2-Chloroacetophenone; CASRN 532-27-4

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR 2-Chloroacetophenone

File First On-Line 10/01/1991

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	not evaluated	
Inhalation RfC (I.B.)	yes	10/01/1991
Carcinogenicity Assessment (II.)	not evaluated	

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — 2-Chloroacetophenone
CASRN — 532-27-4
Primary Synonym — Phenacyl chloride

Not available at this time.

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — 2-Chloroacetophenone
CASRN — 532-27-4

Primary Synonym — Phenacyl chloride
Last Revised — 10/01/1991

The inhalation Reference Concentration (RfC) is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). It is expressed in units of mg/cu.m. In general, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Inhalation RfCs were derived according to the Interim Methods for Development of Inhalation Reference Doses (EPA/600/8-88/066F August 1989) and subsequently, according to Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA/600/8-90/066F October 1994). RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.B.1. Inhalation RfC Summary

Critical Effect	Exposures*	UF	MF	RfC
Squamous hyperplasia of the nasal respiratory epithelium **Chronic rat Inhalation Study** **NTP, 1990**	NOAEL: None LOAEL: 1 mg/cu.m LOAEL(ADJ): 0.18 mg/cu.m LOAEL(HEC): 0.03 mg/cu.m	1000	1	3E-5 mg/cu.m

*Conversion Factors: MW = 154.6. The LOAEL(ADJ) = 1 mg/cu.m x 6 hours/24 hours x 5 days/7 days = 0.18 mg/cu.m. The LOAEL(HEC) was calculated for a gas:respiratory effect in the ExtraThoracic region. MVa = 0.24 cu.m/day, MVh = 20 cu.m/day, Sa(ET) = 11.6 sq.cm., Sh(ET) = 177 sq. cm. RGDR(ET) = (MVa/Sa) / (MVh/Sh) = 0.18. LOAEL(HEC) = LOAEL(ADJ) x RGDR = 0.03 mg/cu.m.

I.B.2. Principal and Supporting Studies (Inhalation RfC)

NTP (National Toxicology Program). 1990. Toxicology and Carcinogenesis Studies of 2-Chloroacetophenone (CAS No. 532-27-4) in F344/N Rats and B6C3F1 Mice (Inhalation Studies). Technical Report No. 379.

The NTP conducted a 2-year inhalation study (with a 15-month interim sacrifice) of 2-chloroacetophenone (CN) in F344/N and B6C3F1 mice (NTP, 1990). The formulation used to generate CN vapor 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%) comprising the rest of the formulation. The CN was volatilized leaving behind the magnesium oxide. CN was measured by GC/EC and actual concentrations were within +/-10% of nominal values. Sixty animals/sex/group/species were exposed to CN vapor at the following average concentrations 6 hours/day, 5 days/week for 103 weeks: 0, 1, or 2 mg/cu.m (rats) or 0, 2, or 4 mg/cu.m (mice). The duration-adjusted concentrations were 0, 0.18, or 0.36 mg/cu.m for rats, and 0, 0.36, or 0.71 mg/cu.m for mice. At 15 months, blood samples were taken from up to 10 animals/sex/group and the animals were necropsied. Complete histopathological examinations, which included the entire respiratory tract, were performed on all of the control and high- and low-concentration animals.

No significant treatment-related effects on survival, clinical signs, or body weight were observed in the exposed rats. After 15 months of exposure, rats did not exhibit any clearly treatment-related hematological effects, although the lymphocyte count and the nucleated erythrocyte count of the male rats exposed to 2 mg/cu.m were significantly elevated. The female rats exposed to 1 mg/cu.m exhibited a significant increase in leukocyte and lymphocyte count, but this effect was not seen in the female rats exposed to 2 mg/cu.m. Brain, liver, kidney, and body weight were not affected by exposure to CN vapor in the rats sacrificed at 15 months; brain weight was increased in the 1 mg/cu.m female group, but this effect was not seen at 2 mg/cu.m.

The incidence of focal squamous metaplasia and hyperplasia of the respiratory epithelium was increased in a concentration-related manner in both sexes. The incidence of hyperplasia in male rats was 12/46, 17/50, and 44/49 at 0, 1, and 2 mg/cu.m, respectively. In female rats, the incidence was 20/48, 31/50, and 38/49 at 0, 1, and 2 mg/cu.m., respectively. The incidence of squamous metaplasia was 2/46, 11/50, and 27/49 (males) and 1/48, 7/50, and 26/49 (females), at 0, 1, and 2 mg/cu.m, respectively. The authors suggest that the irritant effects of CN on the nasal mucosa 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. Inflammation, ulcers, and squamous hyperplasia of the forestomach was observed in the exposed female rats. These effects may have been due to a

direct effect of CN resulting from ingestion of the compound from the fur during grooming, since the compound has a low vapor pressure. Based on nasal respiratory hyperplasia findings, the LOAEL is 1 mg/cu.m. The LOAEL(HEC) of 0.03 mg/cu.m was calculated using the ventilation rate for female rats.

In mice, the only sign of clinical toxicity was rapid, shallow breathing during the first 6 months in animals of the 4 mg/cu.m-group, and in all exposed mice during months 3-6. There were no exposure-related effects on body weight. Survival in females of the 2 mg/cu.m group only was significantly less than controls when both natural and moribund deaths were tabulated. A number of hematological parameters were significantly decreased in females of both exposure groups and in males at the highest concentration. However, these alterations were not considered to be exposure-related by the investigators. There was little indication of an effect of exposure on the nasal cavity. In females of the 4 mg/cu.m-group only, the incidence of squamous metaplasia of the respiratory epithelium was 4/49 and for respiratory hyperplasia, 2/49. The incidence of squamous metaplasia in males at 4 mg/cu.m was 2/48 and no respiratory hyperplasia was reported. These effects were not seen in control animals or animals in the 2 mg/cu.m-groups. Based on the low incidence of nasal effects, the NOAEL is established in mice at 4 mg/cu.m [NOAEL(HEC) = 0.13 mg/cu.m].

It should be noted that this NOAEL is tempered by the likelihood that the clinical signs noted are indicative of reflex apnea, a characteristic response of mice to irritating agents. If this is the case, the apparent NOAEL would likely overestimate the actual concentration delivered to the nasal respiratory epithelium. Mice have previously shown an ability to decrease their minute volume by approximately 75% as compared with 45% in rats when exposed to formaldehyde (Barrow et al., 1983; Chang et al., 1983). Mice did not exhibit the tolerance demonstrated by rats. A theoretical 75% reduction in the NOAEL(HEC) would result in a value of 0.1 mg/cu.m for mice. Since minute volume was not monitored in either species, the LOAEL in rats is used despite the concern of concomitant respiratory infection. Since rats did not show clinical signs of irritation and because an effect is established, this results in the most conservative HEC estimate for operational derivation of the RfC.

I.B.3. Uncertainty and Modifying Factors (Inhalation RfC)

UF — The uncertainty factor of 1000 reflects a factor of 10 to protect unusually sensitive individuals, 10 for the use of a LOAEL rather than a NOAEL, and an additional 10 for both interspecies extrapolation, and for the lack of data on neurotoxicity and reproductive/developmental effects.

MF — None

I.B.4. Additional Studies/Comments (Inhalation RfC)

Since CN has been used extensively as a tear gas agent, there are numerous reports in the literature on the effects of acute inhalation exposure to this compound. Several estimations have been made with regard to safe, irritating, and lethal concentrations of CN. For example, Punte et al. (1962a) estimated that the maximum concentration of CN that is free from systemic toxicity is 350 mg-min/cu.m for up to 5 minutes. Dosage for the inhalation of irritant compounds is often expressed as the function of the atmospheric concentration of the irritant (C) and the time of exposure (T) such that the inhalation exposure dose (CxT) is a product of C (in mg/cu.m) and T (in min) and expressed as mg-min/cu.m. The median incapacitating dose of CN has been estimated to be approximately 80 mg-min/cu.m (Taylor, 1975), and the LC50 has been estimated to be 8,000-11,000 mg-min/cu.m (Taylor, 1975).

One human study is available in which four volunteers were exposed to concentrations of CN that ranged from 40-350 mg/cu.m until they could no longer tolerate the effects or a maximum of 4 minutes exposure was attained (Punte et al., 1962b). The subjects complained of tingling of the nose and rhinorrhea, burning of the throat, burning of the eyes with lacrimation, and some degree of blurred vision. Other complaints included burning of the skin around the eyes and throat, which was worse when the subjects sweated; blinking; burning in the chest with dyspnea; slight gagging and nausea; and slight transient increases in airway resistance. The EC50 (airborne concentration that produces a 50% response in a group of subjects during the time indicated) was 213 mg-min/cu.m for 1 minute, 119 mg-min/cu.m for 2 minutes, and 93 mg-min/cu.m for 3 minutes. All effects subsided after removal from the CN atmosphere.

Several reports are available that describe the outcome of the use of CN alone or in combination with other lacrimating agents such as chlorobenzalmalononitrile (CS), in riot control situations in prisons. Chapman and White (1978) reported the death of one 33-year-old male inmate 46 hours after an initial gassing with tear gas containing CN and CS. His death was diagnosed as being due to “acute necrotizing laryngotracheobronchitis” resulting from exposure to tear gas. Exact exposure concentrations were not available, but the authors estimated a C x T (for a combination of CN and CS) of 41,000 mg-min/cu.m based on the dimensions of the room and the reported amount of tear gas used.

In another prison, CN was sprayed into 44 prison cells resulting in the hospitalization of 8 inmates and the outpatient care of another 20 inmates (Thorburn, 1982). The inmates whose cells were sprayed directly were estimated to have received a dose of 1.75 g of CN. Those who required hospitalization presented with one or more of the following: laryngotracheobronchitis, first and second degree chemical burns, apparent allergic reaction including severe systemic illness, uncontrollable emesis, or syncope. Other symptoms noted in the hospitalized patients included malaise, lethargy, dysuria, cough, pruritis, and conjunctivitis. Those requiring

outpatient clinic had primarily dermal and ocular injuries. All 28 patients recovered from the effects of exposure to CN.

Dermal exposure to CN is irritating (Punte et al., 1962a) and can result in severe second and third degree chemical burns (Thorburn, 1982). These effects are exacerbated when the skin is wet. CN has also been shown to be a dermal sensitizer in humans (Penneys, 1971). CN caused contact sensitization or delayed hypersensitivity in guinea pigs following either dermal or intradermal application (Chung and Giles, 1972). In addition, cross- reactivity to 1-bromoacetophenone; 1,1-dichloroacetophenone; and acetophenone was seen in animals that were sensitized to CN.

Chloroacetophenone has been found to react irreversibly with free sulfhydryl groups of proteins and enzymes. This reaction was observed to be the main cause of denaturation associated with sensory nerve activity (Chung and Giles, 1972).

Since CN is a sensory irritant, Ballantyne et al. (1977) determined the RD50, or the concentration required to cause a 50% depression of respiratory rate, for this compound in mice. Animals were exposed to an aerosol of CN for 1 minute, and respiratory rate was recorded 15 seconds prior to exposure, during exposure, for 30 seconds after exposure, and at 1 minute intervals for up to 10 minutes. Respiratory rate was measured with a plethysmograph. The calculated RD50 for CN aerosol was 52 mg/cu.m.

Punte et al. (1962a) exposed groups of male rats, mice, and guinea pigs to various concentrations of CN aerosol for 5-90 minutes and calculated LC50 values based on the mortality data obtained. The mass median diameter of the CN aerosol particles was 2.0 micrometers. The LC50 values for the three species tested were 3700, 73,500, and 3500 mg-min/cu.m for rats, mice, and guinea pigs, respectively. Thus, it would appear that mice are far less susceptible to the toxic effects of CN than rats or guinea pigs. All animals exhibited similar signs during exposure: hyperactivity following by nasal and ocular irritation, lacrimation, and salivation. After 5-15 minutes the hyperactivity gave way to lethargy then labored breathing which persisted for 1-2 hours after exposure. Death was usually attributed to asphyxia after pulmonary congestion, hemorrhage, and edema. Animals exposed to concentrations of CN at less than or equal to 1000 mg-min/cu.m exhibited no treatment-related histopathological effects.

A similar sort of investigation was conducted by Ballantyne and Swanston (1978) in which rats, rabbits, mice, and guinea pigs were exposed to 250-750 mg/cu.m of CN aerosol for 15-60 minutes. The calculated LC50 values in mg- min/cu.m for the various species were as follows: 8750 (male rat); 11,480 (female rabbit); 13,140 (female guinea pig); and 18,200 (male mouse). These values are similar to those obtained by Punte et al. (1962a) with respect to the relative sensitivities of the various species to the toxic effects of CN aerosol. The clinical signs and

histopathological findings seen in this study are similar to those described by Punte et al. (1962a).

In the 14-day range-finding NTP studies (NTP, 1990), groups of 5 animals/sex from both rats and mice were exposed to 0, 4.8, 10, 19, 43, or 64 mg/cu.m CN vapor 6 hours/day, 5 days/week. All rats exposed to more than or equal to 19 mg/cu.m and all mice exposed to more than or equal to 10 mg/cu.m died during the study. Clinical signs evident during the exposures include dacryorrhea in both species and dyspnea, erythema, partially closed eyelids, and epistaxis in rats. Rats that were exposed to 4.8 and 10 mg/cu.m lost weight in an exposure-related manner. Reddened lungs were observed at necropsy in several of the mice that died, but no compound-related lesions were observed in mice exposed to 4.8 mg/cu.m CN vapor. Although results were not further described, histopathological examinations were performed on 2 rats and 3 mice of each sex from the 4.8 mg/cu.m-group and 1 rat of each sex from the 10 mg/cu.m-group.

Based on the results of the 14-day studies, exposure concentrations used in the 13-week studies were 0, 0.25, 0.5, 1.2, or 4 mg/cu.m CN vapor (NTP, 1990). Ten animals/sex/group from each species were exposed for 6 hours/day, 5 days/week. None of the exposed rats died, but 1/10 female mice exposed to 4 mg/cu.m and 1/10 female mice exposed to 0.5 mg/cu.m died during the course of the study. A 9% decrease (as compared with the control animals) in body weight was observed in the rats of both sexes exposed to 4 mg/cu.m, and final body weights in the exposed mice ranged from 12-15% lower than controls in the females and 7-12% lower than controls in the males. However, the decrease in body weight did not follow an exposure-related pattern. The only compound- related clinical sign observed in either species was eye irritation during exposure. Relative (but not absolute) liver weights were increased in the female rats exposed to 4 mg/cu.m, and no compound-related lesions were observed in either species at necropsy. Histological examinations were performed for all controls and animals in the 4 mg/cu.m-group and in all animals that died before the end of the study.

No information is available on the toxicokinetics of inhaled CN or its reproductive or developmental toxicity.

I.B.5. Confidence in the Inhalation RfC

Study — Medium
Database — Low
RfC -- Low

Although the NTP study used an adequate experimental design (number of animals, exposure concentrations, controls), and the incidence and severity of the nasal lesions were exposure-related and seen in both genders of rats, this study is given a medium confidence rating because

of the presence of other materials in the exposure atmosphere, the chance that the nasal lesions were exacerbated by concurrent viral infection in the exposed rats, and reflex apnea may have occurred to a greater degree in mice, thereby skewing the concentration-response relationship. Confidence in the database can be considered low to medium because the NTP studies are the only available chronic or subchronic studies on CN, and there are no data on the toxicokinetics, reproductive, or developmental toxicity of CN. Confidence in the RfD can also be considered low to medium.

I.B.6. EPA Documentation and Review of the Inhalation RfC

Source Document — This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation — None

Agency Work Group Review — 03/28/1991

Verification Date — 03/28/1991

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfC for 2-Chloroacetophenone conducted in August 2003 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

I.B.7. EPA Contacts (Inhalation RfC)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — 2-Chloroacetophenone
CASRN — 532-27-4
Primary Synonym — Phenacyl chloride

This substance/agent has not undergone a complete evaluation and determination under US EPA's IRIS program for evidence of human carcinogenic potential.

VI. Bibliography

Substance Name — 2-Chloroacetophenone
CASRN — 532-27-4
Primary Synonym — Phenacyl chloride

VI.A. Oral RfD References

None

VI.B. Inhalation RfC References

Ballantyne, B., M.F. Gazzard and D.W. Swanston. 1977. Irritancy testing by respiratory exposure. Chapter 11. In: Current Approaches in Toxicology, B. Ballantyne, Ed. John Wright and Sons, Ltd., Bristol, England. p. 129-138.

Ballantyne, B. and D.W. Swanston. 1978. The comparative acute mammalian toxicity of 1-chloroacetophenone (CN) and 2-chlorobenzylidene malononitrile (CS). Arch. Toxicol. 40(2): 75-95.

Barrow, C.S., W. H. Steinhagen and J.C.F. Chang. 1983. Formaldehyde Sensory Irritation. Chapter 3. In: Formaldehyde Toxicity, J.E. Gibson, Ed. Hemisphere Publishing Company, Washington, DC.

Chang, J.C.F., E.A. Gross, J.A. Swenberg and C.S. Barrow. 1983. Nasal cavity deposition, histopathology, and cell proliferation after single or repeated formaldehyde exposures in B6C3F1 mice and F-344 rats. Toxicol. Appl. Pharmacol. 68: 161-176.

Chapman, A.J. and C. White. 1978. Death resulting from lacrimatory agents. J. Forensic Sci. 23(3): 527-530.

Chung, C.W. and A.L. Giles, Jr. 1972. Sensitization of guinea pigs to alpha- chloroacetophenone (CN) and ortho-chlorobenzylidenemalononitrile (CS), tear gas chemicals. J. Immunol. 109(2): 284-293.

Gaskins, J.R., R.M. Hehir, D.F. McCaulley and E.W. Ligon, Jr. 1972. Lacrimating agents (CS and CN) in rats and rabbits. Acute effects on mouth, eyes, and skin. Arch. Environ. Health. 24(6): 449-454.

NTP (National Toxicology Program). 1990. Toxicology and carcinogenesis studies of 2-chloroacetophenone (CAS No. 532-27-4) in F344/N rats and B6C3F1 mice (inhalation studies). NTP Technical Report 379.

Park, S. and S.T. Giammona. 1972. Toxic effects of tear gas on an infant following prolonged exposure. Am. J. Dis. Child. 123(3): 245-246.

Penneys, N.S. 1971. Contact dermatitis to chloroacetophenone. Fed. Proc. 30(1): 96-99.

Punte, C.L., T.A. Ballard and J.T. Weimer. 1962a. Inhalation studies with chloroacetophenone, diphenylaminochloroarsine, and pelargonic morpholide -- I. Animal Exposures. Am. Ind. Hyg. Assoc. J. 23: 194-198.

Punte, C.L., P.J. Gutentag, E.J. Owens and L.E. Gongwyer. 1962b. Inhalation studies with chloroacetophenone, diphenylaminochloroarsine, and pelargonic morpholide -- II. Human Exposures. Am. Ind. Hyg. Assoc. J. 23: 199-202.

Taylor, G.D. 1975. Military dog training aids: Toxicity and treatment. NTIS AD/A Rep.; ISS No. 006438/6GA. 36 p.

Thorburn, K.M. 1982. Injuries after use of the lacrimatory agent chloroacetophenone in a confined space. Arch. Environ. Health. 37(3): 182-186.

VI.C. Carcinogenicity Assessment References

None

VII. Revision History

Substance Name — 2-Chloroacetophenone
CASRN — 532-27-4
Primary Synonym — Phenacyl chloride

Date	Section	Description
10/01/1991	I.B.	Inhalation RfC summary on-line
10/28/2003	I.B.6.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — 2-Chloroacetophenone
CASRN — 532-27-4
Primary Synonym — Phenacyl chloride
Last Revised — 10/01/1991

- 532-27-4
- 1-CHLOROACETOPHENONE
- 2-CHLORO-1-PHENYLETHANONE
- 2-CHLOROACETOPHENONE
- ACETOPHENONE, 2-CHLORO-
- ALPHA-CHLOROACETOPHENONE
- CAF
- CASWELL NO. 179C
- CHLORACETOPHENONE
- CHLOROACETOPHENONE
- CHLOROMETHYL PHENYL KETONE
- CLOROACETOFENONA [SPANISH]
- CN
- EPA PESTICIDE CHEMICAL CODE 018001
- ETHANONE, 2-CHLORO-1-PHENYL-
- ETHANONE, 2-CHLORO-1-PHENYL-

- HSDB 972
- MACE (LACRIMATOR)
- MACE [LACRIMATOR]
- NCI-C55107
- NSC 41666
- OMEGA-CHLOROACETOPHENONE
- PHENACYL CHLORIDE
- PHENYL CHLOROMETHYL KETONE
- PHENYLCHLOROMETHYLKETONE
- UN 1697