
2-Chloroacetophenone

(CAS No: 532-27-4)

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-chloroacetophenone by the Committee on Updating of Occupational Exposure Limits, a committee of the Health Council of the Netherlands. The first draft of this document is prepared by N. Smits, M.Sc. (Wageningen University and Research Centre, Wageningen, the Netherlands)*.

The evaluation of the toxicity of 2-chloroacetophenone has been based on the review by the American Conference of Governmental Industrial Hygienists (ACG99). Where relevant, the original publications were reviewed and evaluated as will be indicated in the text. In addition, in December 1999, literature was searched in the databases Medline, Toxline, and Chemical Abstracts, covering the periods 1966, 1985, and 1950, respectively, until December 1999, and using the following key words: chloroacetophenone, chloroacetophenon, and 532-27-4. The Hazardous Substances Data Bank (HSDB) was consulted as well (NLM03). The final literature search was carried out in Toxline and Medline in September 2003.

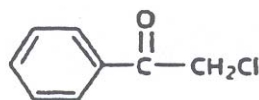
In October 2003, the President of the Health Council released a draft of the document for public review. No comments were received.

2 Identity

name : 2-chloroacetophenone
synonyms : chloroacetophenone; α -chloroacetophenone; ω -chloroacetophenone; 1-chloroacetophenone; chloromethyl phenyl ketone; 2-chloro-1-phenylethanone; phenacyl chloride; phenyl chloromethyl ketone

molecular formula : C_8H_7ClO

structural formula :



CAS number : 532-27-4

Data from ACG99, NLM03.

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3 Physical and chemical properties

molecular weight	:	154.6
boiling point	:	247°C
melting point	:	58-59°C
flash point	:	117.8°C (closed cup; solutions only)
vapour pressure	:	at 20°C: 0.7 Pa
solubility in water	:	insoluble (at 20°C: 0.07 g/100 mL)
log P _{octanol/water}	:	1.93 (estimated)
conversion factors	:	not applicable

Data from ACG99, OIa01, <http://esc.syrres.com>.

2-Chloroacetophenone is a colourless to grey crystalline solid with a pungent odour (ACG99). An air odour threshold (v/v) of ca. 0.2 mg/m³ has been reported (Amo83). When heated, vapours may form explosive mixtures with air (NLM03).

4 Uses

Because of its strong lachrymating capacity, chloroacetophenone is used in tear gas formulations for riot-control and personal-protection devices, under the name of MACE, Chemical Mace[®], or CN (ACG99, NLM03).

5 Biotransformation and kinetics

The committee did not find data on the biotransformation and kinetics of 2-chloroacetophenone.

2-Chloroacetophenone is an alkylating agent that reacts directly with nucleophilic compounds in a bimolecular fashion, i.e., of the S_N2 type. Some toxic effects of 2-chloroacetophenone, particularly following parenteral administration, are probably due to alkylation of SH-containing enzymes (Bal77).

6 Effects and mechanism of action

Human data

2-Chloroacetophenone is potently and severely irritating to the eyes, respiratory tract, and skin (especially if moist). Signs of eye and respiratory tract irritation included burning or stinging sensations in the throat, eyes, and nose, salivation, blepharospasm, lachrymation, coughing, sneezing, rhinorrhoea, constricting sensations in the chest, and breathing difficulties, and also occasionally nausea, vomiting, photophobia, and headache. These harassing effects rapidly developed at concentrations of about 10 mg/m³, but usually disappeared within 20 minutes of the end of exposure, although conjunctivitis persisted for up to 24 hours. At concentrations less than 10 mg/m³, there was usually an inverse relationship between concentration and tolerance time. Higher concentrations might have caused more severe permanent eye injury such as oedema, erosion, ulceration, chemosis, and focal haemorrhages, although this damage might have been due to close-range blasts or other foreign particles rather than CN. High inhalation doses resulting from use in confined spaces resulted in injuries requiring medical attention and death, post-mortem examinations showing oedema and congestion of the lungs, alveolar haemorrhage, necrosis of the mucosal lining of the lungs, and bronchopneumonia. Skin effects reported included primary and allergic contact dermatitis, erythema, oedema, vesication, purpura, and necrosis (Bal77, Hu89, Ola01, Sid97).

Estimates of the human LC_{t50} (i.e., the concentration x time, lethal to 50% of an exposed population) range between 8500 to 22,500 mg·min/m³; estimates of the minimal irritant concentration and the IC_{t50} (i.e., the concentration x time, incapacitating/irritating to 50% of an exposed population) were 0.3-1 and 20-50 mg·min/m³, respectively (Ola01).

Holland and White compared cutaneous irritant reactions produced by 2-chloroacetophenone and (2-chlorobenzylidene)malononitrile (CS), another riot control agent, applied dry or moistened on 4 cm diameter skin for 1 hour. Amounts as little as 0.5 mg of moistened 2-chloroacetophenone produced erythema and vesication in more than 50% of the subjects, compared with faint erythema with quantities in excess of 10.0 mg of CS (Hol72).

There are several case reports on dermal irritation and, confirmed by patch testing, allergic contact dermatitis following to accidental or deliberate exposure of law enforcement personnel or civilians to 2-chloroacetophenone (see e.g.,

Bra95, Cal79, Fra76, Goh87, Kan94, Lee89, Mau86, Pen69, Pen71, Tre99). In one of these case reports, no reactions were observed in 30 'normal' controls tested to a concentration of 0.009% of 2-chloroacetophenone under occlusion for 48 hours. However, several volunteers experienced primary irritant dermatitis from high 2-chloroacetophenone concentrations in range-finding studies to obtain a proper concentration for patch testing. Generally, these reactions resolved within 1 week, leaving an area of hyperpigmentation, but vesicular dermatitis developed at the primary irritant site 14-21 days after the initial exposure in 2 of these volunteers who appeared to have allergic contact sensitivity to 2-chloroacetophenone by additional appropriate patch testing. To evaluate this sensitising potential, 8 volunteers with negative patch-test results to dilute solutions were treated under occlusion with a 0.9% solution of 2-chloroacetophenone in acetone, 14 or 21 days later followed by a challenge application with 0.09%. All subjects developed primary irritant reactions and 5/8 allergic contact sensitivity, showing erythema, oedema, and vesiculation at the patch-test site (Pen69, Pen71). In another, brief communication, Maibach and Marzulli reported a brief sensitising reaction in 5/9 male volunteers in a modified Draize test after uncovered application of 5 drops of a 1% solution of 2-chloroacetophenone in acetone. Most of those subjects sensitised to the 1% concentration had skin reactions when treated with a 0.1% concentration, but not with 0.01%. Most subjects cross-reacted to CS, although at a significantly decreased intensity (Mai71).

Four human volunteers were exposed to concentrations of 2-chloroacetophenone up to 350 mg/m³ until they could no longer tolerate the effects or until a maximum of 4 minute exposure was attained. 2-Chloroacetophenone was primarily a lachrymator. The subjects mainly complained of tingling of the nose and rhinorrhoea, burning of the throat, eyes, and skin around the eyes, lachrymation, and some degree of blurred vision. Less frequent, but more severe symptoms included burning in the chest with difficulties in breathing and slight gagging with nausea. At post-exposure examinations, the only constant sign was a mild to moderate conjunctivitis. There was not any chest congestion or sign of obstruction at any time, and all signs had usually disappeared within 10 minutes. Concentrations as low as 20-30 mg/m³ produced irritation within 2-3 minutes. The EC_{t50} (i.e., the concentration that produces a 50% response - acute irritation) was 213 mg x min/m³ (mg·min/m³) for 1 minute, 119 mg·min/m³ for 2 minutes, and 93 mg·min/m³ for 3 minutes (Pun62b).

When 2-chloroacetophenone was released into 44 prisoner cells (crude estimation of 0.50 to 1.75 g), 28 prisoners required treatment from a physician.

Eight inmates, all complaining of malaise and lethargy, were admitted to the hospital because of laryngotracheobronchitis (in 3) and of first and second degree chemical burns (in 1), chemical facial burns (in 1), apparent allergic reaction including severe systemic illness (in 1), uncontrollable emesis (in 1), and syncope (in 1). The 20 prisoners receiving outpatient physician care had primarily ocular (conjunctivitis, with marked conjunctival oedema, in 10) and dermal (first and second degree chemical burns, mainly on the lower extremities, in 10; papulovesicular rashes in 6) injuries (Tho82). Twelve patients sprayed into the faces and eyes with 2-chloroacetophenone (i.e., Mace) from a distance of 15-30 cm had skin burns and corneal and conjunctival epithelial injuries (necrosis). In 9 patients, with mild exposure, these areas of fluorescein staining disappeared after 72 hours. However, in 3 cases of intense exposure, widespread confluent punctate corneal staining persisted for 14-21 days, and in one of these cases, a peripheral superficial corneal stromal opacity persisted for 5 months. In 2 cases of intense exposure, the corneal sensitivity, which is decreased during the period of staining, remained decreased and corneal epithelial breakdown with scattered punctate staining recurred 3 and 4 months, respectively, after exposure (Ros69).

Animal data

Irritation and sensitisation

Application of 12.5% solution of 2-chloroacetophenone in acetone or corn oil to the clipped dorsal skin of female rabbits and guinea pigs and male rats for 6 hours caused, depending on the species, slight to moderate erythema and slight to marked oedema at the end of the contact period. The effects gradually subsided and disappeared completely between 7 and 14 days post-exposure. At days 4-7, mild to marked desquamation was observed in rats and guinea pigs. Between day 1 and 7, rabbits developed variable sized ecchymoses and scattered necrotic areas, followed by scar tissue formation. In all species, lesions extended beyond the original area of application (Bal78). Following application of 0.5 mL of solutions of 2-chloroacetophenone in trioctyl phosphate to the intact clipped back skin of rabbits for 30 minutes, primary irritation scores (representing mean values from 2 rabbits treated at each of 6 timed intervals between 1 and 30 minutes after exposure) of 4.0 (treated skin not washed) for a 1% solution and of 5.5 (unwashed), 5.2 (skin washed with water), or 2.9 (washed with water and soap) for 4% solutions were calculated. Scores of 5.0 or more were stated to be required to meet the definition for a skin irritant (Gas72).

Rothberg studied the skin-sensitising potential of 2-chloroacetophenone in guinea pigs. Solutions (in acetone) of 0.1 and 1% were injected intradermally or applied topically, respectively, (in)to guinea pigs (n=8/group), 3 times a week, for 4 weeks. After a 2-week rest period, all animals were both intradermally and topically challenged with a 0.1% solution. The challenge doses caused erythema in 13/16 animals. No evidence of skin damage was seen in the vehicle-treated controls (Rot70). Chung and Giles obtained similar results. Topical (0.2 mL of 1% or 0.5% solutions in acetone) or intradermal (0.5 mL containing 10-25 g 2-chloroacetophenone) administration and topical (0.1 mL of 0.1 to 1% solutions in acetone) or intradermal (0.1 mL of a solution in saline containing 1-10 µg/mL) challenge caused contact sensitisation or delayed hypersensitivity. Skin reactions of sensitised guinea pigs to high doses of 2-chloroacetophenone included erythema, oedema, induration, necrosis, and eschar formation (Chu72).

Instillation of doses of 2-chloroacetophenone of about 0.5 and 1 mg into the eyes of rabbits caused lachrymation and severe conjunctivitis, which gradually disappeared within 2 weeks (Pun62a). Direct instillation of liquid Mace, obtained by discharging an aerosol weapon, into the eyes of anaesthetised rabbits and monkeys produced lasting opacities and melanosis. Similar effects were observed when Mace was sprayed into the eyes of monkeys from a distance of 4 cm for 2 seconds. Less marked, transient effects were observed following instillation in conscious animals, with protective reflexes, or when sprayed from a distance of ca. 2 meters (Mac69). The corneal injury that 2-chloroacetophenone may produce was studied by applying filter paper squares (area: 9 mm²) containing amounts of 2-chloroacetophenone of 10 to 400 µg to the cornea of rabbits. Higher doses caused more severe lesions initially. The more severe lesions tended to remain unchanged while the lesser ones improved. At day 56, the end of the experiment, the percentages of eyes with permanent corneal damage amounted to 0, 40, 90, and 100% at doses of 10, 25, 50, and 100 µg or more, respectively (Mac70). Instillation of 1-4% solutions of 2-chloroacetophenone in 1,1,1-trichloroethane into the eyes of rabbits resulted in transient conjunctival redness while solutions of 10 or 20% caused permanent corneal damage. When testing commercial formulations, permanent damage was observed for a sample containing 4.3% but not for samples containing up to 2% 2-chloroacetophenone (Gas72). Ballantyne et al. investigated the effects of 2-chloroacetophenone in solutions (1-10% in polyethylene glycol 300 - PEG 300 - and 5% in different solutions), as a solid (0.1-5 mg), and as aerosols (15 min exposure to 719 mg/m³) on the eye of rabbits. The most notable feature following a 15-minute exposure to a mean aerosol concentration of 719 mg/m³ was a mild blepharitis that lasted for 5 days. Other effects, just detectable, were transient

lachrymation (lasting for 4 hours) and conjunctival congestion (lasting for 1 day). Cornea and iris were not affected. In 1-10% PEG 300 solutions, 2-chloroacetophenone produced inflammatory effects on the eyelids, conjunctivae, and nictitating membrane, severity and duration being concentration related. Marked and persistent corneal injury was observed at concentrations of 5 and 10%, while 2% was the lowest concentration that induced transient just detectable keratitis in a small proportion of the treated rabbits. Comparative testing using 5% solutions clearly showed the solvent influence. Generally, 2-chloroacetophenone produced more marked and longer lasting eye effects when tested in PEG 300 or corn oil than in 1,1,1-trichloroethane or tri(2-ethylhexyl) phosphate. Solid test compound was generally more damaging to the eyes inducing lesions at lower amounts and more severe than similar amounts in solution. The no-effect level for keratitis of solid 2-chloroacetophenone was estimated between 0.1 and 0.25 mg and for solution 1% (Bal75).

With respect to the respiratory tract, the sensory irritation in the upper part was studied by determining the concentration associated with a 50% decrease in the respiratory rate (RD₅₀). Using male Swiss-Webster mice, an RD₅₀ of 0.96 ppm (ca. 6 mg/m³) was obtained (Kan79).

Acute toxicity

Results of acute lethal toxicity tests with 2-chloroacetophenone in are summarised in Table 1.

Table 1 Summary of acute lethal toxicity studies in experimental animals.

exposure route	species	LC ₅₀ , LCt ₅₀ ^a , or LD ₅₀	reference
inhalation	mouse	59 mg/m ³ ^b	NIO03
	rat	23000 mg·min/m ³ ^c	Ola01
	rabbit	15800 mg·min/m ³ ^c	Ola01
	rat	3700-18800 mg·min/m ³ ^d	Ola01
	mouse	18200-73500 mg·min/m ³ ^d	Ola01
	rabbit	5840-11480 mg·min/m ³ ^d	Ola01
	guinea pig	3500-13140 mg·min/m ³ ^d	Ola01
	dog	7033 mg·min/m ³ ^e	Ola01
	dermal	guinea pig	>1000 mg/kg bw
oral	rat (Osborne-Mendel; male, female)	52-258 mg/kg bw ^f	Gas72
	rat (Porton-Wistar; male)	127 mg/kg bw	Bal78
	mouse	139 mg/kg bw	NIO03
	rabbit (New Zealand; female)	118 mg/kg bw	Bal78
	guinea pig (Dunkin Hartley; female)	158 mg/kg bw	Bal78

intravenous	rat (Porton-Wistar; female)	41 mg/kg bw	Bal78
	mouse (Porton albino; male)	81 mg/kg bw	Bal78
	rabbit (New Zealand; male)	31 mg/kg bw	Bal78
	rabbit (New Zealand; female)	30 mg/kg bw	Bal78
	rabbit	20 mg/kg bw	Pun62a
intraperitoneal	rat (Porton-Wistar; male)	36 mg/kg bw	Bal78
	mouse	60 mg/kg bw	NIO03
	guinea pig (Dunkin Hartley; female)	17 mg/kg bw	Bal78

- ^a Inhalation exposure dose (function of concentration and exposure duration) causing mortality in 50% of the animals.
^b Exposure duration unknown; not known whether aerosol or smoke was tested.
^c Pyrotechnically generated.
^d Aerosol; range of values from several literature sources.
^e Aerosol.
^f Depending on vehicle.

Generally, the cause of death following inhalation was from the injurious action of 2-chloroacetophenone on the pulmonary system. Post-mortem examination of the animals that died from exposure to aerosols showed pulmonary congestion, oedema, emphysema, tracheitis, bronchitis, and bronchopneumonia in dogs and pulmonary congestion, oedema, and bronchopneumonia in rats, mice, and guinea pigs. Effects observed during exposure consisted of lachrymation, conjunctivitis, copious nasal secretions, salivation, hyperactivity, dyspnoea, and lethargy. Post-exposure, the most salient finding was dyspnoea while ocular (conjunctivitis) and dermal (erythema) effects, lasting for 3 to 7 days, were noted as well (Ola01).

Following inhalation to sublethal aerosol concentrations of 2-chloroacetophenone aerosols for 60 minutes - 62.6 mg/m³ (0.1 LC₅₀) -, there was a significant increase in compliance in lung function in rats. Total lung phospholipids and sphingomyelin contents decreased significantly following exposure to 2-chloroacetophenone. Histological observations indicated cellular degeneration in the epithelium of the bronchioles and alveolar septal-wall thickening due to the presence of an increased number of mononuclear cells (Kum95).

Short-term toxicity

In 14-day inhalation studies, preceding 13-week and 2-year studies, F344/N rats and B6C3F₁ mice (n=5/sex/group/species) were exposed to vaporised

2-chloroacetophenone* at concentrations of 0, 4.8, 10, 19, 43, or 64 mg/m³** (0, 0.8, 1.6, 3.0, 6.9, 10.2 ppm), 6 hours/day, 5 days/week, for 2 weeks. All rats exposed to 19 mg/m³ or higher and 1/5 male rats exposed to 10 mg/m³ died before study termination. Rats exposed to 10 mg/m³ lost weight while the final mean body weights of male or female rats exposed to 4.8 mg/m³ were 23% and 15%, respectively, lower than those of controls. During exposure, rats exhibited excessive lachrymation and dyspnoea. Erythema was seen in all rats at concentrations of 10 mg/m³ and higher, and partial closure of the eyelids at 19 mg/m³ and higher. Bleeding of the nose was present in 2 exposed males and 7 exposed females (concentration group not indicated). Data from post-mortem examinations in rats were not presented. In mice, all animals exposed to 10 mg/m³ or higher died before the end of the study. Excessive lachrymation was seen during exposure. Final mean body weights of the animals exposed to 4.8 mg/m³ were similar to those of controls. In 7 exposed males and 2 exposed females that died, reddened lungs were observed. No compound-related lesions were seen in mice exposed to 4.8 mg/m³ (no more data presented) (Mel90).

In the subsequent 13-week studies, rats and mice (same strains; n=10/sex/group/species) were exposed to concentrations of 0, 0.25, 0.5, 1, 2, and 4 mg/m³ (0, 0.04, 0.08, 0.16, 0.32, 0.64 ppm) (6 hours/day, 5 days/week). In rats, no mortality was observed. During exposure, compound-related clinical signs observed included eye irritation at levels of 0.5 mg/m³ and higher. The final mean body weights were affected only in male and female rats exposed to 4 mg/m³ and were 9% lower than those of controls. Apart from slightly increased relative liver weights in female animals exposed to 4 mg/m³, no effects were seen at post-mortem evaluations. In mice, one female died in both the 0.5- and 4-mg/m³ concentration group. During exposure, there was eye irritation in animals exposed to 0.5 mg/m³ and higher. Final mean body weights were - not dose-relatedly - decreased in all exposure groups (by 7-12% and 12-15% in males and females) when compared to controls. No compound-related lesions were observed at post-mortem evaluations (Mel90). Based on eye irritation observed during exposure to the next higher concentration of 0.5 mg/m³, the committee concludes that 0.25 mg/m³ is a NOAEL in rats and mice.

* The formulation used to generate 2-chloroacetophenone vapour was 85% pure, with impurities of insoluble material identified as primarily magnesium oxide with traces of silicon dioxide and iron in methylene chloride (11.2%), water (2.2%), and unidentified substances (approximately 1.7%). The 2-chloroacetophenone was volatilised leaving behind the magnesium oxide.

** The chamber atmospheres in the 14-day, 13-week, and 2-year studies were not evaluated for the presence of aerosolised test substance. Because the saturation concentration at 20°C is about 50 mg/m³, the presence of aerosolised material was thought to be unlikely.

2-Chloroacetophenone has been found to react irreversibly with free sulphhydryl groups of proteins and enzymes. This reaction was observed to be the main cause of denaturation associated with sensory nerve activity (Chu72).

Long-term toxicity and carcinogenicity

In the 2-year toxicology and carcinogenicity studies, F344/N rats and B6C3F₁ mice (n=60/sex/group/species) were exposed to 0, 1, and 2 mg/m³ (0, 0.16, 0.32 ppm) (rats) or to 0, 2, and 4 mg/m³ (0, 0.32, 0.64 ppm) (mice), 6 hours/day, 5 days/week. During month 15, up to 10 animals/group were sacrificed for blood analysis and organ weight (brain, liver, kidney) determination and for complete histological examinations (in controls and high-concentration group only). In rats, no mortality, compound-related clinical signs, and body weight changes were observed. In the interim sacrificed animals, effects observed were limited to increased incidences of minimal-to-mild squamous metaplasia and hyperplasia of the respiratory epithelium in rats exposed to 2 mg/m³. In the animals killed at the end of the study, there was no compound-related increase in the incidence of any neoplastic lesion in any of the male exposure groups. In female animals, incidences of (benign) fibroadenomas - but not of (malignant) adenocarcinomas or carcinomas - of the mammary gland were increased with positive trends, being statistically significant in the 2-mg/m³ group (1 mg/m³: 19/50; 2 mg/m³: 23/50; controls: 12/50). Non-neoplastic effects were limited to those of the nose. In the male animals of the high-concentration, there was a statistically significant increase in the incidence of minimal-to-mild suppurative inflammation of the nasal mucosa. Further, hyperplasia and squamous metaplasia of the nasal respiratory epithelium were observed at dose-dependently increased incidences and severity in exposed male and female rats (see Table2).

The authors of the study suggested that these irritant effects may have been exacerbated by viral infection, since serologic determinations for sentinel or control animals were positive for antibodies to rat coronavirus or sialodacryoadenitis virus at months 6, 12, 18, and 24 of the studies.

Table 2 Incidences and severity of nasal lesions in rats exposed to 2-chloroacetophenone, 6 hours/day, 5 days/week, for 2 years (Mel90).

	males			females		
	0 mg/m ³ (46) ^a	1 mg/m ³ (50)	2 mg/m ³ (49)	0 mg/m ³ (48)	1 mg/m ³ (50)	2 mg/m ³ (49)
nasal passage						
suppurative inflammation	26	36	46**	29	27	33
nasal respiratory epithelium						
hyperplasia	12 (1.5) ^b	17 (1.3)	44** (1.6)	20 (1.2)	31* (1.5)	38** (2.2)
squamous metaplasia	2 (1.0)	11* (1.3)	27** (1.8)	1 (1.0)	7* (1.6)	26** (1.7)

^a Number of animals examined.

^b Mean severity grade: 1=minimal, 2=mild, 3=moderate, 4=marked.

* p<0.05.

** p<0.01.

In mice, there were lower survival rates in female animals (25/50, 32/50 vs. 40/50 in controls), being statistically significant when compared to controls in the low-concentration group after week 98, and decreased mean body weights (by 5-12%) in the male animals of the high-concentration group. Clinical signs reported included rapid, shallow breathing of mice of the high-concentration group during the first 6 month of exposure and of the low-concentration group from month 3 through 6. No exposure-related effects were seen in the animals killed at month 15. In the animals exposed for 2 years, there were no exposure-related, statistically significant increases in the incidences of neoplastic lesions. Non-neoplastic lesions were limited to those of the nasal passage and included respiratory epithelial squamous metaplasia in 4/49 female and 2/48 male mice of the high-concentration group, which was not seen in any animal of the low-concentration or control group (Mel90). From this study, the committee considers 2-chloroacetophenone not to be a carcinogenic compound following exposure by inhalation. Based on the slightly increased incidences of nasal respiratory epithelial squamous metaplasia and slightly decreased body weights (in males), the committee concludes that 2 mg/m³ is a NOAEL in mice. In rats, the committee could not set a NOAEL since nasal lesions were found at 1 mg/m³, the lowest level tested.

In a study of Gwynn et al., 2-chloroacetophenone showed a co-carcinogenic potential since it increased the incidence of epidermal papillomas in skin of mice previously given dermal applications of 0.3 mL of 0.15% 9,10-dimethyl-1,2-benzanthracene (DMBA) dissolved in acetone. Twenty-one days after administration of DMBA, 0.3 mL of 0.4-0.8% 2-chloroacetophenone in acetone was applied twice a week for 12 weeks and once a week for the following 15

weeks. Twenty epidermal neoplasms were found in 9/12 mice treated with DMBA and 2-chloroacetophenone, compared to 1/12 in acetone-treated controls (Gwy52).

Mutagenicity and genotoxicity

2-Chloroacetophenone was negative when tested in a pre-incubation assay in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 in the presence and absence of S9 (hamster liver or rat liver) (dose range: 0.3-333 µg/plate). Depending on strain and metabolic activation, doses of 33 µg/plate were (slightly) cytotoxic (Zei87; see also Mel90).

Using *in vitro* mammalian cell systems, 2-chloroacetophenone did not induce sister chromatid exchanges when tested with and without metabolic activation in Chinese hamster ovary cells (dose ranges: 0.16-5.0 and 0.016-0.5 µg/mL, respectively), but, at the highest dose tested without metabolic activation, i.e., 3.0 µg/mL, there was an increase in the percentage of cells with chromosomal aberrations along with marked cytotoxicity (Mel90).

The committee did not find data from other *in vitro* (including on mutations in mammalian cell systems) or *in vivo* studies.

Reproduction toxicity

The committee did not find *in vivo* studies on the potential reproduction toxicity of 2-chloroacetophenone.

In vitro experiments were discussed in the NTP report on the toxicology and carcinogenicity studies (see above). Incubation of chick embryos in the primitive streak stage with 0.5-3 mM 2-chloroacetophenone for 15-120 minutes was reported to increase the frequency of abnormalities in the nervous system including improper differentiation and incomplete closure of the brain. In separate studies, well-differentiated closed neural tubes were seen when embryos were incubated with 2-chloroacetophenone and subsequently exposed to sulphhydryl agents. Embryos incubated with 2-chloroacetophenone at the head-process showed normal development. The inhibitory effect of 2-chloroacetophenone on morphogenesis of the nervous system was concluded to be reversible (Mel90).

Immunotoxicity

Kumar et al. evaluated the effects of 2-chloroacetophenone on the immune system. Short-term repeated exposure of 22 Swiss albino male mice to 2-chloroacetophenone vapours at a concentration of 153 mg/m³ for 15 minutes daily on 10 consecutive days resulted in increased mortality to *L. monocytogenes*. Significantly elevated bacterial growth was observed in the spleen and liver of exposed animals compared to controls. Increased susceptibility to infection was considered to be the function of immune alteration due to 2-chloroacetophenone exposure. This may be attributed to immunotoxic effects on T-cell-mediated macrophage functions (Kum92).

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for 2-chloroacetophenone in the Netherlands is 0.3 mg/m³ (0.05 ppm), 8-hour TWA.

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

8 Assessment of health hazard

The main occupational routes of exposure to 2-chloroacetophenone are inhalation of aerosols and vapours and skin contact, during manufacture and packaging operations, during loading of solutions for aerosols, and during carrying a canister in a holster. The committee did not find data on occupational exposure levels.

In humans, 2-chloroacetophenone is severely irritating to the eyes (lachrymator), respiratory tract, and skin; it is a skin-sensitising compound as well. Ocular and dermal harassment rapidly occurs at levels of 10 mg/m³. When human volunteers were exposed to 2-chloroacetophenone aerosol concentrations of up to 350 mg-min/m³ for up to 4 minutes, they most frequently complained of symptoms indicative of eye, nose, and throat irritation and less frequently of more severe symptoms such as burning in the chest with breathing difficulties and slight gagging with nausea. Post-exposure, mild to moderate conjunctivitis was the only constant sign; all signs had usually disappeared within 10 minutes. Estimates of the minimal irritant concentration and the IC_{t50} (i.e., the concentration x time, incapacitating/irritating to 50% of an exposed population) were 0.3-1 and 20-50 mg-min/m³, respectively. Use in confined spaces can cause serious morbidity and mortality, autopsy revealing pulmonary oedema and

congestion and necrosis of airway mucosa. Estimates of the LC₅₀ (i.e., the concentration x time, lethal to 50% of an exposed population) ranged between 8500 to 22,500 mg-min/m³

In experimental animals, 2-chloroacetophenone caused severe primary and allergic contact dermatitis and lachrymation, blepharospasm, and severe and permanent corneal lesions. During acute inhalation exposure, lachrymation, conjunctivitis, copious nasal secretions, salivation, hyperactivity, dyspnoea, and lethargy occurred while dyspnoea, conjunctivitis, and erythema were the most salient post-exposure findings. In animals that died, pulmonary system injury (pulmonary congestion, oedema, bronchopneumonia) was the cause of death. In one study, cellular degeneration in the epithelium of the bronchiole and alveolar septal-wall thickening were observed in rats exposed to 62.6 mg/m³ for 60 minutes.

In repeated inhalation studies, 2-chloroacetophenone did not cause gross or microscopic lesions in male and female rats and mice exposed to concentrations ranging from 0.25 to 4 mg/m³, 6 hours/day, 5 days/week, for 13 weeks. Effects observed were slightly decreased (by 9%) body weights in male and female rats, slightly increased relative liver weights in female mice exposed to 4 mg/m³ and eye irritation in both species during exposure to concentrations of 0.5 mg/m³ and higher. The NOAEL was 0.25 mg/m³. In a 2-year study, at exposure levels of 1 and 2 (rats) or 2 and 4 (mice) mg/m³, however, no eye irritation or any other clinical sign was noticed in any of the treated groups. Apart from increases in the incidences of benign mammary gland fibroadenomas in female rats (significant positive trend test; increase significant in high-concentration group), there were no increases in the incidence of any benign or malignant tumour in any of the groups. In rats, the only effects observed were minimal-to-mild nasal passage lesions (squamous epithelial metaplasia and hyperplasia) showing dose-dependent increases in incidence and severity. Based on these findings, the committee concludes that, in this study, 1 mg/m³, the lowest level tested, is a minimal-observed-adverse-effect level in rats. In mice, there were very slight increases in the incidences of nasal lesions in male and female and slight decreases in body weights in male animals exposed to 4 mg/m³, 2 mg/m³ being the NOAEL.

The committee concluded that 2-chloroacetophenone was negative in a *S. typhimurium* mutation assay and in a test for SCEs and chromosome aberrations in CHO cells, the only tests available.

Based on the results of the carcinogenicity and (limited number of) genotoxicity studies, the committee is of the opinion that 2-chloroacetophenone will not be a carcinogenic risk to occupationally exposed workers.

The committee did not find data from reproduction toxicity studies with 2-chloroacetophenone.

Contrary to the 13-week inhalation study, no eye irritation (or other clinical signs) was seen at higher levels in the subsequent 2-year study. Therefore, the committee prefers to take the minimal irritation of the nasal passages at 1 mg/m³ in a 2-year rat inhalation study as a starting point in deriving a health-based recommended occupational exposure limit (HBROEL). For the extrapolation to a HBROEL, an overall assessment factor of 8 is established. This factor covers the following aspects: the absence of a NOAEL, intra- and interspecies variation, and the type of effect. Thus applying this factor and the preferred-value approach, a health-based occupational exposure limit of 0.1 mg/m³ is proposed for 2-chloroacetophenone.

Based on threshold estimates for eye (lachrymation) and respiratory tract irritation in humans, the committee recommends a short-term exposure limit of 0.3 mg/m³ in order to prevent irritation from peak levels.

The committee recommends a health-based occupational exposure limit for 2-chloroacetophenone of 0.1 mg/m³, as inhalable dust, as an 8-hour time-weighted average, and a short-term exposure limit of 0.3 mg/m³, as inhalable dust, as a 15-minute time-weighted average.

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Annex

Occupational exposure limits for 2-chloroacetophenone 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	0.05	0.3	8 h	administrative		SZW03
Germany - AGS	-	0.3				TRG00
- DFG MAK-Kommission	-	-				DFG03
Great-Britain - HSE	0.05	0.32	8 h	OES		HSE02
Sweden	-	-				Swe00
Denmark	0.05	0.3	8 h			Arb02
USA - ACGIH	0.05	-	8 h	TLV	A4 ^c	ACG03b
- OSHA	0.05	0.3	8 h	PEL		ACG03a
- NIOSH	0.05	0.3	10 h	REL		ACG03a
European Union - SCOEL	-	-				EC04

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

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

^c 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.

