
2-Chlorotoluene

(CAS No: 95-49-8)

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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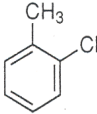
1 Introduction

The present document contains the assessment of the health hazard of 2-chlorotoluene 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 evaluation of the toxicity of 2-chlorotoluene has been based on the reviews by the American Conference of Governmental Industrial Hygienists (ACG99) and the German GDCh-Advisory Committee on Existing Chemicals of Environmental Relevance (BUA) (BUA92, BUA96). Where relevant, the original publications were reviewed and evaluated as will be indicated in the text. In addition, in May 1999, literature was searched in the databases Toxline, Medline, and Chemical Abstracts, starting from 1981, 1966, and 1937, respectively, and using the following key words: 2-chlorotoluene, *o*-chlorotoluene, *o*-tolylchloride, 1-chloro-2-methylbenzene, and 95-49-8. The final literature search was carried out in Toxline and Medline in October 2003.

In October 2003, the President of the Health Council released a draft of the document for public review. No comments were received.

2 Identity

name	:	2-chlorotoluene
synonyms	:	<i>o</i> -chlorotoluene; 1-chloro-2-methylbenzene; 2-chloro-1-methylbenzene; <i>o</i> -tolyl chloride
molecular formula	:	C ₇ H ₇ Cl
structural formula	:	
CAS number	:	95-49-8

3 Physical and chemical properties

molecular weight	:	126.59
melting point	:	-36°C
boiling point	:	159°C
flash point	:	46°C
vapour pressure	:	at 20°C: 0.36 kPa
solubility in water	:	insoluble (at 20°C: 5 mg/100 mL)
log P _{octanol/water}	:	3.4 (experimental); 3.18, 3.50 (estimated)
conversion factors	:	at 20°C, 101.3 kPa: 1 mg/m ³ = 0.19 ppm 1 ppm = 5.27 mg/m ³

Data from BUA92, NLM03, <http://esc.syrres.com>.

2-Chlorotoluene is a colourless liquid with an odour resembling that of chlorobenzene (ACG99). Odour thresholds of 1.7 mg/m³ (0.3 ppm) in air and of 0.98 mg/L in water have been reported (San89, You96).

As a consequence of its low conductivity, the liquid can be electrostatically charged. Under certain conditions, toxic and corrosive vapours can be formed upon heating and combustion (Che99).

4 Uses

2-Chlorotoluene is widely used as a solvent and intermediate in the synthesis of other organic chemicals, dyes, pharmaceuticals, and synthetic rubber compounds (ACG99).

Commercially produced monochlorotoluene consists of 60% *ortho*- and 40% *para*-isomers (ACG99).

5 Biotransformation and kinetics

Within 24 hours after giving male Harlan rats (n=3) single oral (gavage) doses of ¹⁴C-labelled 2-chlorotoluene of 320 mg/kg bw, 81 and 3% of the radioactivity were excreted in urine and faeces, respectively, while only minor amounts of radioactivity (1.1 and 0.5%, respectively) were excreted in the subsequent 24 hours. In expired air, ca. 10% of the radiolabel was excreted in the first 6 hours, followed by an additional 1.5% during the next 18 hours. While only unchanged parent compound was identified in expired air, it was not found in urine or faeces. Metabolites found in the urine included 2-chlorobenzyl alcohol

glucuronide (41% of the radioactivity administered), chloro-methyl-phenylmercapturic acid (22%), and 2-chlorohippuric acid (19%), and minor amounts (1% each) of 2-chlorobenzyl alcohol, 2-chlorobenzoic acid, 2-chlorobenzoic acid glucuronide, and unidentified metabolites (Wol74).

Four days after rats (Sprague-Dawley; n=4/sex) were given single oral doses of 2-chloro[U-*ring*-¹⁴C]toluene of 1 mg/kg bw, 85-92% of the radioactivity administered was excreted in the urine and 5-8% in the faeces, most of it in the first 24 hours after dosing. The major urinary metabolites were a glycine conjugate of 2-chlorobenzoic acid (2-chlorohippuric acid) and a β-glucuronide and mercapturic acid of 2-chlorobenzylalcohol, representing 20-23, 35-42, and 21-28% of the urinary ¹⁴C, respectively. One to 4% of the administered dose was eliminated as volatile ¹⁴C, at least 84% of which was identified as unmetabolised 2-chlorotoluene. 2-Chlorotoluene was rapidly absorbed and metabolised. Two hours after dosing, radioactivity reached a peak level in plasma, 2-chlorobenzyl alcohol mercapturic acid and glucuronide being the 2 major components accounting for 38 and 25% of plasma radioactivity, respectively. Within 4 days after dosing, virtually all of the administered quantity had been eliminated from the rats (<1% remained in the carcass). No significant metabolic differences were found between males and females. Similar qualitative and quantitative distribution of metabolites was found when single oral doses of about 100 mg/kg bw were given to female rats (n=2) (Qui83).

In an unpublished study performed by the same institute, rats (sex and number not specified) were intravenously injected with a single dose of 0.7 mg ¹⁴C-labelled 2-chlorotoluene. The amount of radiolabel excreted in expired air, urine, and faeces amounted to 14-18% (almost all parent compound), 69-81%, and 1-3%, respectively. The urinary metabolites identified were 2-chlorobenzyl alcohol mercapturic acid (22-23%), 2-chlorobenzyl alcohol glucuronide (13-20%), and 2-chlorohippuric acid (7-11%). Unidentified polar metabolites accounted for 11%. Nearly 100% of the dose was eliminated within 4 days (BUA92).

Daily oral (gavage) administration of doses of 2-chlorotoluene (purity: 96.4%; see Wor74) of 20, 80, or 320 mg/kg bw, 7 days/week, for 14 days or 3 months to rats (Harlan; n=5/sex/group) or of 5, 20, or 80 mg/kg bw to dogs (Beagle; n=4/sex/group), 7 hours/day, for 3 months, did not have a significant effect on the rate of hepatic *O*-demethylation of *p*-nitroanisole to *p*-nitrophenol, assuming the increases observed in the male rats of the mid- and high-dose groups at day 14 were due to the unusual low rates on the control animals (Hof74).

6 Effects

Human data

Two separate industry communications stated that their production workers never had skin irritation, dermatitis, or any other form of poisoning from exposure to 2-chlorotoluene (no more data presented) (ACG99).

Animal data

Irritation and sensitisation

All experimental animal data on the potential irritation and sensitisation were from unpublished studies. Since the original reports were mostly not available to the committee, the findings presented below are from the brief information cited in the ACGIH (ACG99) and BUA (BUA92, BUA96) reviews.

A single, 24-hour-occlusive application of 1 mL (1083 mg/kg bw) 2-chlorotoluene to the shaven skin of rats (n=5/sex) caused intense pain for up to 2 hours after the start of the exposure. After the end of the exposure, the skin appeared normal (BUA92). The shaven back skin of 3 female rats were treated with 0.2 mL of 2-chlorotoluene under occlusion on alternate days for 5 applications, while occlusive dressings were removed and skins cleaned on the intervening days. After the second application, hyperkeratinisation occurred. At histological examination, necrosis of the epidermis, superficial dermis with adjacent hyperplasia of the epidermis, and marked fibroblastic reaction of the dermis were observed. In a separate experiment, 0.2 mL was applied to the skin of 3 animals for 6 non-occluded applications. Hyperkeratinisation was seen after the second application, which developed to ulceration in one animal. At histological examination, similar, but less severe skin lesions were seen as in the occluded animals (Bar70). Moderate skin irritation was observed in rabbits in a 24-hour patch test on abraded and intact skin (ACG99). 2-Chlorotoluene was found to be slightly irritating in rabbits in a test performed according to relevant OECD guidelines (BUA96). Topical treatment with 0.5 mL (540 mg) caused intense erythema and deep erosions on the rabbit ear after 24 hours of exposure under occlusive conditions. Not until 6 days after the application, the erythema became slight and the erosions merely superficial. Within 2 hours of exposure, the animals exhibited slight erythema and superficial erosion of the skin during

the entire follow-up period. A 1-hour exposure led to low-grade erythema that lasted up to 2 days (BUA92). Repeated - 5 days/week, for 4 weeks - dermal application of 0.1, 0.3, or 1 mL/kg bw (ca. 100, 300, or 1000 mg/kg, respectively) caused moderate to severe dermal irritation in rabbits, due to defatting of the tissues. The area and severity of the injury were directly proportionate to the volume of the dose (Art74b). In guinea pigs (n=1/dose), moderate to intense skin irritation was found after a 24-hour occlusive application of 1 or 10 mL of undiluted material (1083 or 10,835 mg/kg bw) (ACG99).

Female guinea pigs (n=10/group) were dermally treated with 0.1 mL of emulsions of 10 or 25% of 2-chlorotoluene in 5% acacia solutions, 3 times weekly, for 3 weeks, followed by a challenge after a 10-day exposure-free period. After treatment, sites were maintained under occlusion for 6 hours, and dermal responses were recorded 24 hours post-treatment using the standard Draize scale. Application of the 10 and 25% emulsions caused moderate and severe irritation, respectively (maximum mean irritation ratings of 2.7 and 7.2, respectively; maximum score possible: 8.0), but there were no indications for a sensitising potential (Art74d). The application of undiluted 2-chlorotoluene on 3 consecutive days to the inner surface of the ears of 4 guinea pigs was followed on day 7 after the first administration by the application of a 10% or 1% emulsion to the shaven flanks. While this brought about slight erythema, there was no indication of a sensitising effect (Bar70).

However, in a Magnusson and Kligman maximisation test, performed according to relevant OECD and EEC guidelines, there was no indication of a skin-sensitising potential in male guinea pigs upon topical application of undiluted test substance and intradermal induction of a 5% solution, followed by a challenge with undiluted material (BUA96).

Instillation of one drop of undiluted 2-chlorotoluene into the eye of a rabbit caused delayed moderate conjunctival erythema. After 24 hours, the anterior portion of the cornea was opaque having returned to normal 14 days later (ACG99). Instillation of 0.1 mL of undiluted material into the eyes of albino rabbits produced moderate conjunctival irritation that disappeared by the fifth day. No evidence of corneal damage was seen upon fluorescein staining on day 7 (ACG99). In another study, instillation of 0.1 mL into the conjunctival sac of the eye of a rabbit caused immediate, slight to moderate conjunctival erythema lasting for up to 24 hours (BUA92). Instillation of a similar amount into the eyes of 3 rabbits caused immediate blinking and slight mucopurulent discharge in 2 animals and redness round the rim of the eye of the third animal. All eyes were

normal 48 hours later (Bar70). 2-Chlorotoluene was found to be not irritating in rabbits in a test performed according to relevant OECD guidelines (BUA96).

In 2 separate reports concerning respiratory tract (sensory) irritation, concentrations that reduced the respiratory rate in mice by 50% (RD₅₀) were reported to be about 3000 mg/m³ (570 ppm) (Ala95, Mul84).

Acute toxicity

Data on the acute lethal toxicity of 2-chlorotoluene in experimental animals are summarised in Table 1. Generally, the primary toxic effects observed in these experiments consisted of effects on the nervous system (BUA92).

Table 1 Summary of acute lethal toxicity studies for 2-chlorotoluene in experimental animals.

exposure route	species (sex)	LC ₅₀ /LD ₅₀	reference
inhalation	rat (male)	>20,583 mg/m ³ (1 hour)	BUA92
	rat (male, female)	>63,900 mg/m ³ (1 hour)	Art74a
	mouse (male)	>20,583 mg/m ³ (1 hour)	BUA92
dermal	rat (male, female)	>1083 mg/kg bw	BUA92
	rabbit (male, female)	>2165 mg/kg bw	Art74a
oral	rat	>1600 mg/kg bw	ACG99
	rat (male, female) ^a	1659 mg/kg bw	Art74b
	rat (male)	3227 mg/kg bw	BUA92
	rat (female)	3860 mg/kg bw	BUA92
	rat (male)	3464 mg/kg bw	Art74a
	rat (female)	3031 mg/kg/bw	Art74a
	rat	3900 mg/kg bw	NIO03
	rat	5700 mg/kg bw	Pis81
	mouse	2500 mg/kg bw	NIO03
	mouse (male)	3776 mg/kg bw	Art74a
	mouse (female)	3902 mg/kg bw	Art74a
	mouse	4400 mg/kg bw	Pis81
	guinea pig	3000 mg/kg bw	Pis81

^a 48-72-hours-old animals.

No effects were seen in rats (Harlan; n=10/sex) exposed to 63,900 mg/m³ (12,141 ppm) for 1 hour (Art74a). However, when rats, mice, and guinea pigs were exposed to 22,200 mg/m³ (4218 ppm), breathing difficulties, ataxia, and convulsions were seen in mice after 30 minute of exposure and in rats and guinea pigs 15 minutes later. All animals were comatose within 60 minutes. All rats and mice and 7/10 guinea pigs died during exposure and 1 guinea pig during the

14-day observation period (ACG99, BUA92). When male rats (n=5/group) and mice (n=10/group) were exposed to 9333 or 20,583 mg/m³ (1733, 3910 ppm) for 1 hour, the general condition of the animals was impaired for up to 4-hour post-exposure, remaining normal thereafter through the remainder of the 14-day observation period, at the higher level. No effects were seen at 9333 mg/m³ (BUA92). In rats (n=3/group; sex unknown) exposed to 0, 21,000, 73,000, 900,000 mg/m³ (3990, 13,870, 171,000 ppm) for 6 hours, the signs of toxicity observed in the low-concentration animals included coordination loss (after 1.5 hours), prostration (after 1.75 hours), and tremors (at 2 hours), as well as and marked vasodilation. Exposure to 73,000 mg/m³ induced coordination loss, vasodilation, laboured respiration, and narcosis. All rats in these 2 exposure groups survived the 14-day observation period. In the high-concentration group, one animal died while severe prostration was seen in the other 2 surviving animals (ACG99).

Repeated-dose toxicity

When rats (Alderley Park; n=4/sex/group) were exposed to vapour concentrations of 2-chlorotoluene of 0, 2635, 5270, 210,800 mg/m³ (0, 500, 1000, 4000 ppm), 6 hours/day, for 3 weeks, no effects were seen in the low-concentration group. In mid-concentration group, there were lethargy, diminished response to noise, traces of blood around the nostrils, and low body weight gain. No changes were observed in haematology and urinalysis parameters. There were no abnormal macroscopic or microscopic findings upon post-mortem examinations of the liver, kidneys, spleen, thymus, and ileum, while some isolated foamy macrophages were seen in the alveoli. Exposure to 210,800 mg/m³ was lethal to all animals within 3 minutes (Bar70).

Head-only exposure of rats (Harlan; n=10/sex/group) to aerosol concentrations of 2-chlorotoluene (purity: 96.4%; see Wor74) 0, 33,000, or 62,000 mg/m³, 1 hour/day, 5 days/week, for 3 weeks, resulted mortality in 2 males and 3 females of the high-concentration group (5 dying from 'respiratory embarrassment' while being held in the holding chamber; 1 female from suffocation in the holding chamber) and 1 female of the low-concentration group (cause of death: acute necrotising pneumonia). In high-concentration animals, severe ataxia followed each exposure, about half of the animals becoming prostrate for 15 to 30 minutes, and body weight gain was decreased, especially in females. In low-concentration animals, slight ataxia was observed, but body weight gain was similar to that in controls. Evaluation of haematology and clinical chemistry parameters (haematocrit, haemoglobin, red blood cell

morphology, erythrocyte and total and differential leukocyte counts, prothrombin times, blood glucose, blood urea nitrogen, and serum alanine aminotransferase) only showed statistically significantly increased red blood cell counts in males of the low- and high-concentration groups (by 4.5 and 8%, respectively). Exposure did not affect mean relative organ weights (liver, kidneys, heart, spleen, thyroid, adrenals, prostate, testes, uterus, ovaries). Post-mortem macroscopic and microscopic evaluations did not demonstrate compound-related, toxicologically relevant effects (Art74c).

When rats (CrI:COBS CD[®](SD) BR; n=10/sex/group) were exposed to actual vapour concentrations of 2-chlorotoluene (purity: 96.5%) of 0, 4000, 7700, 11,400, or 15,300 mg/m³ (760-2907 ppm), 6 hours/day, for 14 consecutive days, mortality occurred in 1/10 males and 1/10 females exposed to 15,300 mg/m³ and in 1/10 females exposed to 11,400 mg/m³. Clinical signs observed included dose-related salivation, lachrymation, CNS depression, and ataxia at concentrations of 7700 mg/m³ and higher, and slight irritation and CNS depression at 4000 mg/m³. Other signs included increased incidences of alopecia and brown-stained fur, occurring in males at 11,400 mg/m³ and higher and in females at 7700 mg/m³ and higher. Body weight gain was significantly, dose-relatedly decreased in all male dose groups. Post-mortem observations included increased liver and kidney weights in all male dose groups and the 3 highest female dose groups. The effect was dose-related for liver, and for kidney in females only. There was a dose-related decrease in spleen weight in males at 7700 mg/m³ and higher and in females at 11,400 mg/m³ and higher. Macroscopic and microscopic findings only included increased incidences of alopecia and stained fur in males at 11,400 mg/m³ and higher and in females at 7700 mg/m³ and higher, and centrilobular hepatocyte enlargement in 6/9 females of highest dose group (Ros83).

When rabbits (New Zealand white; n=5/sex/group) were exposed to actual vapour concentrations of 2-chlorotoluene (purity: 96.5%) of 0, 4000, 7800, 11,500, or 15,600 mg/m³ (760-2964 ppm), 6 hours/day, for 23 consecutive days, no mortality occurred. After each exposure, animals exhibited increased respiration. Salivation and lachrymation were seen at 15,600 and 11,500 mg/m³ and slight salivation at 7800 mg/m³. Food consumption was less in all dose groups, being statistically significant at the high level only; there were dose-related decreases in body weight gain in all dose groups and weight loss at 15,600 mg/m³. At post-mortem gross examinations (no microscopy), there were no abnormal treatment-related findings in any of the groups (Ros83).

No systemic toxicity and only moderate to severe irritation at the application site was found in rabbits (New Zealand; n=4/sex/group) following repeated - 5

days/week, for 4 weeks - dermal application of doses of 2-chlorotoluene (purity: 96.4%; see Wor74) of 0.1, 0.3, or 1 mL/kg bw (ca. 100, 300, or 1000 mg/kg, respectively) (Art74b).

Rats (strain: unknown; n=7/sex) were given daily oral (gavage) 2-chlorotoluene doses of 270 mg/kg bw, for 14 days. Two animals/sex were killed 24 hours after the last dose and the remaining 6 days later. Animals exhibited normal appearance and behaviour throughout the study. There were no changes in body and liver weights and haematology findings. Macroscopic and microscopic examination of the animals killed 24 hours after the last dose showed pale enlarged kidneys without accompanying histological changes in one male and one female and 2 animals (sex not indicated) with stomach lesions (inflammation, oedema). The livers of these animals were investigated by electron microscopy and showed dilation of the smooth and rough endoplasmatic reticulum and evidence of slight mitochondrial damage and hypertrophy of the Golgi apparatus. Of the animals killed 6 days post-exposure, 2 males had enlarged kidneys without histological lesions and 3 males minimal signs of stomach inflammation (Bar70).

In white rats, daily intragastric administration of 550 mg/kg bw in oily solution (= 0.1 LD₅₀), for 2 months, caused stimulation of haematopoiesis, CNS depression, and impaired function of liver, kidneys, and immune system. With the same dosing regimen, 55 mg/kg bw led to considerably less marked symptoms (no more data or details presented) (BUA92).

Rats (Harlan; n=20/sex/group) were given daily oral (gavage) doses of 2-chlorotoluene (purity: 96.4%; see Wor74) of 0, 20, 80, or 320 mg/kg bw, 7 days/week, for 3 months. At day 14, 5 rats/sex/group were killed for determination of the effect on the rate of hepatic *O*-demethylation of *p*-nitroanisole while similar determinations were performed in another 5 rats/sex/group at study termination (see Section 'Biotransformation and kinetics'). Prior to necropsy, blood samples were obtained from each rat for haematology and clinical chemistry determinations (haematocrit, haemoglobin, red and white blood cell counts; prothrombin times on the serum of half of the animals, and blood urea nitrogen, alanine aminotransferase, and glucose on the serum of the other half of the animals). Post-mortem, weights of liver, kidneys, heart, spleen, thyroid, adrenals, prostate, testes, uterus, and ovaries were determined and liver, kidneys, heart, spleen, thyroid, adrenals, prostate, testes, uterus, ovaries colon, duodenum, ileum, jejunum, lungs, lymph nodes, mammary, pancreas, parathyroid, salivary glands, skin, stomach, striated muscle, thymus, and urinary bladder histologically examined. Apart from notations on the protocol of 'increased urine output' (which was not based on actual volumetric data), 'nasal

discharge', or 'bloody nasal discharge', there were no treatment-related changes in behaviour, survival rate, haematology, clinical chemistry, or histological organ findings. In the male animals of the mid- and high-dose groups, statistically significantly decreased body weights were observed while mean body weights in the low-dose groups and in the females of the mid- and high-dose groups were similar to that in controls. Changes in relative organ weights were seen in male animals only and included increased adrenal weights in the mid- and high-dose group (by 27 and 24%, respectively) and increased heart weights (by 14%) in the high-dose group (Gib74a). From this 3-month oral study, the committee concludes that 20 mg/kg bw/day is a NOAEL in rats based on the decreased body weights observed in male animals at 80 mg/kg bw/day.

When dogs (Beagle; n=4/sex/group) were given daily oral (by capsule) doses of 0, 5, 20, and 80 mg/kg bw of 2-chlorotoluene (purity: 96.4%; see Wor74), 7 days/week, for 3 months, no treatment-related effects on behaviour, survival, eyes, haematology, clinical chemistry, urinalysis, bone marrow, and organs (weight, macroscopic and microscopic evaluation) were observed in any of the dose groups (Gib74b). From this 3-month oral study, the committee concludes that 80 mg/kg bw/day, the highest level tested is a NOAEL in dogs.

Mutagenicity and genotoxicity

In vitro, 2-chlorotoluene did not induce mutations or was negative:

- a mutation assay, using *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538, with and without induced rat liver metabolic activation (Lit82d)
- a forward mutation assay in mouse lymphoma L5178Y cells, with and without rat liver metabolic activation (Lit82c)
- a chromosome aberration assay in Chinese hamster ovary cells, with and without rat liver metabolic activation (Lit82a)
- the umu test, to detect the induction of error-prone DNA repair, using *S. typhimurium* TA1535/pSK1002 with and without rat liver metabolic activation (Ono92)

in vivo in:

- a chromosome aberration assay in bone marrow of rats, after 1 or 5 daily oral doses (Lit82b)

and further in:

- an *in vitro* cell transformation assay using Balb/3T3 cells, with and without rat liver metabolic activation (Lit83)

Reproduction toxicity

Pregnant rats (CrI:COBS CD[®](SD) BR; n=25/group) were exposed to 2-chlorotoluene concentrations of 0, 1000, 3000, or 9000 mg/m³ (190, 570, 1710 ppm), 6 hours/day, on gestational days 6 to 19. During exposure to 9000 and 3000 mg/m³, the rats showed slight to moderate and slight ataxia, respectively. At 9000 mg/m³, food consumption was significantly reduced (p<0.05), while mean water consumption was significantly increased at 9000 and 3000 mg/m³. Maternal body weight gains were markedly and slightly reduced at 9000 and 3000 mg/m³, respectively. At 9000 mg/m³, significantly reduced litter and fetal weights (p<0.01 and p<0.001, respectively) and increased incidences of malformations, skeletal anomalies, and skeletal variants were seen. At 1000 and 3000 mg/m³, the offspring did not show any treatment-related effects (Edw83a).

Pregnant New Zealand white rabbits (n=16/group) were exposed to 2-chlorotoluene concentrations of 0, 1500, 4000, and 10,000 mg/m³ (285, 760, 1900 ppm), 6 hours/day, on gestational days 6 to 28. At 10,000 mg/m³, lachrymation, salivation, and ptosis were observed during initial exposures. At 10,000 and 4000 mg/m³, there was a significant dose-related reduction in food consumption during the treatment period, which resulted in retardation of mean maternal body weight gain between the onset of treatment and day 9 of gestation. The treatment had no significant effect on litter size, pre- and post-implantation loss, litter or fetal weight, or incidence of skeletal anomalies and variants (Edw83b).

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for 2-chlorotoluene in the Netherlands is 50 ppm (250 mg/m³), 8-hour TWA, with a skin notation.

Existing occupational exposure limits for 2-chlorotoluene in some European countries and in the USA are summarised in the annex.

8 Assessment of health hazard

The committee did not find human data on the toxicokinetics or on the effects following exposure to 2-chlorotoluene.

The committee did not find experimental animal data on the toxicokinetics following inhalation of 2-chlorotoluene. When given intravenously or orally (gavage) to rats, 2-chlorotoluene was rapidly absorbed and metabolised, and almost completely excreted within 24 hours. 2-Chlorotoluene was oxidised at the methyl group to chlorobenzyl alcohol and chlorobenzoic acid, and excreted mainly in the urine (ca. 70-90%) as the glucuronide or mercapturic acid of the alcohol or as chlorohippuric acid, and in small amounts in expired air (ca. 5-15%; basically parent compound) and faeces (ca. 2-7%).

Data on skin and eye irritation are conflicting. On one hand, they indicate that 2-chlorotoluene is corrosive to the skin and irritating to the eyes while on the other hand, unpublished studies (not available to the committee) performed according to OECD guidelines should lead to the conclusion that the compound is slightly irritating to the skin and not irritating to the eyes. There were no indications for a skin-sensitising potential.

Acute inhalation, dermal, and oral lethal toxicity data included 1-hour LC₅₀ values in rats and mice of higher than ca. 21,000 mg/m³, dermal LD₅₀ values of higher than ca. 1100 and 2200 mg/kg bw in rats and rabbits, respectively, and oral LD₅₀ values of 2500 mg/kg bw and above in mice, rats, and guinea pigs. The primary effects observed in the inhalation studies consisted of symptoms such as laboured breathing, loss of coordination, prostration, and narcosis.

The committee found only limited information from repeated inhalation studies, in which animals were either exposed intermittently (5 days/week) for 3 weeks (rats) or for 14 or 23 consecutive days (rats and rabbits, respectively). Intermittent exposure - 6 hours/day, 5 days week, for 3 weeks - of rats to vapour concentrations of 2635 mg/m³ (500 ppm) did not induce any effects while lethargy, diminished response to noise, blood around the nostrils, and decreased body weight were seen at the next higher concentration of 5270 mg/m³ (1000 ppm). Consecutive exposure - 6 hours/day, for 14 (rats) or 23 (rabbits) days - to vapour concentrations of 4000 mg/m³ (760 ppm), the lowest level tested, caused slight irritation, CNS depression, and increased liver weights (males only) in rats and decreased body weight gain in rabbits.

In 3-month oral studies in rats and dogs, which included a limited number of haematology and clinical chemistry findings and adequate post-mortem examinations (Gib74a, Gib74b), daily doses of 80 mg/kg bw caused non-specific

effects like depressed growth and increased relative adrenal weights in male rats only while no effects were observed at 20 mg/kg bw or in female rats up to 320 mg/kg bw, the highest dose tested. In dogs, no effects were seen at doses up to 80 mg/kg bw, the highest dose tested. The committee did not find data from long-term repeated-dose toxicity studies, including carcinogenicity, on 2-chlorotoluene.

In *in vitro* assays, 2-chlorotoluene did not induce mutations or DNA damage in bacteria or mutations or chromosome aberrations in mammalian cell systems. *In vivo*, the compound did not induce an increase in the incidence of chromosome aberrations in bone marrow from rats following single or repeated oral administration.

No developmental toxicity was observed in rats after inhalation exposure to 3000 mg/m³ (570 ppm), 6 hours/day, on gestational days 6 to 19, a concentration that induced slight ataxia and slightly reduced maternal body weight gains. At the next higher concentration of 9000 mg/m³ (1710 ppm), there was developmental toxicity (reduced litter and fetal weights, increased incidences of malformations, skeletal anomalies, and skeletal variants) accompanied by marked maternal toxicity (slight to moderate ataxia; markedly reduced body weight gain). Tested similarly in rabbits, no developmental toxicity was seen at concentrations up to 10,000 mg/m³ (1900 ppm), the highest level tested. Maternal toxicity observed included retarded body weight gain in the first 3 exposure days at 4000 and 10,000 mg/m³ (760, 1900 ppm) and lachrymation, salivation, and ptosis during initial exposures to 10,000 mg/m³.

The committee is of the opinion that, because of limitations in study design (short duration, continuous exposure), the quality of the inhalation studies is insufficient to be used as a basis for deriving a health-based recommended occupational exposure limit (HBROEL). Therefore, the committee takes the NOAEL of 20 mg/kg bw of the better designed 3-month oral rat study (Gib74a) as a starting point. Since workers are exposed for 5 days a week, this NOAEL from a continuous study (i.e., 7 days a week) is adjusted by multiplying with a factor of 7/5 resulting in a no-adverse-effect level (NAEL) of 28 mg/kg bw. For the extrapolation to a HBROEL, a factor of 4 for allometric scaling from rats to humans, based on caloric demand, and an overall factor of 18, covering inter- and intraspecies variation and the differences between experimental conditions and the exposure pattern of the worker, are applied, resulting in a NAEL for humans of 0.4 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 HBROEL of 2 mg/m³ is recommended for 2-chlorotoluene.

The committee recommends a health-based occupational exposure limit for 2-chlorotoluene of 2 mg/m³ (0.4 ppm), as an 8-hour time-weighted average (TWA).

The committee did not find kinetic data to evaluate absorption through the skin. However, in view of the low acute lethal toxicity following dermal and inhalation exposure, an exclusion criterion in the decision scheme to decide on a skin notation (ECE98), the committee does not recommend a skin notation.

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Annex

Occupational exposure limits for 2-chlorotoluene 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	50	250	8 h	administrative	S	SZW03
Germany - AGS	-	-				TRG00
- DFG MAK-Kommission	-	-				DFG03
Great Britain - HSE	50	264	8 h	OES		HSE02
Sweden	-	-				Swe00
Denmark	50	285	8 h		S	Arb02
USA - ACGIH	50	-	8 h	TLV		ACG03b
- OSHA	-	-				
- NIOSH	50	250	10 h	REL		ACG03a
	75	375	15 min	STEL		ACG03a
European Union - SCOEL	-	-				EC04

^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.