
2,4,5-T

(CAS No: 93-76-5)

Health-based Reassessment of Administrative
Occupational Exposure Limits

Committee on Updating of Occupational Exposure Limits,
a committee of the Health Council of the Netherlands

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1 Introduction

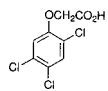
The present document contains the assessment of the health hazard of 2,4,5-T by the Committee on Updating of Occupational Exposure Limits, a committee of the Health Council of the Netherlands. The first draft of this document was prepared by MA Maclaine Pont, M.Sc. (Wageningen University and Research Centre, Wageningen, the Netherlands).

The committee mainly used the toxicological review on 2,4,5-T made in 1995 by the German Commission for the Investigation of Health Hazards of Chemical compounds in the Work Area (DFG98) as a basis for the hazard assessment and to establish a health-based occupational exposure limit. The German report is included in Part 2 of this document.

Data considered to be critical were evaluated by reviewing the original publications. In addition, literature was retrieved from the databases Toxline, Medline, and Chemical Abstracts covering the periods of 1981 until May 2000, 1980 until May 2000, and 1992 until April 2000, respectively, and using the following key words: trichlorophenoxyacetic; acetic acid, (2,4,5-trichlorophenoxy)-; 93-76-5. The final literature search was carried out in May 2000.

In September 2001, the President of the Health Council released a draft of the document for public review. The committee received no comments.

2 Identity

name	:	2,4,5-T
synonyms	:	2,4,5-trichlorophenoxyacetic acid; acetic acid, (2,4,5-trichlorophenoxy)-
molecular formula	:	$C_8H_5Cl_3O_3$
molecular structure	:	
CAS number	:	93-76-5

Data from ACG99, How92.

3 Physical and chemical properties

molecular weight	: 255.48
melting point	: 157°C; 98% technical grade: 150-151°C
boiling point	: decomposes
flash point	: not applicable
vapour pressure	: at 20°C: approx. 0 Pa
solubility in water	: insoluble (at 25°C: 28 mg/100 mL)
odour threshold	: not applicable
log P _{octanol/water}	: at 25°C: 3.31; 3.38; at unknown temperature: 3.13
conversion factors (20°C, 101.3 kPa)	: not applicable

Data from ACG99, Jaf90, Lid99, Mag91.

2,4,5-T is a colourless to tan, odourless, non-combustible solid.

4 Uses

2,4,5-T is a systemic herbicide; it has been used for the control of woody and herbaceous weeds by air or ground spray application. In combination with 2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-T was used exclusively as a defoliant in Vietnam as the so-called preparation 'Agent Orange', which may also have contained more than 30 ppm 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) (ACG99).

According to the database of the Dutch Pesticide Authorisation Board (CTB), 2,4,5-T is at the present not registered for its use as an active ingredient in pesticides in the Netherlands.*

5 Biotransformation and kinetics

See Part 2, Chapter 2.

* At <http://www.ctb-wageningen.nl/geel.html>.

6 Effects and mechanism of action

Human data

The majority of the studies deals with reproduction toxic effects in herbicide sprayers or in army personnel who came into contact with Agent Orange during the Vietnam war. Exposure was never to 2,4,5-T alone but to mixtures containing, e.g., in particular the impurity TCDD, which is far more toxic than 2,4,5-T, or 2,4-D (in the case of 'Agent Orange'). The available data indicate that after agricultural use of 2,4,5-T, there is no marked increase in the incidence of malformations or stillbirths. When 2,4,5-T is contaminated with TCDD, reproduction toxicity cannot be excluded (see Part 2, Chapter 3).

Several epidemiological studies investigate the carcinogenicity of 2,4,5-T. However, since the 2,4,5-T was highly contaminated with TCDD, no conclusions can be made as to the carcinogenic effects of 2,4,5-T in man (see Part 2, Chapter 3).

Animal data

Irritation and sensitisation

2,4,5-T was not irritating for rabbit skin, however, it was strongly irritating in rabbit eyes. Well-performed studies on the sensitisation of 2,4,5-T have not been found (see Part 2, Chapter 4).

Acute toxicity

Exposure to aerosol concentrations of 830 mg/m³, for 1 or 4 hours, only caused a merely transient decline in 'well-being' of male and female rats. Dermal LD₅₀ values were >5000 mg/kg bw (species not mentioned). Following oral administration, LD₅₀ values of about 400 to 800 mg/kg bw have been reported for rats, mice, and guinea pigs, and of 100 mg/kg bw for dogs. Symptoms observed included effects on the nervous system and body weight while lesions of the lungs, liver, kidney, and intestine were seen upon post-mortem examinations (see Part 2, Chapter 4.1).

Repeated-dose toxicity

In 13-week studies, in which dogs were given 2,4,5-T containing unknown amounts of TCDD in the diet, only minor effects (decreased glutamate pyruvate transaminase) were seen in one study at 2.4 and 13.3 mg/kg bw while there were no effects in 2 other studies at 2.4 (highest dose tested) or up to 10 mg/kg bw. In the latter study, all animals died at the next higher dose of 20 mg/kg bw (see Part 2, Chapter 4.2). In a 13-week rat study in which a similar substance was given at similar doses as in a 2-year rat study (see below Koc79), no effects were seen at a dose of 3 mg/kg bw/day while there was an increase in the excretion of coproporphyrin in male animals given 10 mg/kg bw (see Part 2, Chapter 4.2).

Carcinogenicity

Groups of 50 male and 50 female Sprague-Dawley rats received 2,4,5-T via the diet at dosages of 0, 3, 10, or 30 mg/kg bw/day, for 2 years. The control group consisted of 86 males and 86 females. An additional 10 rats of each sex were included for each treatment and control group for the interim kills on days 118 and 119. The purity of the compound was 99%; other phenoxy acid impurities amounted to 1.3% (w/w). TCDD, hexachlorodibenzo-*p*-dioxin, heptachlorodibenzo-*p*-dioxin and octachlorodibenzo-*p*-dioxin were not detected, the limits of detection being 0.33, 0.12, 0.40, and 0.40 µg/kg, respectively. A complete gross post-mortem examination was performed on all rats at the interim kills and at the end of the study. Representative sections of 35 organs and tissues were preserved for histological examination. Sections of tissues from control and high-dose animals of the interim groups and from all treated and control rats dying or killed during the 2-year study or killed at termination were subjected to histological examination. At the highest dose level, there was a decrease in body weight gain in the females ($p < 0.05$). At the interim kill, high-dose male rats had an increased relative kidney weight, an increase in the volume of urine excreted and increased excretion of coproporphyrin and uroporphyrin ($p < 0.05$). High-dose females had an increased excretion of coproporphyrin ($p < 0.05$). These parameters were not affected after 2 years. After 2 years, slight morphological changes in liver, kidneys, and lung were observed ($p < 0.05$ in all cases; more changes in males than in females). The kidney changes involved primarily the presence of mineralised deposits in the renal pelvis (females only). High-dose male rats showed a decreased

incidence of liver enlargement and an increased incidence of focal biliary hyperplasia and periportal inflammation and the females an increased incidence of focal aggregation of reticuloendothelial cells adjacent to degenerate or necrotic hepatocytes and a decreased incidence of multiple foci of hepatocellular change (swollen hepatocytes). The lungs showed some changes that, directly or indirectly, may have been the result of treatment. High-dose males had an increased incidence of focal pulmonary interstitial inflammation, focal accumulations of alveolar macrophages, and cholesterol clefts, while a few females showed focal accumulations of secreted material in the alveoli. At the mid-dose level (10 mg/kg bw/day), only minimal effects were noted, primarily an increased incidence of mineralised deposits in the renal pelvis and, in the males and only during the early phase of the study, an increase in urinary excretion of coproporphyrin. At the low-dose level (3 mg/kg bw/day), there were no treatment-related effects. There was no treatment-related increase in the incidence of any tumour in any of the dosed groups (Koc79). The committee concludes that 2,4,5-T is not carcinogenic for rats when given via the diet at doses up to and including 30 mg/kg bw (the highest dose tested) for 2 years. The NOAEL in this study was 3 mg/kg bw/day based on minor urinary and renal effects observed at the next higher dose of 10 mg/kg bw/day.

Mutagenicity and genotoxicity

Many studies have been performed, but in only a few cases, the TCDD content of the 2,4,5-T has been assayed. No mutagenic or genotoxic effects have been found in *in vitro* tests for gene mutations and DNA damage in bacteria and in a mitotic gene conversion tests in yeast. Positive outcomes were found in the prophage induction assay in *E. coli* (only with metabolic activation; in the high-dose range) and in assays for chromosomal aberrations (only with metabolic activation; slight increase in the high-dose range) and sister chromatid exchanges (without metabolic activation; questionable with metabolic activation) in Chinese hamster ovary cells. In addition, 2,4,5-T inhibited intercellular communication in Syrian hamster fibroblasts (V79 cells). Furthermore, negative results were obtained in a host-mediated assay in mice, in a dominant lethal assay in mice and rats (doses in rats were stated to be too low), in micronucleus and chromosomal aberration tests in somatic cells of mice, and in a chromosome aberration test in germ cells of Chinese hamsters. In *D. melanogaster*, there were both negative and positive results, the positive

results being weak (less than 3 times control values) and observed at high doses only (see Part 2, Chapter 4.6).

Reproduction toxicity

No compound-related gross or histological changes were reported upon post-mortem examination of — amongst others — testes, epididymis, accessory male sex glands, uterus, and ovary of rats orally exposed to 2,4,5-T doses of 3, 10, or 30 mg/kg bw/day (highest dose tested), for 2 years (Koc79). In 2 separately performed 3-generation studies in which rats were given similar oral doses, no consistent, compound-related effects on fertility were observed. In dominant lethal assays, fertility was not affected in female rats, orally given 0.1 or 10 mg/kg bw for 8 weeks, and in male mice, given a single intraperitoneal dose of 100 mg/kg bw (see Part 2, Section 4.5.1).

The effects of 2,4,5-T when given orally during organogenesis have been studied in several species and strains. In mice, the lowest dose found to cause decreased fetal body weights was 15 mg/kg bw while the NOAELs in the various studies ranged from 8 to 40 mg/kg bw. Increases in resorptions and cleft palates were reported at doses of 30 mg/kg bw and higher. Maternal toxicity was observed at doses of 80 mg/kg bw and higher. In rats, NOAELs of approximately 50 mg/kg bw were found while in other studies, administration of 50 mg/kg bw/day induced delayed ossification and increases in resorptions. Maternal toxicity was observed at 75 mg/kg bw and higher. In Rhesus monkeys, no maternal or fetal toxicity was seen at 10 mg/kg bw while a slight tendency towards reduced fetal body weights occurred at 40 mg/kg bw. In case TCDD-containing 2,4,5-T samples were tested, the amounts of TCDD present were insufficiently high to produce effects on reproduction toxicity parameters as was shown in separate experiments with TCDD alone (see Part 2, Section 4.5.3).

In a 3-generation study in which male and females Sprague-Dawley rats (n=10-32/sex/group) were fed doses of 2,4,5-T — containing less than 0.03 ppb TCDD (i.e., the detection limit) — of 0, 3, 10, or 30 mg/kg bw/day, the gestation and 21-day post-natal survival index was affected. Significant decreases in the gestation survival index were seen in the F1 and F2 generation of the high-dose group. Post-natal survival was decreased in the F2 litters of the mid-dose group and the F1, F2, and F3a litters of the high-dose group (all: $p < 0.05$). No statistically significant increase in the incidence of any morphological anomaly was found in any of the generations at any of the dose

levels when compared to controls. No effects were reported in adults upon post-mortem examinations. In weanling rats, relative organ weights changes — among which increased relative liver weights and decreased relative thymus weights in the F2 and/or F3a and F3b generation — were seen (Smi81). Based on consistent effects on neonatal survival at 30 mg/kg bw, the committee concludes that 10 mg/kg bw was a NOAEL in this 3-generation study.

No effects were reported in another, similar, unpublished rat study at similar dose levels indicating a NOAEL of ≥ 30 mg/kg bw (see Part 2, Section 4.5.2).

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for 2,4,5-T in the Netherlands is 10 mg/m³, 8-hour TWA.

Existing occupational exposure limits for 2,4,5-T in some European countries and in the USA are summarised in the annex.

8 Assessment of health hazard

Since the German evaluation in 1995, no new data have been found that would have been relevant for the hazard assessment of 2,4,5-T.

2,4,5-T is readily absorbed both orally and dermally. From studies with spray workers who wore containers with 2,4,5-T herbicides on the back, absorption by skin contact and inhalation was determined to be 0.08-1.85 and about 0.002 mg/kg bw, respectively. 2,4,5-T is eliminated via the kidneys mainly unchanged while small amounts of glycine and taurine conjugates and 2,4,5-trichlorophenol were detected as well.

Many studies on humans have been performed after they had been exposed to 2,4,5-T. However exposure was never to 2,4,5-T alone, but always to mixtures containing, e.g., TCDD or 2,4-D. Therefore, the committee considers these data not suitable to draw conclusions on the toxicity of 2,4,5-T for humans.

In experimental animal studies, 2,4,5-T was not irritating to the skin of rabbits, but strongly irritating when instilled into the eyes of rabbits. The committee considers the toxicity following acute or single inhalation or dermal exposure as low. Exposure to aerosol concentrations of 830 mg/m³, for 1 or 4 hours, only caused a merely transient decline in 'well-being' of male and female rats. Dermal LD₅₀ values were >5000 mg/kg bw.

2,4,5-T was not carcinogenic in adequately performed long-term oral studies in rats and mice.

The results of a few *in vitro* tests suggest that 2,4,5-T may have some weak clastogenic potential. However, based on the outcome of the variety of tests in bacteria, yeast, mammalian cell systems, *Drosophila*, and intact animals, the committee concludes that 2,4,5-T is not mutagenic or genotoxic. Combined with the negative results in carcinogenicity studies, the committee considers 2,4,5-T as non-carcinogenic.

In a 2-year study and two 3-generation studies using rats, daily oral doses up to 30 mg/kg bw (highest dose tested) did not induce compound-related gross or histological changes in male and female reproductive organs or effects on fertility, respectively. In one of the 3-generation studies, neonatal survival was decreased at 30 mg/kg bw/day. When given during organogenesis to mice, rats, and monkeys, decreased fetal body weights, increased resorptions, and cleft palate were seen in mice, increased resorptions and delayed ossification in rats, and (a slight tendency towards) decreased fetal body weight in monkeys at doses that were not maternally toxic. NOAELs for decreased fetal body weight of 8 and 10 mg/kg bw/day were found in mice and monkeys, respectively, although NOAELs up to 40 mg/kg bw/d were reported in mice as well.

From 13-week and 2-year feeding studies in rats, the committee considers the liver and the kidney to be the target organs, 3 mg/kg bw being the NOAEL in both studies. At the next higher dose, 10 mg/kg bw per day, minimal effects were observed in the kidneys: primarily an increased incidence of mineralised deposits in the renal pelvis, and, in the males and only during the early phase of the study, an increase in urinary excretion of coproporphyrin. The committee considers these effects of questionable relevance to humans.

The committee takes the NOAEL of 3 mg/kg bw/day from this 2-year study as a starting point for deriving a health-based recommended occupational exposure limit (HBROEL). To take into account that the rats received 2,4,5-T during 7 days per week, and that occupational exposure is during 5 days per week, a factor of 7/5 is introduced resulting in a NAEL of 4.2 mg/kg bw. For the extrapolation to an HBROEL, a factor of 3.4* for the allometric scaling from rat to man, based on basal metabolic rate, and an overall factor of 9 for inter- and intraspecies variation are applied resulting in a NAEL for humans of 0.14 mg/kg/ bw/day. Assuming a 70-kg worker inhales 10 m³ of air during an 8-hour working day and a retention of 100%, and applying the preferred value approach, a health-based occupational exposure limit of 1 mg/m³ is

* From $(bw_{man})^{0.25}/(bw_{rat})^{0.25} = 70^{0.25}/0.5^{0.25}$, based on a male rat body weight of ca. 500 g after 95 days on test.

recommended for 2,4,5-T*. The committee is of the opinion that this level is sufficiently low to protect against developmental effects.

The committee recommends a health-based occupational exposure level for 2,4,5-T of 1 mg/m³ as inhalable dust, as an 8-hour time-weighted average (TWA).

The committee notes that this HBROEL is only valid for 2,4,5-T in pure form. When TCDD is present in the product, other arguments play a role: TCDD is carcinogenic to humans and classified in group I by IARC (IARC97).

Skin notation

The committee did not find quantitative data on dermal absorption. However, it is stated that workers spraying 2,4,5-T herbicides from containers worn on the back, the average dermal absorption was determined to be 0.08-1.85 mg/kg bw (DFG98). This is in the same order of magnitude as the quantity taken up when exposed to the HBROEL for 8 hours. Therefore, the committee finds a skin notation justified.

References

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* Due to differences in procedures for establishing an HBROEL, e.g., scaling based on caloric demand and application of assessment factors (see paragraph 1.4 of the General introduction), between the committee and the German Commission, a lower OEL is derived by the committee.

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Annex

Occupational exposure limits for 2,4,5-T in various countries.

country -organisation	occupational exposure limit		time-weighted average	type of exposure limit	note ^a	reference ^b
	ppm	mg/m ³				
the Netherlands						
- Ministry of Social Affairs and Employment	-	10	8 h	administrative		SZW02
Germany						
- AGS	-	10 ^c	8 h		S	TRG00
	-	40 ^c	15 min			
- DFG MAK-Kommission	-	10 ^c	8 h		S, ^e	DFG02
	-	20 ^c	15 min ^d			
Great Britain						
- HSE	-	10	8 h	OEL		HSE02
		20	15 min			
Sweden	-	-				Swe00
Denmark	-	5	8 h		S	Arb02
USA						
- ACGIH	-	10	8 h	TLV	A4 ^f	ACG02b
- OSHA	-	10	8 h	PEL		ACG02a
- NIOSH	-	10	10 h	REL		ACG02a
European Union						
- SCOEL	-	-				EC02

^a S = skin notation; which means that skin absorption may contribute considerably to the body burden; sens = substance can cause sensitisation.

^b Reference to the most recent official publication of occupational exposure limits.

^c Inhalable fraction.

^d Maximum number per shift: 4, with a minimum interval between peaks of 1 hour.

^e Classified in pregnancy risk group C, i.e., there is no reason to fear a risk of damage to the embryo or fetus when MAK and BAT values are observed.

^f Classified in carcinogenicity category A4, i.e., not classifiable as a human carcinogen: agents which cause concern that they could be carcinogenic for humans but which cannot be assessed conclusively because of a lack of data. *In vitro* or animal studies do not provide indications of carcinogenicity which are sufficient to classify the agent into one of the other categories.

Part 2

