumer exposure.

generally assumed that application of these pesticides result in peak exposure levels during short periods above a continuous, low exposure to pesticides through the diet (Figure 3). This continuous low exposure to pesticides can of course also be superimposed by higher exposure levels due to the incidental consumption of a fruit / vegetable that contains a much higher level of the compound than the average, long-term concentration. This is the so-called acute dietary exposure to a pesticide, which may be of relevance if the pesticide is known to be acute toxic. However, how acute levels of intake relate to the levels to which operators are exposed is not clear. In the most worst-case situation it could be that a peak exposure to a pesticide due to application coincides with a possible high intake via the diet, resulting in exposures that are not addressed in the current safety assessments and result in undesirable risks. In the most positive scenario peak operator exposures are that high that even incidental high dietary exposure levels are marginal compared to that, and hardly add to the risk due to application.

3.4 Aggregate models for exposure to compounds present in consumers products

Another field of exposure in which aggregate exposure is of importance is the field of exposure to compounds present in consumer products. People come in contact with chemicals present in consumer products (ranging from shoe polish, to detergents, to pesticides) via different pathways. The most well-known model developed in this field is ConsExpo (Van Veen 1995)[9]. ConsExpo stands for Consumer Exposure and Uptake and is a model developed by the National Institute of Public Health and the Environment (RIVM) in the Netherlands. With this model the exposure to hazardous compounds via contact with consumer products is estimated. It assesses the exposures via inhalation, ingestion or dermal contact routes, and does not include a dietary exposure component.

However the way in which ConsExpo operates at the moment does not facilitate aggregate exposure assessments. The evaluations are performed for one product and one chemical at the time, and the exposure is calculated for single exposure events.

[9] www.rivm.nl/en/healthanddisease/productsafety/ConsExpo.jsp

4 Possible stakeholders interested in aggregate exposure assessments, including diet

In 2005 a new pesticide regulation has come into force, Regulation (EC) No 396/2005[10]. In this Regulation it is stated that within the safety evaluation of pesticides 'the possible presence of pesticide residues arising from sources other than current plant protection, and their known cumulative and synergistic effect' should be addressed. The **European Food Safety Authority** (EFSA) has been asked to write an opinion on how aggregate (and also cumulative) exposure can be addressed when setting maximum residue limits (MRLs). It is therefore clear that in the field of pesticide regulation aggregate exposure may become an issue. It is at this stage unclear what is meant with all sources. In a document by the EC made in preparation of the new pesticide regulation it is stated that in the 'risk equation, detailed data on dietary intakes from all sources (all food types - including portion sizes - as well as water and other sources) are required. Therefore, the Regulation proposes that EFSA maintain a database of all uses of plant protection products in the Community to complement a second database on dietary intakes of each type of food among various population subgroups' (EC 2003). According to this explanation at least drinking water should be included in the assessment and all foods that may contain the contaminant. Other possible sources could be exposure as bystander (e.g. somebody passing a field which is being treated with pesticides), via air pollution and / or via contaminated consumer products such as shampoo. However, the sentence 'data on dietary intakes from all sources' is unclear and seems to indicate that the sources to be looked at should be linked with dietary intake. So for example air pollution via deposition of chemicals on agricultural products used for human consumption. Despite this vagueness of what is meant it is clear that aggregate exposure will become important in MRL setting in the future.

Another possible party interested in aggregate exposure is the **Dutch Food and Consumer Product Safety Authority (VWA)**. Problems as encountered in 'De Kempen' may demand more sophisticated models than used presently to assess the risk of exposure to environmental contaminants. Also changes in EU legislation in relation to pesticides may demand another form of risk assessment as performed now by the VWA. Furthermore **The Health Council of the Netherlands** in a report 'Pesticides in food: assessing the risk to children' recommends that simultaneous exposure via different sources (diet, water, residential use) should be addressed when assessing the risks of pesticides (Health Council of the Netherlands 2004). This recommendation is supported by Dutch environmental organisations[11]. Also in the European Framework Programme attention may be asked for aggregate exposure.

These developments show that assessing the exposure to chemicals, and predominantly pesticides, from different sources / routes is a field of research with potential relevance and possibilities. These developments should be monitored closely by RIKILT in view of its expertise (probabilistic modelling of dietary exposure to harmful substances present in food).

[10] eur-lex.europa.eu/LexUriServ/site/en/oj/2005/l_070/l_07020050316en00010016.pdf

[11] www.weetwatjeeet.nl

5 Discussion and conclusions

In this report an overview is given of the possible relevance of aggregate exposure to harmful compounds present in at least food. It is clear that for some of these compounds this type of exposure is or may be relevant. The group of compounds that seem to be most relevant at the moment, in view of stakeholder needs and models available, are the pesticides. This agrees well with the expertise within RIKILT. However the main problem addressing these compounds at the national and European level will be data availability.

Population- and person orientated approach
We discussed two types of aggregate exposure models: population- and person orientated models. Population orientated models are models that use a parametric approach to simulate exposure to chemicals via different routes, but ignore potential correlations between these routes. Person-orientated models take the individual as a starting point, aggregating the exposure at an individual basis. Depending on the goal of an assessment either of the approaches can be selected. For acute exposure assessments, such as the exposure during one specific day, person-orientated models are essential. In these types of assessments, it will be necessary to construct exposure profiles of people on a day-to-day basis. So what is the probability that simultaneous exposure to a (mixture of) pesticide(s) occurs via food, and via the use of a product containing the compound? For chronic exposure assessments this approach is problematic because data to reliably estimate long-term exposure patterns are generally lacking. There are indications that correlations between exposure routes may be less relevant for estimating chronic exposure because the relatively long time span allows for compensation of high exposure situations by low exposure situations. However, this does not hold true for specific patterns such as people that have a persistent allergy or dislike for particular food products or activities. It is therefore important that the impact of correlations between exposure routes on chronic exposures is further studied.

It should be noted that there are statistical methods available that make it possible to estimate long-term exposure patterns via food from individual consumption patterns of minimally two consumption days per individual (Hoffmann et al. 2002). These methods include those developed by Slob (1993) and Nusser et al.(1996, 1997), which are implemented in MCRA. In an exercise in which long-term exposure was calculated following different scenarios[12] demonstrated that advanced statistical modelling resulted in decreased upper percentiles compared to the observed sample distribution of individual means (Van Klaveren et al. 2006).Using this approach a distribution of long-term exposure is generated, in which the individual persons are lost. The implementation of this approach to model long-term exposure via food in population-orientated models like NORMTOX has the potency to improve the estimates of aggregate exposure.

The American models described in Section 3.2 take a person-orientated approach when calculating chronic exposure. They model chronic exposures (of 1 year or longer) by simulating the daily exposure

[12] Scenario's included were 1. daily food consumption patterns linked to mean levels of the compound in foods, including statistical modeling for long-term exposure, 2. daily food consumption patterns linked to mean levels of the compound in foods without statistical modeling for long-term exposure and 3. mean consumption patterns over two food recording days per respondent linked to mean levels of the compound in foods

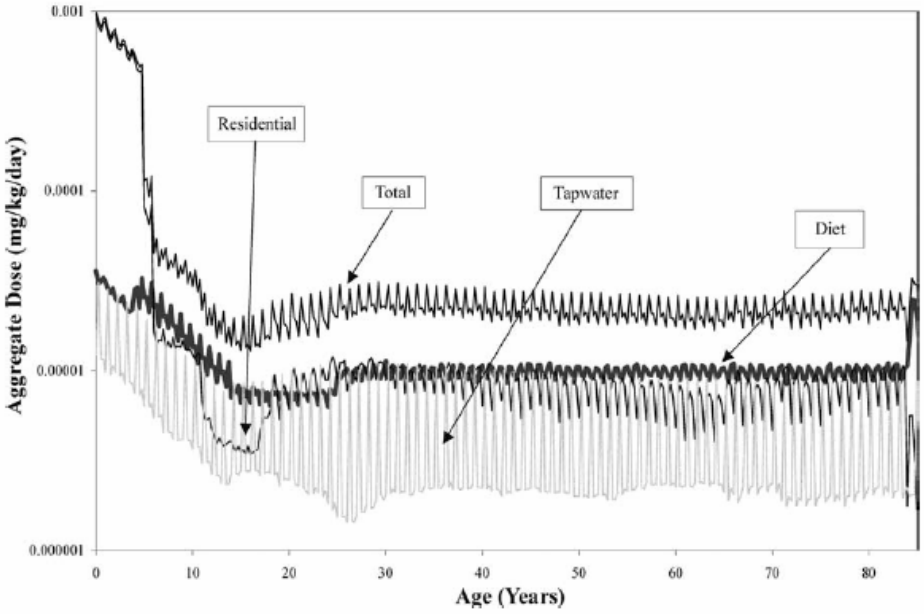

Figure 4. Average daily doses of pesticide Alpha by age for the modelled population. The doses include the average dose for tap water, diet, and residential sources as well as the total (aggregate) dose for all routes. Obtained from (Price et al. 2001) as modelled with LifeLine.

of one person during one year or during his / her lifetime via different routes. By repeating this for many thousands of individuals a population exposure distribution is generated covering a year or longer (for an example see Figure 4). In our view, the amount of data needed for these types of assessments is huge, making this approach in many cases unfeasible. Furthermore, the representativeness of the simulated exposure patterns (i.e. the uncertainty in the predictions) should be quantified before such an approach can be advocated.

Aggregate exposure to pesticides

Aggregate exposure to pesticides is, in view of stakeholder needs and model availability, the most obvious thing to focus on if the interest is aggregate exposure development. A close look at the American models would then be the first step to take, with a preference for the model CARES® due to its open source code policy. Despite their limitations (e.g. based on American databases), these models show that aggregate exposure assessments at the individual level can be performed, and much can be learned from these models on how to model exposure via residential sources of pesticide use.

A major problem that needs to be faced when implementing the residential exposure route of pesticide use will be data availability. The level of information is very limited and mainly at the level of sale figures, which are of no use when assessing individual aggregate exposure levels. Also it is not clear whether aggregate exposure to pesticides is relevant for the Dutch, or even European, situation. The use of pesticides by the consumer is certainly less widespread in Europe compared to America. However, data is lacking on actual uses making it very difficult to establish whether it is really not relevant. In the new Pesticide Regulation 396/2005[10], it is mentioned that in MRL setting also ‘sources other than current plant protection’ should be addressed (if the methodology is available). In view of these developments it is very likely that aggregate exposure will become important in the future. The question to be answered then: is it worthwhile to invest time and money in developing the methodology for this

so that when EFSA is ready to deal with this issue, RIKILT can be in the front line demonstrating its expertise as is currently the case with the cumulative assessment. Or should RIKILT stay back awaiting the developments at EFSA and step in when it is clearer what is meant with 'sources other than current plant protection'? In view of the developments in the field of risk assessment, more advanced modelling of exposure (cumulative exposure, risk-benefit issues, integrating exposure and effect modelling (SAFE FOODS[13])), the development of a methodology to assess aggregate exposure would a desirable step forward.

Aggregate exposure to environmental contaminants
As discussed in Section 3.1. NORMTOX is an aggregate model that estimates the long-term exposure to environmental contaminants via different sources including food. The model uses a population-oriented approach to estimate long-term exposure to all sources, including food. MCRA takes a more person-orientated approach to exposure via food, applying, when dealing with long-term exposure, statistical methods to extrapolate daily exposure levels to long-term exposure levels at population level, as described above. We recommend that models developed in food science and models developed in environmental science should be made compatible. The European context is different from the American context regarding data generation and data ownership, making another approach advisable.

Combining the exposure via food generated by MCRA with the exposure via other sources as generated by NORMTOX would be a way forward in assessing aggregate exposure within the Netherlands and Europe. A first step of such cooperation would be to compare the dietary exposure to a compound using the approach taken by NORMTOX and MCRA. This step has been taken in May 2007. A case study will be performed to assess the aggregate exposure to lead, where the dietary exposure will be assessed both with NORMTOX and MCRA. This project may identify other options for modelling aggregate exposure, including pesticides if expedient. To bring aggregate exposure modelling within the Netherlands further it is recommended to start a joint activity towards the Dutch Ministry of Agriculture, Nature Management and Food Quality and the Ministry of Housing, Spatial Planning and the Environment stressing the importance and assets of aggregate model development.

Another development is the aggregate model development within the EU-project NoMiracle, in which the Radboud University Nijmegen is a participant. In this project, the aggregate exposure to environmental compounds via different sources is addressed, except food. The reason for this is that food is already addressed in the EU-project SAFE FOODS. Also here cooperation between food and environmental sciences in exposure model development is advisable. We recommended that the coordinators and responsible scientists involved in the EU Projects SAFE FOODS and NoMiracle should discuss future possibilities within Europe with DG Research and DG Sanco.

Aggregate exposure to chemicals present in consumer products
Another source of aggregate exposure that may be relevant for RIKILT is exposure via chemicals (other than pesticides) present in food and consumer products. The model ConsExpo, developed by RIVM, presently addresses this type of exposure. However, this model does not perform the assessments in an aggregated fashion and also food is not addressed. In this field model development would be called for in the recognition that the same persons may use consumer products containing the same compound.

[13] www.safefoods.nl

The expertise of this type of modelling is at the moment present at the RIVM. Initiatives in this field of exposure should therefore be discussed in close cooperation with this institute.

Aggregate exposure in the operator field
Another field of aggregate exposure is operator exposure to pesticides. The models that are used to assess this type of exposure are mostly crude deterministic models. Exposures per route are summed up to arrive at one deterministic level of exposure for a certain application. Furthermore, these models do not include exposure via the diet, while operators also consume foods. It seems therefore obvious that also operator exposure should include a dietary component. It is however unclear whether the exposure due to application is in all cases so high that dietary exposure, and especially acute, only contributes marginally to the total exposure, and can therefore safely be neglected. Also here cumulative exposure may be relevant, which could ask for also including a dietary component in the assessment.

There is one (American) operator model that has an individual based approach when calculating operator exposure: AHED. This model results in individual exposure levels that can be exported to an Excel file. Linking these data with individual randomly selected daily intakes via food (assuming that operators have no different eating habits compared to the general public) could result in a form of aggregate exposure for operators that includes a dietary component.

RIKILT has the expertise to model the exposure to harmful compounds via multiple foods in a probabilistic manner. Extension to other routes / sources seems a desirable step forward, in view of international developments in risk assessment. A first step in this direction has already been taken by cooperating with the Radboud University Nijmegen. Other possibilities of developing an expertise in aggregate exposure (of consumer but possibly also operator risk assessment) are in projects solely including RIKILT and other Science Groups within Wageningen UR (e.g. aggregate exposure to pesticides based on the U.S. models) or in cooperation with other institutes in for example EU-projects. In these larger projects, RIKILT can bring in its expertise of probabilistic modelling of dietary exposure.

Conclusions
The following conclusions can be drawn:

- For some harmful compounds present in food exposure via other sources is or may be relevant. The group of compounds that seem to be most relevant at the moment, in view of stakeholder needs and models available, are the pesticides. This agrees well with the expertise within RIKILT.
- In view of the developments in the field of risk assessment, more advanced modelling of exposure (cumulative exposure, risk-benefit issues, integrating exposure and effect modelling), the development of a methodology to assess aggregate exposure would a desirable step forward.
- Models are available to estimate aggregate exposure. These include models assessing the exposure using a person- or population-orientated approach. Depending on the goal of the assessment, the time frame of the exposure assessment and the required accuracy of the resulting estimation a choice of the model can be made.
- In long-term population-orientated models correlations between exposure routes are not addressed. For specific patterns this may however be relevant. It is therefore important that the impact of correlations between exposure routes on long-term exposure is studied further.

- Data availability regarding the exposure via different routes is minimal. This is true for all compounds addressed in the report. Generation of data to perform aggregate exposure assessments will therefore be as important as aggregate model development.
- We recommend that models developed in food and environmental sciences should be made compatible. A first step along this pathway has been taken in May 2007 by initiating cooperation between NORMTOX and MCRA regarding the aggregate exposure to lead. This project may identify other options for modelling aggregate exposure, including pesticides.
- To stimulate aggregate exposure modelling within the Netherlands it is recommended to start a joint activity of RIKILT and the Radboud University Nijmegen towards the Dutch Ministries of Agriculture, Nature Management and Food Quality (LNV), of Health, Welfare and Sports (VWS) and of Housing, Spatial Planning and the Environment (VROM) to stress the importance of aggregate model development and its added value for policy making.
- Cooperation between the EU-projects NoMiracle (all sources except food) and SAFE FOODS (only food) would be a big step forward in aggregate model development within Europe. It is therefore recommended that the coordinators and responsible scientists involved in both EU Projects should discuss future possibilities within Europe with DG Research and DG Sanco.

Overall, we conclude that aggregate exposure is important for several compounds and that aggregate model development following both a person- and population-orientated approach should be advanced both in the Netherlands and Europe following the recommendations mentioned above.

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