

ACUTE TOXICITY SUMMARY

MERCURY (INORGANIC)

Molecular Formula	Molecular Weight	Synonyms	CAS Registry Number
Hg ⁰	200.59	mercury quicksilver colloidal mercury	7439-97-6
HgCl ₂	271.52	mercuric chloride mercuric bichloride mercury perchloride	7487-94-7
HgNO ₃	262.60	mercurous nitrate mercury protonitrate	10415-75-5
Hg(NO ₃) ₂	324.66	mercuric nitrate mercury pernitrate	10045-94-0
Hg ₂ O	417.18	mercurous oxide mercury oxide	15829-53-5
HgO	216.59	mercuric oxide CI 77760 santar	21908-53-2
HgSO ₄	296.68	mercuric sulfate mercury bisulfate	7783-35-9

I. Acute Toxicity Summary (1-hour exposure)

Inhalation reference exposure level **1.8 µg/m³**

Critical effect(s) behavioral deficits after in utero exposure

Hazard Index target(s) Reproductive/developmental

II. Physical and Chemical Properties (HSDB, 1994)

Specific gravity HgCl₂: 5.44 @ 25°C

HgO: 9.8 @ 25°C

HgSO₄: 6.47

Boiling point Hg⁰: 356.7°C

HgCl₂: 302°C

Melting point Hg⁰: -38.9°C

HgCl₂: 276°C

HgHNO₃: 70°C

Hg(HNO₃)₂: 79°C

Vapor pressure Hg: 0.002 mm Hg @ 25°C

HgCl₂: 1 mm Hg @ 136°C

Flashpoint not applicable

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<i>Explosive</i>	not applicable
<i>Solubility</i>	Hg ⁰ : 0.28 μmoles/L water @ 25 C HgCl ₂ : 69 g/L water, soluble in acetic acid. HgO: insoluble in water, soluble in nitric acid. HgSO ₄ : soluble in hydrochloric acid Most Hg ⁺ forms are water soluble. Hg ²⁺ forms are not water soluble.
<i>Odor threshold</i>	odorless
<i>Odor description</i>	odorless
<i>Metabolites</i>	methylmercury (CH ₃ Hg)
<i>Description</i>	Hg: silver-white liquid, colorless gas Hg salts: white crystalline solids mercurous oxide: black powder
<i>Conversion factor</i>	1 ppm = 8.34 mg/m ³ (Hg ⁰ vapor) @ 25°C

III. Major Uses or Sources

Mercury compounds have a very wide range of chemical uses. Mercuric chloride is used as a wood preservative, a photographic intensifier, a dry battery depolarizer, a tanning agent for leather, and for separating lead from gold (HSDB, 1994). Mercuric nitrate is used in the manufacture of felt, and in the manufacture of bronze (HSDB, 1994). In addition to the above chemical uses, mercury is also released during municipal hazardous waste generation. Elemental mercury (Hg⁰) vapor is the dominant form in the atmosphere, followed by mercuric ionic species (Hg²⁺) and methylmercury (CH₃Hg).

IV. Acute Toxicity to Humans

The respiratory tract is the first organ system affected in the case of acute inhalation poisonings (Levin *et al.*, 1988). Acute exposure to Hg⁰ can lead to shortness of breath within 24 hours and a rapidly deteriorating course leading to death due to respiratory failure (Kanluen and Gottlieb, 1991).

In a case report, Kanluen and Gottlieb (1991) observed 4 individuals from a private home where silver was being smelted from dental amalgam containing an unknown amount of Hg⁰. All individuals died 9-23 days post-exposure from respiratory distress despite treatment with dimercaprol, a mercury chelator. At autopsy, necrotizing bronchiolitis with edema, emphysema, and inspissated fibrin was observed. Concentrations of mercury to which the individuals were exposed and duration of exposure were not estimated.

Central nervous system (CNS) effects such as tremors or increased excitability are sometimes seen in cases of acute accidental exposures (Goyer, 1993). Long-term effects from a single exposure to Hg⁰ have been reported in 6 male workers exposed to an estimated concentration of 44 mg Hg/m³ for a period of several hours (McFarland and Reigel, 1978). Long-term CNS effects included nervousness, irritability, lack of ambition, and loss of sexual drive for several years. Shortness of breath also persisted for years in all cases. Similar cases of CNS

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disturbances, including irritability, insomnia, malaise, anorexia, fatigue, ataxia, and headache have been reported in children exposed to vapor from spilled elemental mercury in their home (Florentine and Sanfilippo, 1991).

Acute inhalation exposure of Hg⁰ vapors from broken thermometers resulted in generalized skin eruptions in 15 individuals (Nakayama *et al.*, 1983). The doses and durations of exposure were not estimated.

An infant exposed in an incubator to Hg⁰ from a broken thermometer exhibited very high urinary (0.34 mg/L) and fecal (quantity not specified) mercury levels, but mercury levels in the blood were undetectable (McLaughlin *et al.*, 1980). The infant recovered from the exposure within days with no lasting effects.

Mercury vapor is efficiently absorbed (76-100%) through inhalation via the nose over concentrations ranging from 4-30 µg/m³ (Oikawa *et al.*, 1982). Absorption is markedly decreased to 20% if the breathing is done only through the mouth. The biological half-life of mercury in the human brain is reported to be 21 days, and the half-life in the kidney is 64 days (Hursh *et al.*, 1976). Mercury has been shown to accumulate in the placentae of women even in the absence of a particular history of mercury exposure (Suzuki *et al.*, 1971).

Predisposing Conditions for Mercury Toxicity

Medical: Unknown

Chemical: Unknown

Other: People who consume significant amounts of fish from areas with advisories for daily fish intake due to mercury contamination may be more susceptible to the acute toxicity of airborne mercury.

V. Acute Toxicity to Laboratory Animals

An LD₅₀ value of 2.6 mg Hg/kg as mercuric nitrate by intravenous injection in chickens has been reported (HSDB, 1994).

Severe cellular degeneration and necrosis was observed in the kidneys, brain, colon, and heart tissue of 2 rabbits exposed for 4 hours to 29.7 mg Hg/m³ (Ashe *et al.*, 1953). Exposure of rabbits to 31.3 mg Hg/m³ for 1 hour resulted in moderate pathological changes (unspecified), but no necrosis, in the brain and kidney; in contrast, heart and lung tissues showed mild pathologic changes (Ashe *et al.*, 1953). Increased duration (6 hours/day for 5 days) of exposure at this concentration was lethal.

Livardjani *et al.* (1991) exposed 64 rats to 26 mg Hg/m³ for 1 hour, with an elevation in lung superoxide dismutase activity observed 3 days following exposure. Lethality was observed in 50% of rats 5 days following a 2-hour exposure to the same concentration.

Berlin and Johansson (1964) showed that inhaled mercury vapor (10 mg/m³ for 4 hours) resulted in a ten-fold greater brain burden of mercury in mice than the same dose administered intravenously (IV). Berlin *et al.* (1969) later showed that the inhalation route of exposure results in approximately 10-fold greater accumulation of mercury in the brain tissue of rats, rabbits, and monkeys than IV injection.

Induction of autoimmune glomerulonephritis, as measured first by elevated serum IgE levels and later by anti-laminin antibodies and proteinuria, has been observed in rats exposed to 1 mg Hg/m³, 6 hours/day, for 14 days (Hua *et al.*, 1993).

VI. Reproductive or Developmental Toxicity

Mercury compounds, including inorganic forms, are listed under California Proposition 65 (Cal/EPA, Safe Drinking Water and Toxic Enforcement Act of 1986) as developmental toxins.

In rats, elemental mercury readily crosses the placental barrier and accumulates in the placenta following inhalation (Clarkson *et al.*, 1972). Gale (1974) reported decreased crown-rump length and increased incidence of edema in hamster fetuses following single subcutaneous administration of 4 mg/kg Hg as mercuric acetate on day 8 of gestation. Exposure to 2.5 mg/kg Hg resulted in no significant developmental defects in these hamsters. Gale (1981) later showed that the most common manifestations of mercury-induced embryotoxicity in hamsters were resorption, edema, and cardiac abnormalities.

Pregnant rats exposed by inhalation to 1.8 mg/m³ of metallic mercury for 1 hour or 3 hours/day during gestation (days 11 through 14 plus days 17 through 20) bore pups that displayed significant dose-dependent deficits in behavioral measurements 3-7 months after birth compared to unexposed controls (Danielsson *et al.*, 1993). Behaviors measured included spontaneous motor activity, performance of a spatial learning task, and habituation to the automated test chamber. The pups also showed dose-dependent, increased mercury levels in their brains, livers, and kidneys 2-3 days after birth.

VII. Derivation of Acute Reference Exposure Level and Other Severity Levels (for a 1-hour exposure)

Mild Adverse Effect Level

The most sensitive endpoint for inorganic mercury toxicity is developmental toxicity, which is considered a serious effect. Therefore, there is no mild adverse effect level for inorganic mercury.

Reference Exposure Level (protective against severe adverse effects): 1.8 µg/m³

<i>Study</i>	Danielsson <i>et al.</i> , 1993
<i>Study population</i>	groups of 12 pregnant rats
<i>Exposure method</i>	inhalation of metallic mercury vapors
<i>Critical effects</i>	CNS disturbances in offspring
<i>LOAEL</i>	1.8 mg/m ³
<i>NOAEL</i>	not observed
<i>Exposure duration</i>	1 hour per day
<i>Extrapolated 1 hour concentration</i>	1.8 mg/m ³
<i>LOAEL uncertainty factor</i>	10
<i>Interspecies uncertainty factor</i>	10
<i>Intraspecies uncertainty factor</i>	10
<i>Cumulative uncertainty factor</i>	1,000
<i>Reference Exposure Level</i>	0.0018 mg/m ³ (1.8 µg/m ³)

Maternal rats exposed by inhalation to 1.8 mg/m³ of metallic mercury for 1 hour/day or 3 hours/day during gestation bore offspring that displayed significant dose-dependent deficits in behavior 3-7 months after birth compared to controls.

Level Protective Against Life-threatening Effects

No recommendation is made due to the limitations of the database.

NIOSH lists a revised IDLH of 10 mg/m³ based on acute inhalation toxicity data of mercury vapor in animals (Ashe *et al.*, 1953). Severe damage in the kidneys, lungs, and colon of rabbits resulted from exposure for a single 4-hour period to 28.8 mg/m³. Mild damage to most of the organs occurred after 1 hour of exposure. It is not clear why this result would make 10 mg/m³ a life-threatening level for humans.

VIII. References

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ACUTE TOXICITY SUMMARY

METHANOL

(methyl alcohol, wood spirit, carbinol, wood alcohol, wood naphtha)

CAS Registry Number: 67-56-1

I. Acute Toxicity Summary (for a 1-hr exposure)

<i>Inhalation reference exposure level</i>	28,000 µg/m³
<i>Critical effect(s)</i>	subtle impairment in the performance of complicated tasks
<i>Hazard Index target(s)</i>	Nervous System

II. Physical and Chemical Properties (HSDB, 1993 except as noted)

<i>Molecular formula</i>	CH ₃ OH
<i>Molecular weight</i>	32.04
<i>Specific gravity</i>	0.7915 @ 20°C
<i>Boiling point</i>	64.5°C
<i>Melting point</i>	-97.8°C
<i>Vapor pressure</i>	92 mm Hg @ 20°C
<i>Flashpoint</i>	12°C, closed cup
<i>Explosive limits</i>	lower = 7.3% upper = 36%
<i>Solubility</i>	methanol is miscible with water, ethanol, ether and many other organic solvents
<i>Odor threshold</i>	160 ppm (geometric mean) (AIHA, 1989)
<i>Odor description</i>	sour/sweet (AIHA, 1989)
<i>Metabolites</i>	metabolized to formaldehyde, then formate
<i>Description</i>	colorless liquid
<i>Conversion factor</i>	1 ppm = 1.31 mg/m ³ @ 25°C

III. Major Uses and Sources

Originally distilled from wood, methanol is now manufactured synthetically from carbon oxides and hydrogen. Methanol is primarily used for the manufacture of other chemicals and as a solvent. It is also added to a variety of commercial and consumer products such as windshield washing fluid and de-icing solution, duplicating fluids, solid canned fuels, paint remover, model airplane fuels, embalming fluids, lacquers, inks and as alternative motor fuel. Methanol is released in large quantities from pulp and paper mills.

IV. Acute Toxicity to Humans

Methanol is easily absorbed following ingestion, inhalation, or dermal exposure and is metabolized by the liver to formaldehyde, then formate. The latter metabolite is responsible for the metabolic acidosis and ocular effects characteristic of acute methanol poisoning. Odor and irritation are not adequate warnings of overexposure to methanol (Reprotext, 1993).

Upon ingestion or inhalation, methanol initially has a narcotic effect followed by an asymptomatic period of approximately 10 to 15 hours (Rowe and McCollister, 1978). After this period, methanol may produce nausea, vomiting, dizziness, headaches, vertigo, respiratory difficulty, lethargy, abdominal pain, pain in the extremities, visual disturbances, and metabolic acidosis (ATSDR, 1993; NIOSH, 1976). The visual disturbances vary from spots or cloudiness of vision to complete blindness (Grant, 1986). Methanol toxicity can result in coma and death by respiratory or cardiac arrest.

In one study, symptoms of blurred vision, headaches, dizziness, nausea, and skin problems were reported in teachers' aides who were exposed to duplicating fluid containing 99% methanol while working with "spirit duplicators" (Frederick *et al.*, 1984). A dose-response relationship was observed between the amount of time spent at the duplicator and the incidence of symptoms. The concentrations of methanol in the breathing zones near the machines in 12 schools ranged from 485 to 4,096 mg/m³ (365 to 3,080 ppm) for a 15 minute sample.

Employees working in the proximity of direct process duplicating machines complained of frequent headaches and dizziness (Kingsley and Hirsch, 1954). Air concentrations of methanol ranged from 15 ppm (20 mg/m³) to 375 ppm (490 mg/m³).

In a pilot study, 12 young, paid, male volunteers were exposed to filtered air and to 250 mg/m³ (192 ppm) methanol vapor for 75 minutes and were administered a battery of 20 neurobehavioral and neurophysiological tests before, during, and after exposure (Cook *et al.*, 1991). Methanol had no significant effect on the subjects' performance for all but two of the tests. Although statistically significant effects were observed in one test measuring fatigue and concentration (fatigue scale score, $p = 0.02$) and a trend was observed in a test measuring the latency of visual evoked potentials (P200 component of event-related potentials, $p = 0.02$), both the effects were small and, according to the authors, did not exceed the normal range during the sham exposures. A trend was observed for decreased performance of the Sternberg memory task following exposure to methanol ($p = 0.055$) although it is of borderline statistical significance. Consistent with this finding, subjects reported higher levels of fatigue and there was a trend toward decreased ability to concentrate and less vigor when exposed to methanol vapors compared to control conditions. According to the authors, these changes did not affect the subjects' ability to maintain vigilance or to respond quickly to stimuli.

Predisposing Conditions for Methanol Toxicity

Medical: Persons with skin, eye, respiratory or neurological conditions may be more sensitive to the adverse effects of methanol (Reprotext, 1993). There is a great

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range of individual response to the toxic effects of methanol, probably due to the variability in individual capacity to generate toxic metabolites (Bennet, 1953; NIOSH, 1976).

Chemical: Persons simultaneously exposed to formaldehyde or formic acid may be more sensitive. Those ingesting ethanol may be less sensitive to methanol toxicity.

V. Acute Toxicity to Laboratory Animals

With the exception of non-human primates, the signs of methanol toxicity in laboratory animals are quite different from the signs observed in humans (Gilger and Potts, 1955). The major effect of methanol in non-primates is CNS depression similar to that produced by other alcohols. Metabolic acidosis and ocular toxicity are not observed. The differences in toxicity are attributed to the ability of non-primates to more efficiently metabolize formate than humans and other primates (Tephly, 1991). The lethal oral dose of methanol in humans is estimated at approximately 1/3 and 1/9 the equivalent oral dose in monkeys and rats, respectively (Gilger and Potts, 1955).

In one poorly described study, 11 rhesus monkeys, 12 rabbits, and 46 rats were exposed by inhalation to methanol concentrations ranging from 1,000 ppm to 40,000 ppm (1,300 to 52,400 mg/m³) for 1-18 hours/day for up to 41 hours (McCord, 1931). Of the species studied, monkeys were the most sensitive to the effects of methanol. Some animals (number and species unidentified) died after exposure to 1,000 ppm for at least 41 hours. Exposure at 40,000 ppm for 4 hours led to immediate death in all animals. A 1-hour exposure at this concentration led to "sickness in [all] animals within 2-3 days and eventually to death."

Twenty-four cynomolgus monkeys were exposed by inhalation to methanol vapor at concentrations up to 6,650 mg/m³ (5,010 ppm) for 6 hours per day, 5 days per week for 4 weeks (Andrews *et al.*, 1987). No deaths occurred and no treatment-related effects, including ocular damage, were observed.

Methanol has been shown to be a mild irritant to the eyes and skin of rabbits when applied topically (Rowe and McCollister, 1978).

Additionally, NIOSH (1976) cites studies by Flury and Wirth (1933) which reported a Lowest Lethal Concentration (LCLo) in cats of 33,082 ppm after a 6-hour exposure, and by Izmerov *et al.* (1982) which reported an LCLo in mice of 37,594 ppm after a 2-hour exposure.

VI. Reproductive or Developmental Toxicity

Exposure to methanol along with other solvents is believed to cause central nervous system birth defects in humans (Holmberg, 1979). However, because of mixed or inadequate exposure data, it is not considered a known human teratogen.

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In two separate studies in male rats, inhalation exposure to methanol at concentrations ranging from 260 to 13,000 mg/m³ (200 to 9,900 ppm) for 6 to 8 hours per day for either 1 day or 1, 2, 4, or 6 weeks resulted in a significant reduction in circulating testosterone levels (Cameron *et al.*, 1984; 1985). However, a dose-response relationship was not observed.

Pregnant rats were exposed by inhalation to methanol at concentrations ranging from 5,000 to 20,000 ppm (6,600 to 26,000 mg/m³) for 7 hours per day on days 1-19 of gestation, and days 7-15 for the highest dose group (Nelson *et al.*, 1985). A dose-related decrease in fetal weight and increases in extra or rudimentary cervical ribs and in urinary and cardiovascular defects were observed. Exencephaly and encephalocele were observed in the 20,000 ppm dose group. The no observable adverse effect level (NOAEL) was 5,000 ppm.

Rogers *et al.*, (1993) exposed pregnant mice to methanol vapors at concentrations ranging from 1,000 to 15,000 ppm (1,300 to 20,000 mg/m³) for 7 hours per day on days 6-15 of gestation. Increased embryonic and fetal death, including an increase in full-litter resorptions, was observed at 7,500 ppm (9,800 mg/m³) and higher. Significant increases in the incidence of exencephaly and cleft palate were observed at 5,000 ppm (6,600 mg/m³) and higher. A dose-related increase in the number of fetuses per litter with cervical ribs (usually small ossification sites lateral to the seventh cervical vertebra) was observed at 2,000 ppm (2,600 mg/m³) and above. The NOAEL was 1,000 ppm (1,300 mg/m³) methanol.

**VII. Derivation of Acute Reference Exposure Level and Other Severity Levels
(for a 1-hour exposure)**

Reference Exposure Level (protective against mild adverse effects): 21 ppm (28,000 µg/m³)

<i>Study</i>	Cook <i>et al.</i> , 1991
<i>Study population</i>	twelve healthy male volunteers
<i>Exposure method</i>	inhalation of 192 ppm (250 mg/m ³)
<i>Critical effects</i>	subtle impairment in the performance of complicated tasks
<i>LOAEL</i>	not observed
<i>NOAEL</i>	192 ppm
<i>Exposure duration</i>	75 minutes
<i>Extrapolated 1 hour concentration</i>	214 ppm (192 ² ppm * 1.25 h = C ² * 1 h) (see Table 12 for information on “n”)
<i>LOAEL uncertainty factor</i>	1
<i>Interspecies uncertainty factor</i>	1
<i>Intraspecies uncertainty factor</i>	10
<i>Cumulative uncertainty factor</i>	10
<i>Reference Exposure Level</i>	21 ppm (28 mg/m ³ ; 28,000 µg/m ³)

The only exposure concentration tested, 250 mg/m³ (192 ppm), was considered a free-standing NOAEL for subtle neurologic effects. Reevaluation of the mild adverse effect level is

recommended when a study of the neurobehavioral effects of methanol using a larger sample size becomes available.

Level Protective Against Severe Adverse Effects

A NOAEL of 1,000 ppm (1,300 mg/m³) for congenital malformations was observed in mice exposed for 7 hours/day on days 6 through 15 of gestation (Rogers *et al.*, 1993). The investigators calculated maximum likelihood estimates (MLEs) and benchmark concentrations (BC, the lower 95% confidence limit of the MLEs) for both 1% and 5% added risks above background. The most sensitive developmental toxicity endpoint was an increase in the incidence of cervical ribs. The MLE₀₁ and BC₀₁ for cervical ribs were 302 ppm (393 mg/m³) and 58 ppm (75 mg/m³), respectively. The MLE₀₅ and BC₀₅ for this endpoint were 824 ppm (1,072 mg/m³) and 305 ppm (397 mg/m³), respectively.

The use of a quantitative dose-response model to estimate a benchmark dose has been described by Crump (1984). The recommended serious adverse effect level was calculated by adjusting the BC₀₅ by an uncertainty factor (UF) of 30, 3 to account for interspecies variation since the BC approach accounts for some degree of variation and 10 to account for intraspecies extrapolation.

$$7\text{-hour level} = \text{BC}_{05}/(\text{UF})$$

The 7-hour value was extrapolated to a 1-hour REL, using the formula $C^n * T = K$, where $n=2$. The resulting level protective against severe adverse effects is 27 ppm (35 mg/m³). Revision of this level, designed to protect against serious adverse effects is recommended when a primate reproductive study is available.

Level Protective Against Life-threatening Effects

No recommendation is made due to the limitations of the database.

NIOSH (1995) lists a (revised) IDLH for methyl alcohol of 6,000 ppm (7,860 mg/m³) based on the Izmerov *et al.* (1982) mouse acute inhalation toxicity data. NIOSH used the LCLo of 37,594 ppm from that study to calculate an adjusted 0.5-hour Lethal Concentration value of 60,150 ppm using a Correction Factor (CF) of 1.6, which was then divided by a safety factor of 10 to provide the IDLH value of 6,000 ppm (7860 mg/m³). NIOSH asserts that this may be a conservative value due to the lack of relevant acute toxicity data for workers exposed to concentrations between 1,000 and 30,000 ppm. Additionally, NIOSH (1995) notes that the lethal human oral dose for methanol has been reported as being between 143 and 6,422 mg/kg, which they found equivalent to a 70kg worker being exposed to about 7,000 to 225,000 ppm for 30 minutes, assuming a breathing rate of 50 liters per minute and 100% absorption. Assuming a 1-hour exposure and a breathing rate of 20 m³/day, the equivalent lethal inhalation exposure would be 3,864 - 124,200 ppm. Thus, the IDLH of 6000 ppm may not be adequate protection for the general public.

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ACUTE TOXICITY SUMMARY

METHYL BROMIDE

(bromomethane; monobromomethane)

CAS Registry Number: 74-83-9

I. Acute Toxicity Summary (for a 1-hour exposure)

<i>Inhalation reference exposure level</i>	3,900 µg/m
<i>Critical effect(s)</i>	serious CNS effects: labored breathing, prostration, decreased activity, tremors, lacrimation
<i>Hazard Index target(s)</i>	Nervous System; Respiratory System; Reproductive/developmental

II. Physical and Chemical Properties (HSDB, 1994)

<i>Molecular formula</i>	CH ₃ Br
<i>Molecular weight</i>	94.95
<i>Specific gravity</i>	1.73 @ 0°C
<i>Boiling point</i>	3.6°C
<i>Melting point</i>	-93.7°C
<i>Vapor pressure</i>	1,420 mm Hg @ 20°C
<i>Flashpoint</i>	unknown
<i>Explosive limits</i>	unknown
<i>Solubility</i>	soluble in ethanol, benzene, carbon disulfide, and 1.75% (w/w) in water
<i>Odor threshold</i>	20.6 ppm
<i>Odor description</i>	sweetish odor
<i>Metabolites</i>	methanol, bromide, 5-methylcysteine
<i>Description</i>	colorless gas
<i>Conversion factor</i>	1 ppm = 3.89 mg/m ³ @ 25°C

III. Major Uses or Sources

Methyl bromide (MeBr), introduced in the U.S. from Europe in the 1920s, was used historically as an industrial fire extinguishing agent. Current uses of MeBr include the fumigation of homes and other structures for termites and other pests. Methyl bromide is also used to fumigate soil before planting, and fruits and vegetables after harvest. In 1981, 6.3 million pounds of MeBr were reported to have been used in California (Alexeeff and Kilgore, 1983). In 1991, its use had grown to 18.7 million pounds in the state (Cal/EPA, 1993).

IV. Acute Toxicity to Humans

Symptoms (in approximate increasing severity) following acute exposure to MeBr include: 1. dizziness and headache; 2. anorexia, nausea, vomiting, and abdominal pain; 3. lassitude, profound weakness, slurring of speech, and staggering gait; 4. transient blurring of vision, diplopia, and even temporary blindness; 5. mental confusion, mania, tremors, and epileptiform convulsions; 6. rapid respiration, associated with signs of severe pulmonary edema, cyanosis, pallor, and collapse; 7. coma, areflexia, and death from respiratory and circulatory collapse (HSDB, 1994).

Low-level subchronic vapor exposures have produced a syndrome of persistent numbness in the hands and legs, impaired superficial sensation, muscle weakness, unsteadiness of gait, and absent or hypoactive distal tendon reflexes. Late sequelae include bronchopneumonia, renal failure with anuria due to tubular degeneration, and severe weakness with or without evidence of paralysis (HSDB, 1994).

Acute fatal exposures of unspecified duration to airborne levels of 300-400 ppm (1,164 - 1,552 mg/m³) have been reported (HSDB, 1994). A lethal concentration of at least 60,000 ppm (233 g/m³) MeBr for two hours was reported. Toxic effects preceding death included convulsions, in addition to nausea or vomiting (Wyers, 1945). The lowest lethal level was reported in a child exposed to 257 ppm (1,000 mg/m³) MeBr for 2 hours; marked exposure-related changes in clotting factors were found after death (HSDB, 1994). The absence of warning qualities, the severity of symptoms, the poor prognosis of the patients, and the variety of CNS effects possible make this compound of particular concern for health effects (Alexeeff and Kilgore, 1983).

A workplace concentration of 35 ppm (136 mg/m³) for short, unspecified durations induced anorexia, nausea, vomiting, and corrosion of the skin, although methods for estimation of methyl bromide concentrations were crude (Watrous, 1942). Irritant dermatitis, with necrosis of keratinocytes and neutrophil infiltration, was observed in humans exposed dermally to a concentration of 9,000 ppm MeBr (35 g/m³ for 40 minutes) (Hezemans-Boer *et al.*, 1988).

Predisposing Conditions for Methyl Bromide Toxicity

Medical: Individuals with psychiatric or neurologic disorders, or those with lung, liver, or kidney disorders may be more sensitive to the toxic effects of methyl bromide (Reprotext 1993).

Chemical: Methyl bromide exposure may prolong the period of somnolence associated with barbiturates (Honma *et al.*, 1985).

V. Acute Toxicity to Laboratory Animals

An LC_{Lo} of 300 ppm (1,167 mg/m³) for 9 hours is reported in guinea pigs (U.S. Public Health Service, 1929). A 30-minute LC₅₀ in rats was 2,828 ppm (11,000 mg/m³) (Bakhishev, 1973).

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An 8-hour LC₅₀ in rats was 302 ppm (1,175 mg/m³), with significant decreases in body weight gains noted at concentrations of 125 ppm (486 mg/m³) or higher. Thiopental sleep-time was also increased in rats exposed to 63 ppm (245 mg/m³) or higher (Honma *et al.*, 1985). In mice, the LC₅₀ is 1,164 ppm (4,700 mg/m³) for 1 hour (Alexeeff *et al.*, 1985) and 396 ppm (1,540 mg/m³) for 2 hours (Izmerov *et al.*, 1982). Mice exposed to 200 ppm (778 mg/m³) methyl bromide for 6 hours/day, 5 days/week, for 14 days showed a survival rate of 25% (males 1/10, females 4/10) (NTP, 1992).

In five short-term studies, dogs were exposed to methyl bromide for one (233-394 ppm), four (55-283 ppm), 23-24 (25-100 ppm), 30 (10 ppm, then 150 ppm), or 34 (5 ppm) exposure days for 7 hours per day, 5 days per week (Pharmaco LSR, Inc., 1994). One day exposure of 6 dogs to concentrations of methyl bromide between 233 and 394 ppm resulted in CNS effects (tremors, decreased activity, excessive salivation) within 3-7 hours of initiation of exposure. Signs of respiratory effects (labored breathing and gasping) were also observed in 2 dogs. The post-exposure observation period lasted anywhere from 4 to 14 days. However, all dogs appeared to recover from the CNS and pulmonary effects by the second day following exposure.

In the 4 day study, no effects were observed during exposure in the 55 ppm group. Dogs (one of each sex per group) exposed to 156 or 268 ppm methyl bromide showed no effects after one day of exposure. However, all dogs in both groups began exhibiting CNS effects during the second (268 ppm group) or third (156 ppm group) day of exposure. In dogs exposed to 283 ppm, 1 of 3 animals exhibited CNS (excessive salivation and emesis) and pulmonary (labored breathing) effects within 6 hours of exposure on day one. Dogs at the 2 highest concentrations were sacrificed after 2 days of exposure due to severe signs of neurotoxicity, including delirium, thrashing and vocalization, tremors, traumatizing behavior (defined as slamming the head and body into cage walls), depression, ataxia, and irregular gait. Labored breathing was also observed in most of these dogs. Organ weights (brain, kidneys, adrenals, liver, lungs, testes) were not affected and no brain lesions were detected microscopically in animals at any exposure level. The spinal cord and peripheral nerves were not examined microscopically.

In the 30-day exposure study, dogs (4 animals/sex/group) previously exposed to 10 ppm for 24 days without signs of toxicity were exposed to 150 ppm for 6 days. The dogs showed decreased activity starting on the second day of exposure to 150 ppm and were in a poor condition during the final (6th) exposure. The next day, 3 of the 150 ppm males had to be euthanized due to severe neurotoxicity. Histological examinations indicated brain lesions in all treated dogs. In the 23-24 exposure day study, dogs exposed to 103 ppm began exhibiting signs of neurotoxicity (mainly decreased activity) on day 9, but apparently did not progress to more severe CNS effects before the end of the study. No effect was observed at 50 ppm.

VI. Reproductive or Developmental Toxicity

Data on human reproductive or developmental toxicity from methyl bromide exposure are presently unavailable. No maternal toxicity was observed in pregnant rats exposed to methyl bromide up to 70 ppm (272 mg/m³) from gestation days 1 to 19 (Sikov *et al.*, 1981). The only

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developmental effect was an increase in the incidence of delayed skull ossification of the supraoccipital plate. The NOAEL was 20 ppm methyl bromide for developmental effects.

Rats exposed to methyl bromide up to 90 ppm 5 days per week at pre-mating and during gestation showed decreased fertility in the dams (American Biogenics Corp., 1986). Pups born to these dams showed decreased body weights postnatally. Since the pups were not directly exposed to methyl bromide until after weaning, the decreased body weight may be due to in utero exposure. The NOAEL for these effects was 3 ppm.

In an abbreviated developmental toxicity study, pregnant rabbits exposed to 70 ppm starting on gestation day 1 showed severe neurotoxicity and mortality after 1 week of exposure (Sikov *et al.*, 1981). Exposure of the rabbits was stopped after gestation day 15 (Hardin *et al.*, 1981). No developmental effects were observed in the fetuses of the one survivor. A NOAEL for developmental toxicity cannot be determined from this study since it was terminated prematurely. The NOAEL for maternal toxicity was 20 ppm.

In two subsequent studies, pregnant New Zealand white rabbits exposed to methyl bromide at 80 ppm from gestation days 7 to 19 showed neurotoxicity and decreased body weight (Breslin *et al.*, 1990). Developmental effects observed in the fetuses of the 80 ppm group included gall bladder agenesis, fused sternebrae, and decreased fetal body weight. No effects on the fetuses and does were observed at 40 ppm (155 mg/m³).

After consideration of the above studies showing developmental effects in rabbits and rats, the California Department of Pesticide Regulation concluded that these effects were significant and warranted regulation on the use of methyl bromide to decrease human exposure. However, the California Developmental and Reproductive Toxicity (DART) Committee for Proposition 65 concluded the animal evidence insufficient in meeting the listing standard of “clearly shown to cause developmental or reproductive toxicity” for the purposes of Proposition 65.

VII. Derivation of Acute Reference Exposure Level and Other Severity Levels (for a 1-hour exposure)

Mild Adverse Effect Level

The lowest concentration reported to cause adverse effects results in severe central nervous system toxicity in dogs. Severe CNS toxicity constitutes a serious effect. Since this effect occurs at or below the threshold for mild irritation, there is no mild adverse health effect available for methyl bromide. The REL is a severe adverse effect level.

Reference Exposure Level (protective against severe adverse effects): 1 ppm (3,900 µg/m³)

<i>Study</i>	Pharmaco LSR (1994) (unpublished)
<i>Study population</i>	dogs
<i>Exposure method</i>	acute inhalation of 103 to 394 ppm
<i>Critical effects</i>	CNS and pulmonary effects; lacrimation

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<i>LOAEL</i>	156 ppm
<i>NOAEL</i>	103 ppm
<i>Exposure duration</i>	7 hours
<i>Extrapolated 1 hour concentration</i>	103 ppm (no extrapolation; see below)
<i>LOAEL uncertainty factor</i>	1
<i>Interspecies uncertainty factor</i>	10
<i>Intraspecies uncertainty factor</i>	10
<i>Cumulative uncertainty factor</i>	100
<i>Reference Exposure Level</i>	1 ppm (3.9 mg/m ³ ; 3,900 µg/m ³) (Cal/EPA consensus value)

CNS and pulmonary effects were observed within 7 hours in dogs exposed individually to concentrations of methyl bromide between 233 and 394 ppm. Signs of toxicity included tremors, decreased activity, excessive salivation, labored breathing, and gasping. In the 4-day study (exposed 7 hours/day), 1 of 3 dogs exposed to 283 ppm exhibited similar signs of CNS and pulmonary toxicity on the first day of exposure. Dogs (2 per group) exposed to 156 and 268 ppm showed signs of neurotoxicity during the second or third day of exposure. Lacrimation was observed after 5 hours exposure to 156 ppm in one dog, and lacrimation combined with labored breathing, prostration, and decreased activity was observed in both dogs on days 3 and 4. At 233 ppm, trembling extremities, panting, rapid eye blink, and tremors were observed after 5 hours. Dogs exposed to 103 ppm exhibited no adverse effects after a single exposure, and less severe signs of neurotoxicity on day 9. A 7-hour (1 day) exposure to 103 ppm was therefore chosen as the NOAEL for this study.

Using the data supplied by Pharmaco-LSR, Inc. (1994), staff from OEHHA and the California Department of Pesticide Regulation (DPR) determined an empirically-based time extrapolation value of “n” for the modified Haber’s equation $C^n T = K$. The method employed minimizes variation in response rate with a chi-square test in a probit analysis. Using this method, values for “n” of 3.9 and 4.3 were obtained using SAS statistical software and Probit software (ICF Kaiser, Inc., 1993). However, upon review by independent scientists, this analysis was discouraged due to the limited nature of the data in forming a basis for the calculation of a value of “n”. Specifically, the number and size of distinct dose-groups was insufficient for analysis using the log-normal model. Instead, the reviewers recommended removing the more complex analysis and using the appropriate acute NOAEL from the Pharmaco-LSR study, combined with a margin of safety, as the basis for determining an REL. Thus, the data were insufficient to determine how to extrapolate across time, and it was suggested by the reviewers to avoid time extrapolation in this instance. Therefore, though the key study is based on a 7-hour observation, the resulting REL is for any acute time-frame, including a duration of 1 hour.

Level Protective Against Life-threatening Effects

Dogs exposed individually to concentrations of methyl bromide between 233 and 394 ppm (233, 314, 345, 350, or 394 ppm) did not show signs of CNS or pulmonary toxicity by day 2 of the post-exposure observation period (Pharmaco LSR, Inc, 1994). However, the observation period was inconsistent from animal to animal, lasting from 4 to 14 days. In the 4-day study, 1 of 3

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dogs was “humanely sacrificed” following one 7-hour exposure to 283 ppm methyl bromide due to “extreme clinical (CNS and pulmonary) signs.” These signs included delirium, thrashing and vocalization, tremors, traumatizing behavior (defined as slamming the head and body into cage walls), depression, ataxia, and irregular gait, rales, and a cachectic appearance. After the second day of exposure, all the dogs in the 268 ppm group and the other 2 dogs in the 283 ppm group were sacrificed due to extreme clinical signs. Dogs exposed to 156 ppm for 4 days had irregular gait, decreased activity, and labored breathing. However, the post-exposure observation time before necropsy was unspecified. Based on these results, the highest nonlethal level observed in dogs was 268 ppm for a 7-hour exposure. Dogs exposed for longer durations at this level or exposed to higher concentrations were humanely sacrificed due to severe CNS and pulmonary toxicity. The CNS toxicity was severe enough to be considered life-threatening.

A comparison of the toxicity data for mice and dogs suggests that dogs are more sensitive to methyl bromide, even though the dogs were humanely sacrificed before they actually died from exposure. The CNS and pulmonary effects at concentrations higher than the NOAEL (268 ppm) were severe enough in the dogs to be considered life-threatening effects. For identical reasons to those discussed under the REL section above, no time-extrapolation was performed. Using an uncertainty factor of 100 for interspecies and intraspecies extrapolation, the level protective against life-threatening effects is 2.7 ppm (10.5 mg/m³).

Comparison with studies in mice

By using data from an LC₅₀ study in Swiss-Webster mice (Alexeeff *et al.*, 1985), a benchmark concentration could be determined for 1-hour exposure to MeBr. Exposure concentrations ranged from 870 to 5,929 mg/m³ (224 to 1,524 ppm) and clinical signs of toxicity were observed for up to 7 days following exposure. Dose-dependent mortality was observed at the 4 highest concentrations (1/6, 4/6, 5/6, and 5/6 deaths, respectively for the 3,824, 4,696, 5,770, and 5,929 mg/m³ groups). A log-normal probit analysis (Crump, 1983) of the 1-hour mouse lethality data was employed to determine a benchmark concentration. The maximum likelihood estimate (MLE) associated with a 5% incidence of lethality was 896 ppm. The 95% lower confidence limit (LCL) on the concentration resulting in 5% lethality (BC₀₅) was 747 ppm (2,906 mg/m³). An uncertainty factor of 3 to account for interspecies variability since the BC₀₅ accounts for some degree of variability and an additional uncertainty factor of 10 to account for individual variation among people were applied to the LCL of the BC₀₅.

$$\text{level protective against life-threatening effects} = \text{BC}_{05}/(\text{UF})$$

The total uncertainty factor was 30. The final level for MeBr based on mice was therefore 747 ppm/30 = 25 ppm (97 mg/m³). However, since dogs are the most sensitive species, we recommend using the value of 2.7 ppm as the level protective against life-threatening effects. The MLE and 95% lower confidence limits (LCL) for the 1% and 5% response rates are compared below.

Response rate	MLE (ppm)	95% LCL (ppm)	Level (ppm)
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5%	896	747	25
1%	790	618	21

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ACUTE TOXICITY SUMMARY

METHYL CHLOROFORM

(1,1,1-trichloroethane, methyltrichloromethane)

CAS Registry Number: 71-55-6

I. Acute Toxicity Summary (for a 1-hour exposure)

Inhalation reference exposure level **68,000 µg/m³**
Critical effect(s) subtle impairment of the central nervous system
Hazard Index target(s) Nervous System

II. Physical and Chemical Properties (HSDB, 1994 except as noted)

<i>Molecular formula</i>	C ₂ H ₃ Cl ₃
<i>Molecular weight</i>	133.42
<i>Specific gravity</i>	1.3376 @ 20°C
<i>Boiling point</i>	74.1°C
<i>Melting point</i>	-30.4°C
<i>Vapor pressure</i>	127 mm Hg @ 25°C
<i>Flashpoint</i>	not applicable
<i>Explosive limits</i>	upper = 10.5% lower = 8.0%
<i>Solubility</i>	soluble in acetone, benzene, methanol, carbon tetrachloride
<i>Odor threshold</i>	390 ppm (geometric mean) (AIHA, 1989)
<i>Odor description</i>	sweet, chloroform-like odor
<i>Metabolites</i>	trichloroethanol, trichloroacetic acid (ACGIH, 1991)
<i>Description</i>	colorless liquid
<i>Conversion factor</i>	1 ppm = 5.46 mg/m ³ @ 25°C

III. Major Uses or Sources

Methyl chloroform is used as a solvent for adhesives and for metal degreasing (ACGIH, 1991). It is also used in the manufacture of vinylidene chloride. Methyl chloroform is also used in textile processing and dry cleaning.

IV. Acute Toxicity to Humans

Cardiac arrhythmia resulting from heightened cardiac sensitivity to epinephrine has been reported in several case reports of high acute inhalation exposures to methyl chloroform (ATSDR, 1990). There are case reports of arrhythmias persisting for two weeks or more after cessation of exposure to methyl chloroform (McLeod *et al.*, 1987).

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Twelve human volunteers were exposed to 250, 350, 450, and 550 ppm (1,400, 1,900, 2,500, and 3,000 mg/m³) methyl chloroform sequentially for 30-minutes per concentration for a total of 2 hours (Gamberale and Hultengren, 1973). Tests to measure manual dexterity, perceptual speed, and reaction time were administered during each of the four exposures. No adverse effects were observed during a 30-minute exposure to 250 ppm (1,400 mg/m³) methyl chloroform. A statistically significant reduction in task performance was observed during the subsequent 30-minute exposure to 350 ppm (1,900 mg/m³) methyl chloroform.

Equilibrium and coordination were impaired as indicated by an abnormal Romberg test and an abnormal Flannagan Aptitude Classification test (a test of coordination) in three of four human subjects exposed to 920 ppm (5,000 mg/m³) methyl chloroform for 70-75 minutes (Torkelson *et al.*, 1958). Slight eye irritation and light-headedness were reported by the subjects.

Six male volunteers were exposed to 35 and 350 ppm (190 and 1,900 mg/m³) methyl chloroform for 6 hours on two separate occasions (Nolan *et al.*, 1984). Absorption was determined to be 25% of the inhaled dose. Of the absorbed dose, 91% was excreted unchanged in the expired air. Although the odor was perceptible for the duration of the exposure, no subjective symptoms were reported by the volunteers.

Transient eye irritation was reported in 3 of 6 human volunteers exposed to a mean concentration of 500 ppm (3,000 mg/m³) methyl chloroform for 78 minutes (Stewart *et al.*, 1961).

Predisposing Conditions for Methyl Chloroform Toxicity

Medical: Those persons using epinephrine containing bronchodilators may be at greater risk of developing cardiac arrhythmias when exposed to methyl chloroform (Reprotext, 1994).

Chemical: Alcohol use concurrent with methyl chloroform exposure has been shown to potentiate methyl chloroform toxicity in rats (Reprotext, 1994).

V. Acute Toxicity to Laboratory Animals

A 1-hour LC₅₀ of 18,400 ppm (1 x 10⁵ mg/m³) methyl chloroform was reported in mice (Moser and Balster, 1985). A separate study exposed mice continuously to 13,500 ppm (7.4 x 10⁴ mg/m³) methyl chloroform (Gehring, 1968). The onset of anesthesia and death were noted as a function of time. The duration of exposure responsible for the onset of anesthetic effects in 50% of the test population (ET₅₀) is reported as 16.3 minutes. The duration of exposure lethal to 50% of the test population (LT₅₀) is reported as 595 minutes.

Heightened cardiac sensitivity to epinephrine following exposure to methyl chloroform has been observed in dogs (Rennick *et al.*, 1949). Sensitivity to methyl chloroform induced arrhythmias was not found to be greater in dogs with experimentally induced myocardial infarctions (Trochimowicz *et al.*, 1976).

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A dose-related increase in response time on a discrimination task was observed in 4 baboons exposed to 1,400, 1,800, or 2,100 ppm (7,600, 9,800, or 11,000 mg/m³) methyl chloroform for 4 hours (Geller *et al.*, 1982). No effect on response time was noted following a 4-hour exposure to 700 ppm (4,000 mg/m³) methyl chloroform.

VI. Reproductive or Developmental Toxicity

No human reproductive studies were located in the literature (Reprotext, 1994). Pregnant rats were exposed to 2,100 ppm (11,000 mg/m³) methyl chloroform 6 hours per day on days 1-20 of gestation (York *et al.*, 1982). Decreased fetal body weight and a significant increase in skeletal and soft tissue variation were observed. No lasting developmental effects were observed as measured by body weight and neurobehavioral tests during postnatal evaluation.

No significant adverse reproductive or developmental effects were observed following the exposure of pregnant rats and mice to 875 ppm (4,780 mg/m³) methyl chloroform 7 hours per day on days 6 through 15 of gestation (Schwetz *et al.*, 1975).

VII. Derivation of Acute Reference Exposure Level and Other Severity Levels (for a 1-hour exposure)

Reference Exposure Level (protective against mild adverse effects): 68,000 µg/m³

<i>Study</i>	Gamberale and Hultengren, 1973
<i>Study population</i>	twelve human volunteers
<i>Exposure method</i>	inhalation of methyl chloroform.
<i>Critical effects</i>	reduced performance in manual dexterity, perceptual speed, and reaction time
<i>LOAEL</i>	350 ppm
<i>NOAEL</i>	250 ppm
<i>Exposure duration</i>	30-minutes (see Table 12 for information on “n”)
<i>Extrapolated 1 hour concentration</i>	125 ppm (250 ¹ ppm * 0.5 h = C ¹ * 1 h)
<i>LOAEL uncertainty factor</i>	1
<i>Interspecies uncertainty factor</i>	1
<i>Intraspecies uncertainty factor</i>	10
<i>Cumulative uncertainty factor</i>	10
<i>Reference Exposure Level</i>	12.5 ppm (68 mg/m ³ ; 68,000 µg/m ³)

Level Protective Against Severe Adverse Effects

No recommendation is made due to the limitations of the database.

Level Protective Against Life-threatening Effects

NIOSH (1995) lists an IDLH of 700 ppm. An abnormal Romberg test was observed in one of three human volunteers exposed to 900 ppm (5,000 mg/m³) methyl chloroform for 20 minutes (Stewart *et al.*, 1961). Two of three subjects reported lightheadedness. In another study, equilibrium and coordination were impaired in three of four human subjects exposed to 920 ppm (5,000 mg/m³) methyl chloroform for 70-75 minutes (Torkelson *et al.*, 1958). Slight eye irritation and light-headedness were reported by the subjects. Although incoordination and loss of equilibrium are non-lethal effects, the NIOSH-IDLH uses these endpoints because such effects could be potentially lethal in the workplace. Thus, the level protective against life-threatening effects is 700 ppm. This level should be re-evaluated when better data become available.

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ACUTE TOXICITY SUMMARY

METHYL ETHYL KETONE

(2-butanone, 3-butanone, methyl acetone, ethyl methyl ketone)

CAS Registry Number: 78-93-3

I. Acute Toxicity Summary (for a 1-hour exposure)

Inhalation reference exposure level **26,000 µg/m³**
Critical effect(s) eye, nose and throat irritation in human volunteers
Hazard Index target(s) Eyes; Respiratory System

II. Physical and Chemical Properties (HSDB, 1993 except as noted)

<i>Molecular formula</i>	C ₄ H ₈ O
<i>Molecular weight</i>	72.10
<i>Specific gravity</i>	0.805 @ 20°C
<i>Boiling point</i>	79.6°C
<i>Melting point</i>	-86.3°C
<i>Vapor pressure</i>	77.5 mm Hg @ 20°C
<i>Flashpoint</i>	-9°C (closed cup)
<i>Explosive limits</i>	1.4% - 11.4%
<i>Solubility</i>	soluble in alcohol, ether, acetone benzene and water
<i>Odor threshold</i>	16 ppm (geometric mean) range = 2-85 ppm (AIHA, 1989)
<i>Description</i>	colorless, sweet, sharp odor (AIHA, 1989)
<i>Metabolites</i>	2-butanol, 2,3-butanediol (NIOSH, 1978)
<i>Conversion factor</i>	1 ppm = 2.94 mg/m ³ @ 25°C

III. Major Uses or Sources

Methyl ethyl ketone (MEK) is a solvent often found in mixtures with acetone, ethyl acetate, n-hexane, toluene, or alcohols. MEK has applications in the surface coating industry and in the dewaxing of lubricating oils. MEK is used in the manufacture of colorless synthetic resins, artificial leather, rubbers, lacquers, varnishes, and glues.

IV. Acute Toxicity to Humans

Symptoms of acute MEK exposure include irritation of the eyes, nose, and throat (HSDB, 1993). In human case studies, inhalation of MEK for its euphoric effect has also resulted in slight excitement, followed by somnolence or unconsciousness at higher concentrations (Glatt, 1977). Humans occupationally exposed to MEK have also complained of mild neurologic effects including headaches, dizziness, and nausea (Markey, 1991). However, these exposures were to multiple solvents. Human volunteers exposed to pure MEK did not report these symptoms.

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In a chamber study, ten human subjects exposed to 100 ppm (300 mg/m³) MEK for 3 to 5 minutes experienced mild throat and nose irritation (Nelson *et al.*, 1943). Mild eye irritation was reported by subjects exposed to 200 ppm (600 mg/m³) for the same duration.

Another chamber study exposed 4 subjects to an increasing concentration of MEK (90 to 270 ppm) over a period of 2 hours (Nakaaki, 1974). The average concentration was 150 ppm for the 2-hour exposure. A relatively strong odor was noted at 90 ppm, upon entry into the room. The odor was described as unpleasant and irritating, but apparently was never offensive enough for the subjects to consider leaving the room early. Irritation of eyes, nose, and throat became more severe as the concentration increased, which eventually led to lacrimation and sneezing sometime during the exposure.

Volunteer subjects were exposed to 200 ppm MEK for 5 minutes followed by 4 hours air or 200 ppm MEK for a total of 4 hours (Dick *et al.*, 1992). Neurobehavioral tests were performed at 2 and 4 hours of exposure and 90 minutes post-exposure. No consistent, statistically significant, neurobehavioral effects were observed. Data on sensory and irritant effects show a significant increase only in perception of strong odor. Therefore, this study identifies a 2-hour free-standing NOAEL of 200 ppm.

In an earlier chamber study by the same research group, human subjects exposed to 200 ppm (600 mg/m³) MEK for 4 hours showed no significant effects as measured by psychomotor, sensorimotor, neurophysiological, and psychological tests (Dick *et al.*, 1989). Effects of exposure on mucous membrane irritation or symptoms such as headache or nausea were not examined in this study.

Predisposing Conditions for Methyl Ethyl Ketone Toxicity

Medical: Persons with eye or neurologic conditions may be more sensitive to the toxic effects of MEK (Reprotext, 1993).

Chemical: Persons exposed to isobutanol may be more sensitive to MEK exposure because MEK is a metabolite of isobutanol (Reprotext, 1993). MEK can potentiate the neurotoxic effects of n-hexane and methyl butyl ketone. MEK may also potentiate the hepatotoxic effects of carbon tetrachloride.

V. Acute Toxicity to Laboratory Animals

The 5-minute RD₅₀ in mice for MEK is reported as 10,745 ppm (32,000 mg/m³) (De Ceaurriz, 1981). Pozzani *et al.* (1959) determined an 8-hour LC₅₀ in rats to be 23.5 mg/l (7993 ppm). A 2-hour LC₅₀ of 40,000 ppm in mice has been reported (Izmerov *et al.*, 1982).

In a time-to-incapacitation and time-to-death study by Patty *et al.* (1935), exposure to 10,000 ppm of MEK produced incoordination in guinea pigs 90 minutes into exposure. Unconsciousness occurred in all animals between 240 and 280 minutes into exposure. At 33,000

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ppm, incoordination occurred 18-30 minutes into exposure and unconsciousness occurred 48-90 minutes into exposure. At 100,000 ppm, incoordination was observed in 3-5 minutes and narcosis in 10-11 minutes. All guinea pigs (6 animals per group) exposed to 33,000 and 100,000 ppm MEK died 200-260 and 45-55 minutes into exposure, respectively. However, lower concentrations (3,300 and 10,000 ppm) did not cause any deaths during exposures up to 13.5 hours. There were no delayed deaths in the guinea pigs that survived exposure (i.e., all deaths occurred during exposure). Death was due to narcosis; lung edema was cited as secondary to the narcosis. Congestion of liver, kidneys and other organs were also noted at lethal concentrations of MEK.

VI. Reproductive or Developmental Toxicity

No studies on the reproductive effects of MEK in humans were available. An increase in the incidence of congenital central nervous system defects was observed among women exposed to a mixture of organic solvents during the first trimester of pregnancy; but MEK alone was not implicated (Holmberg, 1979).

Pregnant rats were exposed to 0, 1,000, or 3,000 ppm MEK for 7 hours per day on days 6-15 of gestation (Schwetz *et al.*, 1974). Statistically significant reductions in fetal body weight and in crown-rump length were observed in the 1,000 ppm group but not in the 3,000 ppm group. The incidence of skeletal anomalies was 95% (21 of 23 litters affected) in the 1,000 ppm group. In the 3,000 ppm exposure group, 4 of 21 litters exhibited gross anomalies (two brachygnathous and two acaudate fetuses) which were significantly elevated as compared to controls. A statistically significant increased incidence in delayed sternebral ossification was also observed in the 3,000 ppm exposure group as was a statistically significant increase in total soft tissue anomalies. No signs of maternal toxicity were observed.

To confirm the findings by Schwetz *et al.* (1974), the same research group conducted a similar, but more extensive, developmental study in which pregnant rats were exposed to 0, 400, 1,000, or 3,000 ppm MEK for 7 hours per day on gestational days 6-15 (Deacon *et al.*, 1981). The dams exhibited decreased weight gain and increased water consumption during exposure. Two types of minor skeletal malformations were observed in litters of rats exposed to 3,000 ppm MEK, which indicated slight fetotoxicity at this level. No adverse effects were observed in either generation following exposure to 400 or 1,000 ppm. Taken together, the authors of the 2 studies (Schwetz *et al.* 1974; Deacon *et al.*, 1981) concluded that the LOAEL for developmental toxicity in rats was 3,000 ppm.

A later study (Schwetz *et al.*, 1991) exposed pregnant mice to 0, 400, 1,000, or 3,000 ppm MEK 7 hours per day on days 6-15 of gestation. Relative liver and kidney weights were statistically significantly increased in dams exposed to 3,000 ppm MEK. Decreased fetal weight was also observed in this exposure group; significant decreases were observed in the male fetuses only. A statistically significant trend in the incidence of misaligned sternebrae (a developmental variation) was observed. The authors concluded that the effects observed in mice were similar and not contradictory to those observed in rats.

VII. Derivation of Acute Reference Exposure Level and Other Severity Levels (for a 1-hour exposure)

Reference Exposure Level (protective against mild adverse effects): 26,000 µg/m³

<i>Study</i>	Nakaaki (1974)
<i>Study population</i>	4 healthy human volunteers
<i>Exposure methods</i>	inhalation chamber
<i>Critical effects</i>	subjective reports of eye, nose, and throat irritation; lacrimation and sneezing
<i>LOAEL</i>	270 ppm
<i>NOAEL</i>	not reported
<i>Exposure duration</i>	2 hours
<i>Extrapolated 1-hour concentration</i>	270 ppm (not extrapolated; see below)
<i>LOAEL uncertainty factor</i>	3 (mild irritation)
<i>Interspecies uncertainty factor</i>	1
<i>Intraspecies uncertainty factor</i>	10
<i>Cumulative uncertainty factor</i>	30
<i>Reference Exposure Level</i>	9 ppm (26 mg/m ³ ; 26,000 µg/m ³)

Nakaaki (1974) reported that eye, nose, and throat irritation was produced in subjects exposed to an increasing concentration of MEK (90 to 270 ppm) over a 2-hour period. Lacrimation and sneezing also occurred during exposure but the precise duration and concentration required to produce these effects were unspecified. Because of the uncertainties in determining a precise duration of exposure leading to onset of symptoms, no time-adjustment was used.

In another study, no consistent significant neurobehavioral effects were observed in human volunteers exposed to 0 or 200 ppm MEK for a total of 4 hours (Dick *et al.*, 1992). Neurobehavioral tests were administered after 2 and 4 hours of exposure and 90-minutes post-exposure. This study identifies a 4-hour free-standing NOAEL for irritation and neurobehavioral effects of 200 ppm. Personal communications with the principal author indicated that this study should not be used, since it was not designed to address irritation thresholds. In addition, the result from the Dick *et al.* (1992) study contradicts the findings of Nelson *et al.* (1943) which reported a 3-minute LOAEL for irritation of 200 ppm. However, the Dick *et al.* (1992) study contained more accurate measurements of MEK, a longer duration of exposure, and a more sophisticated evaluation of irritation than Nelson *et al.* (1943). Control incidences were very high in the Dick *et al.* study and may preclude the determination of a nuisance effect due to MEK.

While it is apparent that the subjects in the Nakaaki study experienced mucous membrane irritation from MEK during exposure, the nature of the study complicates the determination of the NOAEL and LOAEL for irritant effects. It is unclear from the study whether the lowest concentrations of MEK, starting at 90 ppm, resulted in anything other than odor perception. However, by the end of the 2-hour exposure it was clear that the subjects were experiencing mucous membrane irritation. Based on the known concentration of MEK at the end of exposure

(270 ppm), it can be reliably determined that a 2-hour exposure to this concentration will produce mild irritant effects. Therefore, the LOAEL for the Nakaaki study is 270 ppm while the NOAEL is undetermined.

Level Protective Against Severe Adverse Effects

Based on the findings of the three developmental toxicity studies (Schwetz *et al.*, 1974; Deacon *et al.*, 1981; Schwetz *et al.*, 1991), the NOAEL and LOAEL for maternal and fetal toxicity in rats and mice were determined to be 1,000 and 3,000 ppm, respectively. Maternal toxicity consisted of decreased weight gain and increased water consumption in rats, and increased relative liver and kidney weights in mice. Fetal toxicity consisted of increased incidences of gross and skeletal anomalies and delayed sternebral ossification in rats, and decreased fetal weight in mice. The highest actual time-weighted-average NOAEL among the three studies was 1,126 ppm (Schwetz *et al.*, 1974). The 7-hour per day exposure concentration was extrapolated to an equivalent 1-hour exposure concentration using the equation $C^n T = K$, where $n = 2$. An uncertainty factor of 10 was applied to the adjusted NOAEL to account for interspecies differences. An additional uncertainty factor of 10 was applied to account for sensitive individuals, which results in a level protective against severe adverse effects of 30 ppm (88 mg/m³) for 1-hour exposure to MEK.

Level Protective Against Life-threatening Effects

Human exposure data relevant to a life-threatening level determination for MEK could not be found in the literature. Therefore, LC₅₀ studies in experimental animals provided the best source for a life-threatening effect level in humans. Only one citation (LaBelle and Brieger, 1955) was located in the literature that contained sufficient mortality data from which to estimate an LC₅₀, MLE₀₅ (maximum likelihood estimate, corresponding to 5% mortality), BC₀₅, and BC₀₁ (benchmark dose at the lower 95% confidence interval expected to produce a response rate of 5% and 1%, respectively) by log-normal analysis (Crump, 1984; Crump and Howe, 1983). The results are shown below in Table 1. Rats (4 to 8 per group) were exposed for 4 hours by inhalation to concentrations of MEK ranging from 7,850 to 20,200 ppm. Acute toxicity resulted in narcosis with most deaths occurring immediately (i.e., occurring during exposure).

Table 1. Rat Lethality Benchmark Dose Determination from LaBelle and Brieger (1955) for 4-hour Methyl Ethyl Ketone Exposure.

LC ₅₀ (ppm)	MLE ₀₅ (ppm)	BC ₀₅ (ppm)	BC ₀₁ (ppm)	BC ₀₅ (ppm) Adjusted to 1 hour
11,600	8,559	7,062	5,790	14,124

Based on log-normal probit analysis of the lethality data by LaBelle and Brieger (1955), the BC₀₅ was determined to be 7,062 ppm (see Table 1). The BC₀₅ was then adjusted to 1 hour exposure using a modification of Haber's equation ($C^n * T = K$), where the exponent $n = 2$ (for extrapolation of exposure durations greater than 1 hour to 1 hour exposure). The resulting concentration at the BC₀₅ for 1 hour exposure was 14,124 ppm. An uncertainty factor of 3 was

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applied to account for interspecies differences because the BC₀₅ likely accounts for some degree of variability and an uncertainty factor of 10 was applied to account for the increased susceptibility of sensitive human individuals. The total UF was 30.

$$\text{level protective against life-threatening effects} = \text{BC}_{05}/(\text{UF})$$

Incorporation of these factors results in a level protective against life-threatening effects of 471 ppm (1,385 mg/m³) for 1 -hour exposure to MEK.

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ACUTE TOXICITY SUMMARY

METHYLENE CHLORIDE

(dichloromethane, methylene dichloride)

CAS Registry Number: 75-09-2

I. Acute Toxicity Summary (for a 1-hour exposure)

Inhalation reference exposure level **83,000 µg/m³**
Critical effect(s) subtle impairment of the central nervous system
Hazard Index target(s) Nervous System

II. Physical and Chemical Properties (HSDB, 1994 except as noted)

<i>Molecular formula</i>	CH ₂ Cl ₂
<i>Molecular weight</i>	84.93
<i>Specific gravity</i>	1.32 @ 20°C (ACGIH, 1991)
<i>Boiling point</i>	39.75°C
<i>Melting point</i>	-95.1°C (ACGIH, 1991)
<i>Vapor pressure</i>	400 mm Hg @ 24.1°C
<i>Flashpoint</i>	unknown
<i>Explosive limits</i>	upper = 66.4% lower = 15.5%
<i>Solubility</i>	miscible with most organic solvents, slightly soluble in water (ACGIH, 1991)
<i>Odor threshold</i>	160 ppm (geometric mean) (AIHA, 1989)
<i>Odor description</i>	sweet, pleasant, chloroform-like odor
<i>Metabolites</i>	carbon monoxide (Reprotext, 1994)
<i>Description</i>	colorless liquid
<i>Conversion factor</i>	1 ppm = 3.47 mg/m ³ @ 25°C

III. Major Uses or Sources

Methylene chloride (MC) is used in paint and varnish remover, in aerosols as a cosolvent or vapor pressure depressant, and in solvent degreasing and metal cleaning. It is also used in plastics processing and in extraction of fats and oils from food products.

IV. Acute Toxicity to Humans

Frequently reported effects following acute inhalation exposure to MC include CNS depression at concentrations of 1,000 ppm (3,500 mg/m³) or more and increased blood carboxyhemoglobin (COHb) content at lower concentrations due to metabolism of MC to carbon monoxide (Stewart *et al.*, 1972).

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Twelve healthy adult volunteers exposed to 195 ppm (680 mg/m³) MC for 4 hours exhibited impaired performance on dual-task and auditory vigilance tests (Putz *et al.*, 1976). The dual task test required sustained attention divided between two sources of visual stimuli, and the auditory vigilance test required subjects to report relative auditory signal intensity. Statistically significant decrements in performance were first noted after 90 minutes of exposure; increasing decrements in performance were observed with prolonged exposure. These effects would not impair practical performance and thus are not considered adverse. Blood COHb levels rose from 1.35% pre-exposure to 5.1% post-exposure. The study did not address subjective symptoms such as headache, nausea, or irritation of the nose and throat.

In another study, blood COHb levels were significantly elevated (approximately 1% pre-exposure to a mean of 10.1% one hour following cessation of exposure) in three subjects exposed to a mean airborne concentration of 986 ppm (3,400 mg/m³) MC for 2 hours (Stewart *et al.*, 1972). All three subjects exhibited an altered visual evoked response, as compared to pre-exposure measurements; one of the subjects reported mild light-headedness and another reported speech difficulties.

In one case report, use of a MC-based tile remover in a poorly ventilated room resulted in acute renal tubular necrosis and elevated liver enzymes levels indicative of possible hepatotoxicity (Miller *et al.*, 1985). Although COHb levels were not measured, in the opinion of the authors, kidney biopsy findings indicated that mitochondrial anoxic damage may have been caused by substantially elevated COHb levels. Buie *et al.* (1986) described a case of diffuse pulmonary edema, pleural effusions, and hypoxia in a 34-year-old man following the use of furniture stripper containing MC.

Although animal studies have shown COHb-induced cardiovascular effects following MC exposure (Aviado *et al.*, 1977), no such reports exist for humans. Studies of men with coronary artery disease and exercise-induced angina report a decrease in time to onset of exercise-induced angina following exposure to carbon monoxide (CO) at concentrations sufficient to result in blood COHb levels of about 2% (Kleinman *et al.*, 1989; Allred *et al.*, 1989). From a physiologically based pharmacokinetic model of MC and CO it was estimated that a 1-hour exposure to 340 ppm (1,200 mg/m³) MC at a ventilation rate of 9 liters/min would result in a peak blood COHb level of 2% (Andersen *et al.*, 1991; Reitz, 1994). The California Ambient Air Quality Standard for CO is based on a blood COHb level of 2% (CARB, 1982).

Predisposing Conditions for Methylene Chloride Toxicity

Medical: Pregnant women and fetuses may be at increased risk for adverse effects following methylene chloride exposure (Reprotext, 1994).

Chemical: Tobacco smokers typically have chronically elevated COHb levels and may be able to tolerate higher levels of exposure.

V. Acute Toxicity to Laboratory Animals

The 20-minute LC₅₀ for mice is 27,000 ppm (94,000 mg/m³) MC (Aviado *et al.*, 1977). The 6-hour LC₅₀ for guinea pigs is 12,000 ppm (42,000 mg/m³) MC (Balmer *et al.*, 1976).

Hepatocyte lesions were observed at necropsy in mice exposed continuously for 12 hours to 5,000 ppm (20,000 mg/m³) MC (Weinstein *et al.*, 1972). Rats exposed for 24-hours to 1,000 ppm MC exhibited significant decreases in duration of REM sleep compared to pre-exposure measurements (Fodor and Winneke, 1971). Non-significant deviations from pre-exposure sleep patterns were observed in rats exposed for 24 hours to 500 ppm (2,000 mg/m³) MC.

Mortality in mice challenged with an aerosolized streptococcal infection following exposure to 100 ppm (350 mg/m³) MC for a single 3-hour period was significantly greater than in unexposed mice (Aranyi *et al.*, 1986). Significantly reduced pulmonary bactericidal activity, thought to be due to impaired macrophage function, was observed in mice following a 3-hour exposure to 100 ppm MC. No such effects were observed in mice exposed to 50 ppm (170 mg/m³) MC for a single 3-hour period.

Persistent myocardial arrhythmia and decreased cardiac output were observed in anesthetized open-chested dogs following a 5-minute inhalation exposure to 87 mg/m³ (25 ppm) MC (Aviado *et al.*, 1977).

VI. Reproductive or Developmental Toxicity

An increased odds ratio (OR) of borderline significance (OR 2.3; 95% CI = 1.0-5.7) for spontaneous abortion was reported among female pharmaceutical workers exposed to MC (Taskinen *et al.*, 1986). The range of exposure concentration was not reported.

Increased liver weights were noted in female rats exposed to 4,500 ppm (16,000 mg/m³) MC 6 hours per day for 3 weeks prior to mating and during the first 17 days of gestation (Hardin and Manson, 1980). Blood COHb levels were elevated to 7.2-10.1% (baseline measurements were not reported). Fetuses from exposed rats exhibited significantly decreased birth weights compared to controls, but no significant increases in soft tissue or skeletal anomalies were observed.

In rats and mice exposed for 7 hours per day on days 6-15 of gestation to 1,250 ppm (4,300 mg/m³) MC, a significant increase in maternal blood COHb levels was observed after the third 7-hour exposure (Schwetz *et al.*, 1975). The incidence of delayed sternebral ossification was significantly greater in exposed rat pups compared to controls. Of note, control rat pups exhibited a greater number of litters with delayed ossification of lumbar ribs or spurs than exposed rats. In exposed mice, a significant number of litters contained pups with a single extra center of ossification in the sternum. The previously mentioned effects reflect developmental variation and are not adverse effects. No teratogenic effects were observed.

**VII. Derivation of Acute Reference Exposure Level and Other Severity Levels
(for a 1-hour exposure)**

Reference Exposure Level (protective against mild adverse effects): 24 ppm (83,000 µg/m³)

<i>Study</i>	Putz <i>et al.</i> , 1976
<i>Study population</i>	twelve healthy adult volunteers
<i>Exposure method</i>	inhalation of 195 ppm methylene chloride
<i>Critical effects</i>	impaired performance on dual-task and auditory vigilance tests
<i>LOAEL</i>	not observed
<i>NOAEL (LOEL)</i>	195 ppm
<i>Exposure duration</i>	90 minutes
<i>Extrapolated 1 hour concentration</i>	240 ppm (195 ² ppm* 1.5 h = C ² * 1 h) (see Table 12 for information on “n”)
<i>LOAEL uncertainty factor</i>	1
<i>Interspecies uncertainty factor</i>	1
<i>Intraspecies uncertainty factor</i>	10
<i>Cumulative uncertainty factor</i>	10
<i>Reference Exposure Level</i>	24 ppm (83 mg/m ³ ; 83,000 µg/m ³)

In twelve healthy adult volunteers exposed to 195 ppm (680 mg/m³) MC (Putz *et al.*, 1976), significant decrements in performance were first noted after 90 minutes of exposure with increasing decrements in performance observed after prolonged exposure. Blood COHb levels rose from 1.35% pre-exposure to 5.1% post-exposure. No subjective symptoms, such as headache, nausea, or irritation of the nose and throat were reported. Because the performance of most tasks would not be affected at this level and the effects observed would not be considered adverse, the 90-minute exposure to 195 ppm MC is a LOEL. The LOEL is equivalent to a NOAEL for the purpose of developing an REL. An uncertainty factor of 10 was applied to the NOAEL to account for individual variability in response. An equivalent 60-minute exposure was estimated from the 90-minute exposure using the equation $C^n * T = K$, where $n = 2$. Cardiac effects resulting from COHb formation following MC exposure, such as those observed in sensitive human populations following carbon monoxide exposure (Kleinman *et al.*, 1989; Allred *et al.*, 1989), were considered as a possible endpoint of MC toxicity not yet identified in the human toxicological literature. A 2% COHb level results in decreased time to onset of exercise-induced angina in coronary artery disease patients. Based on an available model of blood COHb formation following MC exposure (Andersen *et al.*, 1991), exposure to MC at a concentration of 340 ppm (1200 mg/m³) for 1 hour would result in a blood COHb level of 2%. This is higher than the exposure concentration resulting in the behavioral effects reported by Putz *et al.* (1976). Since angina is considered a severe adverse effect, this latter concentration should be considered in the derivation of a severe adverse effect level.

Level Protective Against Severe Adverse Effects

No recommendation is made due to the limitations of the database.

Level Protective Against Life-threatening Effects

No recommendation is made due to the limitations of the database.

NIOSH (1995) lists a (revised) IDLH for methylene chloride of 2,300 ppm. However, NIOSH notes one report that a 10-minute exposure at 2,330 ppm produced vertigo and also quotes another reliable source which reported no feeling of dizziness after 1 hour of exposure to 2,300 ppm. NIOSH further states that 2 other authors report that no dizziness, but slight nausea, is caused by exposure to 2,300 ppm for 1 hour and that methylene chloride is not lethal at 25,000 ppm, but the citation gives only the authors' names. Thus it was not possible to refer to the original articles.

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ACUTE TOXICITY SUMMARY

NICKEL AND NICKEL COMPOUNDS

Molecular Formula	Molecular Weight	Synonyms	CAS Registry Number
Ni	59	elemental nickel	7440-02-0
NiO	74.69	nickel oxide	1313-99-1
NiCl ₂	129.6	nickel chloride nickel dichloride	7718-54-9
NiSO ₄	154.75	nickel sulfate nickelous sulfate	7786-81-4
NiCO ₃	118.7	nickel carbonate carbonic acid nickel salt	3333-67-3
Ni ₃ S ₂	240.19	nickel subsulfide trinickel disulfide heazlewoodite	12035-72-2

I. Acute Toxicity Summary (for a 1-hour exposure)

Inhalation reference exposure level **11 µg Ni/m³**
Critical effect(s) small decrements in airway function tests, especially in asthmatics
Hazard Index target(s) Respiratory System; Immune System

II. Physical and Chemical Properties (HSDB, 1994 except as noted)

Specific gravity 8.9 (Ni)
Boiling point 2730°C (Ni)
Melting point 1455°C (Ni); 1030°C (NiCl₂)
Vapor pressure not applicable
Flashpoint not applicable
Explosive limits Nickel dust or powder is flammable (CDTSC, 1985).
Solubility Elemental nickel, nickel subsulfide, and nickel oxide are insoluble in water, but are soluble in dilute nitric, hydrochloric, and sulfuric acids. The chloride and sulfate forms of nickel are water soluble.
Odor threshold 0.21-21 mg/m³
Odor description musty odor (Ruth, 1986)
Metabolites Ni²⁺
Description Ni metal: silvery metal
 NiO: black crystals
 NiCl₂: yellow deliquescent crystals (USEPA, 1985)
Conversion factor not applicable for fumes and dusts

III. Major Uses or Sources of Exposure

The most common airborne exposures to nickel compounds are to insoluble nickel compounds such as elemental nickel, nickel sulfide, and the nickel oxides from dusts and fumes. Contributions to nickel in the ambient air are made by combustion of fossil fuels, nickel plating, and other metallurgical processes. The most common oxidation state of nickel is the divalent (Ni^{2+}) form (USEPA, 1985). Elemental nickel is a malleable, silvery-white metal that is highly resistant to strong alkali. Because of its corrosion resistance, nickel is used in the production of stainless steel, permanent magnets, and other alloys that require resistance to extremes of temperature or stress (USEPA, 1985). Nickel is also used in electroplating baths, batteries, textile dyes, and catalysts (USEPA, 1985). Nickel dust or powder is flammable (CDTSC, 1985).

IV. Acute Toxicity to Humans

Soluble nickel compounds appear to be the greatest concern for acute health effects. The soluble forms of nickel are absorbed as Ni^{2+} (Coogan *et al.*, 1989). Divalent nickel competes with copper for binding to serum albumin and is systemically transported in this way (Sunderman, 1986). The kidneys, lungs, and placenta are the principal organs for systemic accumulation of nickel (Sunderman, 1986). In contrast to the long half-life of the insoluble forms of nickel in the nasal mucosa, the elimination half-life of Ni^{2+} in the plasma is 1-2 days in mice (Nieboer *et al.*, 1988).

Nickel fumes from high nickel alloy welding (mean concentration = $440 \mu\text{g Ni/m}^3$, range = $70\text{-}1,100 \mu\text{g Ni/m}^3$) caused complaints of upper respiratory irritation and headache in welders exposed for 4 weeks (Akesson and Skerfving, 1985).

A group of 7 metal plating workers with occupational asthma was evaluated for atopy and pulmonary function challenge in response to inhalational challenge with nickel and other metals (Cirla *et al.*, 1985). Three of the asthmatics tested positive for the presence of nickel-specific IgE antibodies. Positive reactions to skin testing with nickel were found in 3 of the asthmatic workers who also had dermatitis. Six out of the 7 asthmatics exhibited significantly decreased FEV_1 ($> 15\%$) when exposed to 0.3 mg/m^3 nickel sulfate for 30 minutes. Control challenges with other metal salts did not reveal similar deficits in FEV_1 .

Exposure to nickel in occupational settings causes dermatitis and asthma in some individuals with repeated exposures (Davies 1986). The nickel ion, bound to proteins in the dermis, acts as an antigen eliciting a type IV (delayed type) hypersensitivity response. This response, mediated by T-lymphocytes, causes dermal sensitivity. This hypersensitivity can be diagnosed by patch testing (Menne and Maibach, 1989).

Predisposing Conditions for Nickel Toxicity

Medical: Asthmatics or atopic individuals may be especially at risk for developing nickel-induced asthma (Cirla *et al.*, 1984). Cigarette smokers may receive greater nickel exposure, since cigarette smoke contains nickel (Reprotext, 1993). Additionally,

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a review of the literature on nickel toxicity showed that Ni²⁺ causes vasoconstriction in animals and humans which may potentiate the effects of a primary ischemic lesion in the cardiovascular system (USEPA, 1985).

Chemical: In rats, rabbits, and dogs, 1 mg/kg nickel chloride antagonizes the cardiac arrhythmia induced by digoxin by competing with calcium at cardiac membrane sites (Prasad *et al.*, 1980). The implications of this effect for persons with congestive heart failure have not been investigated.

V. Acute Toxicity to Laboratory Animals

Subacute (12-day) inhalation exposures (5 days/week, 6 hours/day) of 10 mice to nickel, as 10 mg Ni₃S₂/m³, caused 100% mortality (Benson *et al.*, 1987). Two of 10 rats also died from this exposure. Although no effect was seen on natural killer cell activity in these animals, lesions in the nasal and lung epithelium and in bronchial lymph node were observed. Pathology revealed emphysematous changes in the lungs of rats exposed to 5 or 10 mg Ni₃S₂/m³, and fibrosis in mice exposed to 5 mg Ni₃S₂/m³. Atrophy of lymphoid tissues, including spleen, thymus, and bronchial lymph nodes, was observed in mice and rats exposed to 5 or 10 mg Ni₃S₂/m³.

Studies by Graham *et al.* (1975, 1978) indicate that the immune system is the most sensitive target for acute nickel toxicity. Mice (female, n = 14-29 per group) exposed by inhalation to 250 µg Ni/m³ as NiCl₂ for 2 hours showed a significant decrease in splenic antibody-forming cells following a challenge with a T-lymphocyte dependent antigen (Graham *et al.*, 1978). A similar suppression in antibody-forming cells was seen in mice exposed intramuscularly to 9.26 µg Ni/g body weight as NiCl₂ (Graham *et al.*, 1975). Haley *et al.* (1987) showed that male cynomolgus monkeys, exposed to intratracheal Ni₃S₂ at a delivered dose of 0.06 µmol Ni/g lung tissue, had impaired pulmonary macrophage phagocytic function and increased natural killer cell activity. Mice also exhibited impairment of pulmonary macrophage function in addition to decreases in antibody-forming spleen cells with inhalation exposure to Ni₃S₂ or NiO (Haley *et al.*, 1990). Natural killer cell activity measured by splenic cytotoxic activity to tumor cells as well as by clearance of melanoma tumors *in vivo* was suppressed in two strains of mice exposed to intramuscular injections of 18.3 mg Ni/kg as NiCl₂ as compared to controls (Smialowicz *et al.*, 1985). The mechanism of nickel-induced immunotoxicity was not demonstrated in the above reports.

A host-resistance study by Adkins *et al.* (1979) showed that mice (80-120 per group) exposed to inhaled soluble nickel for 2 hours in the form of NiCl₂ or NiSO₄ were significantly more susceptible to mortality from streptococcal bacterial infection. The concentrations of nickel that showed these effects were 499 µg Ni/m³ (NiCl₂) and 455 µg Ni/m³ (NiSO₄). No significant change in mortality was seen with exposure to 369 µg Ni/m³ as NiCl₂.

Nickel distributes preferentially to the lungs and kidneys following intratracheal administration of NiCl₂ to rats (Carvalho and Ziemer, 1982). The electrophilic Ni²⁺ ion is reported to be the causative agent of nephrotoxicity in rats; it binds to intracellular nucleophiles in kidney tissue

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such as guanine, adenine, and glutathione 2 hours following intraperitoneal exposure to 10 mg Ni/kg as NiCO₃ (Ciccarelli and Wetterhahn, 1984).

Subcutaneous injections of 10 mg/kg nickel chloride have been shown to increase prolactin secretion in rats 1 day following administration (Clemons and Garcia, 1981). However, an earlier study showed that prolactin secretion in rats is specifically inhibited for 30 minutes following intravenous exposure to 100 µg Ni²⁺ as NiCl₂ (LaBella *et al.*, 1973).

VI. Reproductive or Developmental Toxicity

There is insufficient evidence for developmental or reproductive toxicity of nickel in humans. However, there are numerous reports of teratogenicity and other reproductive effects in laboratory animals exposed to nickel. Mice exposed during pregnancy to NiCl₂ by intraperitoneal injection bore offspring with numerous fetal malformations and skeletal anomalies (Lu *et al.*, 1979). In addition there were increased fetal resorption rates and decreased fetal weights (Lu *et al.*, 1979). Woollam (1972) showed that nickel acetate, when injected intraperitoneally into pregnant hamsters, caused significant fetal mortality at 25 mg/kg.

Intravenous exposure of pregnant rats to 11 mg Ni/kg caused increased fetal mortality and a 16% incidence of fetal malformations including anophthalmia, cystic lungs, and hydronephrosis (Sunderman *et al.*, 1983). Temporary hyperglycemia was seen in pregnant rats exposed intraperitoneally to NiCl₂ at 4 mg/kg (Mas *et al.*, 1985). The authors proposed that this hyperglycemia was a mechanism for teratogenicity.

Male rat reproductive toxicity (damage to epididymal tubules and abnormal spermatozoa) was observed followed a single subcutaneous dose of 5 mg/m³ mmol Ni/kg as Ni₃S₂ (Hoey, 1966). Benson *et al.* (1987) showed that mice and rats exposed to 5 or 10 mg Ni₃S₂/m³ displayed degeneration of testicular germinal epithelium after 12 days exposure (6 hours/day, 5 days/week).

VII. Derivation of Acute Reference Exposure Level and Other Severity Levels (for a 1-hour exposure)

Reference Exposure Level (protective against mild adverse effects): 3.3 µg Ni/m³

<i>Study</i>	Cirla <i>et al.</i> , 1985
<i>Study population</i>	7 volunteer metal plating workers with occupational asthma
<i>Exposure method</i>	inhalation of 0.3 mg/m ³ NiSO ₄ ·6H ₂ O (67 µg Ni/m ³)
<i>Critical effects</i>	significant (> 15%) decrease in FEV ₁
<i>LOAEL</i>	67 µg Ni/m ³
<i>NOAEL</i>	not observed
<i>Exposure duration</i>	30 minutes
<i>Extrapolated 1 hour concentration</i>	33 µg Ni/m ³ ((67 µg Ni/m ³) ¹ * 0.5 h = C ¹ * 1 h) (see Table 12 for information on “n”)
<i>LOAEL uncertainty factor</i>	3

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<i>Interspecies uncertainty factor</i>	1
<i>Intraspecies uncertainty factor</i>	1
<i>Cumulative uncertainty factor</i>	3
<i>Reference Exposure Level</i>	11 µg Ni/m ³

For comparison with the immunotoxicity of nickel, an extrapolation from the 2-hour NOAEL in mice of 110 µg/m³ (Graham *et al.*, 1978) to that of a 1-hour exposure was made using the time adjustment formula $C^n * T = K$, where $n = 2$. This yielded a 1 hour value of 160 µg/m³. Application of an uncertainty factor of 100 to account for interspecies and individual variation would result in a 1-hour REL of 1.6 µg Ni/m³. The Cirila *et al.* (1985) study was selected as the basis for the REL since the study group included sensitive humans (asthmatics), thus reducing uncertainty for this effect. This value should be reevaluated if human immunotoxicity data become available.

Level Protective Against Severe Adverse Effects

No recommendation is made due to the limitations of the database.

Level Protective Against Life-threatening Effects

No recommendation is made due to the limitations of the database.

NIOSH (1995) lists a (revised) IDLH of 10 mg Ni/m³. It is based on acute inhalation toxicity data in mice, reported in a progress report on the toxicity of chemical warfare agents during World War II. An LC_{Lo} of 530 mg Ni/m³ was determined for a 10 minute exposure. This was time-adjusted to an equivalent 30 minute exposure of 92 mg Ni/m³ and divided by 10 to obtain a value of 9.2 mg Ni/m³, which was then rounded to 10 mg Ni/m³.

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ACUTE TOXICITY SUMMARY

NITRIC ACID

(*aqua fortis*, *hydrogen nitrate*)

CAS Registry Number: 7697-37-2

I. Acute Toxicity Summary (for a 1-hour exposure)

<i>Inhalation reference exposure level</i>	86 µg/m³
<i>Critical effect(s)</i>	small increases in airway resistance, especially in asthmatics
<i>Hazard Index target(s)</i>	Respiratory System

II. Physical and Chemical Properties (HSDB, 1993 except as noted)

<i>Molecular formula</i>	HNO ₃
<i>Molecular weight</i>	63.02
<i>Specific gravity</i>	1.50269 @ 25°C
<i>Boiling point</i>	83° C with decomposition
<i>Melting point</i>	-41.59°C
<i>Vapor pressure</i>	62 mm Hg @ 25°C
<i>Flashpoint</i>	not applicable
<i>Explosive limits</i>	not applicable
<i>Solubility</i>	miscible in water
<i>Odor threshold</i>	0.27 ppm (AIHA, 1989)
<i>Odor description</i>	choking odor
<i>Metabolites</i>	oxides of nitrogen, particularly NO ₂ and NO (ACGIH, 1991)
<i>Description</i>	colorless or yellow liquid
<i>Conversion factor</i>	1 ppm = 2.58 mg/m ³ @ 25°C

III. Major Uses or Sources

Nitric acid (HNO₃) is the most common strong acid and also a strong oxidizing agent. It is used to dissolve gold and platinum and in the etching and cleaning of metals. It is also used to make nitrates and nitro compounds, especially organic compounds, many of which are commercial or military explosives. HNO₃ is also used to destroy residues of organic matter. The primary use of nitric acid is the production of ammonium nitrate fertilizer. Nitric acid solutions generally range in strengths from 50 to 99%, with variable amounts of dissolved NO₂ (NIOSH, 1976). White fuming nitric acid (WFNA) contains about 97.5% nitric acid by weight while red fuming nitric acid (RFNA) contains 82.4-85.4%. The percentages of NO₂ content in WFNA and RFNA are about 0.5 and 14%, respectively. Decomposition of HNO₃ releases nitrogen dioxide (NO₂) and

nitric oxide (NO). In practice, HNO₃ is usually found in conjunction with NO₂ which appears to be more hazardous (ACGIH, 1991).

IV. Acute Toxicity to Humans

HNO₃ can be corrosive to the eyes, skin, nose, mucous membranes, respiratory tract, gastrointestinal tract, or any other tissue with which it comes in contact. Severe injury and deaths have resulted from exposure of humans to vapors and gases originating from nitric acid solutions, which ranged in concentration from 34 to 68% (Rossano, 1945; Hejela *et al.*, 1990; Schmid, 1974). Exposure durations were occasionally recorded in the human case reports but concentrations were unknown. Symptoms of respiratory tract irritation following acute HNO₃ exposure include coughing, gagging, chest pain, and dyspnea (Hall and Cooper, 1905; Trieger and Przypyszny, 1947). Cyanosis and acute pulmonary edema have been reported following high acute exposure. Severe pulmonary sequelae due to inhalation of vapors and gases originating from nitric acid solutions have been divided into three categories: (1) immediate fatalities from very high concentrations, (2) delayed effects occurring within 48 hours, and (3) mild immediate effects followed by a short recovery period, but culminating in pneumonia (NIOSH, 1976; Hamilton and Hardy, 1974). Inhalation of gases and vapors originating from nitric acid can be extremely dangerous because they do not set up a violent respiratory reflex, such as occurs with chlorine and ammonia, which serves as a warning property.

Inhalation effects from “nitric acid fumes” are due to a mixture of nitric acid vapor and oxides of nitrogen (NO_x), mainly nitrogen dioxide (NO₂) and nitric oxide (NO). The toxic effects of nitric acid in humans cannot be isolated from those of its reaction products, since contact with air, organic matter and some metals immediately liberates NO_x (Durant *et al.*, 1991). Inhalation of NO₂ originating from nitric acid is considered more hazardous than inhalation of nitric acid vapor itself (Procter *et al.*, 1988). Therefore, caution must be used when estimating exposure to vapors and gases emitted by nitric acid. Factors that affect the NO_x content of nitric acid, and hence its toxicity, include temperature, humidity, and other materials with which the fumes make contact (Henschler, 1992).

Adolescent asthmatics exposed to 0.05 ppm (0.13 mg/m³) HNO₃ via mouthpiece for 40 minutes, including 10 minutes of moderate exercise, exhibited a 4% decrease in FEV₁ (forced expiratory volume) and a 23% increase in total respiratory resistance (Koenig *et al.*, 1989a). A later study by the same author found no significant changes in pulmonary function of adolescent asthmatics following exposure to the same concentration of HNO₃, even though total exercise time during exposure was increased (Koenig, 1989b). The author cautioned that the lack of response to HNO₃ in the latter experiment contradicts the results of two earlier studies performed in her laboratory during the summer months; the results suggest a seasonal variation in pulmonary response.

No significant changes in pulmonary function or symptoms of sensory or respiratory irritation were observed in 10 “ozone-sensitive” adults exposed 2 hours to a fog containing 0.2 ppm (0.5 mg/m³) HNO₃ (Aris *et al.*, 1991). Exercise during exposure at a ventilatory rate of 40 L/min was also part of the protocol. Ozone sensitivity was defined as an FEV₁ decrement of ≥ 10% of the

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baseline value after 3 hour exposure to ozone. A later study by the same research group exposed 10 healthy athletic subjects to 0.21 ppm nitric acid gas for 4 hours during moderate exercise (ventilatory rate = 40 L/min) (Aris *et al.*, 1993). No significant changes in pulmonary function or symptom scores were observed during or immediately after exposure. In addition, bronchoalveolar lavage and bronchial biopsy specimens taken the following day revealed no evidence of proximal airway inflammation.

In other studies, 9 healthy volunteers were exposed to 0.08 ppm nitric acid for 2 hours with 100 minutes of moderate exercise (ventilation rate = 42 L/min) (Becker *et al.*, 1992). Pulmonary function tests, as measured by FEV₁, FVC, and airway resistance, remained unchanged following exposure. Bronchoalveolar lavage fluid, collected 18 hours after exposure, did not present any indicators of inflammation. However, phagocytic activity and antiviral activity (to respiratory syncytial virus) of alveolar macrophages had significantly increased. Sackner and Ford (1981) exposed 5 normal subjects to 1.6 ppm nitric acid via mouthpiece for 10 minutes. Vital capacity, total respiratory resistance, and FEV₁ were unaffected over a 1 hour follow-up period. In another study, 12 mildly asthmatic subjects inhaled hypoosmolar fog (30 mOsm, pH 2) containing nitric acid via mouthpiece until specific airway resistance increased 100% above baseline (Balmes *et al.*, 1989). Inhalation of nitric acid fog (1.05 g/min) for 3 minutes resulted in increased airway resistance. Actual nitric acid concentrations were not reported.

Diem (1907) describes a study in which the author and a colleague exposed themselves to a concentration of nitric acid fumes between 11.5 and 12.2 ml/m³ (ppm) for 1 hour. Initial symptoms included irritation of nasal mucosa resulting in sneezing, moderate burning of eyes resulting in lacrimation, marked secretion from the nose and salivary glands, and burning and itching of the facial skin. Deep inhalation resulted in a feeling of pressure in the chest, slight stabbing pains in the trachea and larynx, and coughing, so the researchers kept their breathing shallow. A mild frontal headache developed and nasal secretion became more marked after 20 minutes of exposure. However, the other symptoms became more tolerable. Many of the symptoms remained for about 1 hour after cessation of exposure. Tiredness, especially in the legs, and the feeling of dry skin of the hands were late or delayed symptoms of the exposure. The researcher concluded that exposure longer than 1 hour to this concentration of nitric acid cannot be tolerated without risk of adverse effects on health. Exposure to 84 ppm nitric acid could only be tolerated for 2 to 3 minutes by the author. Symptoms were the same as the previous exposure, but at a much greater intensity. All symptoms persisted beyond the end of exposure.

Predisposing Conditions for Nitric Acid Toxicity

Medical: Persons with eye, skin, or respiratory conditions may be more sensitive to the irritative effects of nitric acid.

Chemical: Persons who are exposed to other inorganic nitrates or nitrites, or those who drink water with high nitrate content may be more sensitive to the effects of nitric acid exposure (Reprotext, 1993).

V. Acute Toxicity to Laboratory Animals

Abraham *et al.* (1982) reported that exposure to 1.6 ppm HNO₃ vapor for 4 hours did not induce significant changes in airway reactivity to aerosolized carbachol in normal sheep but resulted in mild airway hyperreactivity (up to 52% increase in specific pulmonary resistance) within 24 hours following exposure in allergic animals. Sheep that were considered allergic reacted with bronchospasm to inhalation of *Ascaris suum* extract.

Diem (1907) exposed rabbits and cats individually to various concentrations and durations of nitric acid fumes by warming concentrated acid. A rabbit exposed to 191.2 ppm nitric acid for 100 minutes showed few visible signs of dyspnea but appeared 'apathetic'. Autopsy 1 week later revealed inflammation in the larynx and trachea, hyperemia, and hypostasis in the lower lung. Two rabbits exposed to lower concentrations (15.3 and 68.8 ppm) had no remarkable signs of toxicity. One cat each was exposed individually to 9 different concentrations of nitric acid ranging from 15.3 to 336.5 ppm for varying lengths of time. The highest NOAEL for severe injury or death was ascertained to be 164.4 ppm for 90 minutes. This animal exhibited salivation, nasal secretion, lacrimation, progressive dyspnea, gulping and retching, and clonic convulsions in trunk and extremities. The cat was prostrate and panting at end of exposure. However, the cat appeared to have completely recovered 1 day later. Higher concentrations (191.2 to 336.5 ppm) resulted in death or severe pulmonary injury requiring 8 days to recover. Extensive lung edema was observed in animals that died. Cats exposed to concentrations below 164.4 ppm showed little or no grossly observable effects from exposure; autopsy revealed little to no pulmonary edema in these cats.

In the only other study investigating the lethal effect of nitric acid, a 30 minute and a 4 hour LC₅₀ were determined for red fuming nitric acid in male albino rats to be 138 and 67 ppm, respectively (Gray *et al.*, 1954). The 30 minute LC₅₀ for white fuming nitric acid was estimated to be 244 ppm. However, these LC₅₀'s represent only the concentration of NO₂ during exposure; therefore the concentration generated by nitric acid was likely considerably higher than the measured values. A third group of rats was exposed to pure NO₂ with a post-exposure observation period of 3 days. Similar lethality tests conducted with NO₂ indicated that the primary toxic constituent of red and white fuming nitric acid was NO₂, with nitric acid playing a secondary role as a lung irritant. In all cases, death was due to pulmonary edema. Skin burns were observed on hairless parts of rats exposed to WFNA only. The authors indicated that the 30 minute LC₅₀'s were probably low. Rats from several sources (i.e., different rat strains) were used for the lethality tests. The different rat strains were subsequently found to have widely varying susceptibilities to nitric acid exposure.

Based upon molecular weights and the percentage of NO₂ in white and red fuming nitric acid, NIOSH (1976) determined the total concentration of gases and vapors emitted by nitric acid for the 30 minute LC₅₀ values presented in Gray *et al.* (1954). The LC₅₀ for NO₂ gas (174 ppm) was below the LC₅₀ for both red and white fuming nitric acid, approximately 310 and 334 ppm, respectively (Table 1). NIOSH (1976) stated that, based on the data by Gray *et al.* (1954), nitric acid vapor is approximately half as toxic as NO₂ under acute exposure conditions.

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Table 1. Thirty minute LC₅₀s of male rats exposed to nitric acid (red fuming and white fuming) and NO₂¹.

Chemical agent	LC ₅₀ in ppm (95% confidence limits) for NO ₂ concentration only	LC ₅₀ (ppm) in total concentration of nitric acid and NO ₂
Red Fuming Nitric Acid	138 (123-155)	310
White Fuming Nitric Acid	244 (none) ²	334
NO ₂	174 (154-197)	174

¹ Adapted from Gray *et al.* (1954) and NIOSH (1976).

² Confidence limits could not be established for WFNA due to the unpredictability of deaths.

VI. Reproductive or Developmental Toxicity

No direct evidence of reproductive toxicity following HNO₃ exposure has been reported (Reprotext, 1993). Females working in the photolithographic and diffusion areas in a semiconductor manufacturing plant were found to be at increased risk for spontaneous abortions (Pastides *et al.*, 1988). Silicon ingots are cleaned with acid baths and solvents; however HNO₃ was not specifically mentioned in this study.

VII. Derivation of Acute Reference Exposure Level and Other Severity Levels (for a 1-hour exposure)

Reference Exposure Level (protective against mild adverse effects): 0.033 ppm (86 µg/m³)

<i>Study</i>	Koenig <i>et al.</i> , 1989a
<i>Study population</i>	adolescent asthmatics
<i>Exposure method</i>	inhalation of 0.05 ppm for 40 minutes with 10 minutes of moderate exercise
<i>Critical effects</i>	decrease in FEV ₁ and increase in total respiratory resistance
<i>LOAEL</i>	not observed
<i>NOAEL</i>	0.05 ppm
<i>Exposure duration</i>	40 minutes
<i>Extrapolated 1 hour concentration</i>	0.033 ppm (0.05 ¹ ppm * 2/3 h = C ¹ * 1 h) (see Table 12 for information on “n”)
<i>LOAEL uncertainty factor</i>	1
<i>Interspecies uncertainty factor</i>	1
<i>Intraspecies uncertainty factor</i>	1
<i>Cumulative uncertainty factor</i>	1
<i>Reference Exposure Level</i>	0.033 ppm (0.086 mg/m ³ ; 86 µg/m ³)

Level Protective Against Severe Adverse Effects

No recommendation is made due to the limitations of the database.

Level Protective Against Life-threatening Effects

No recommendation is made due to the limitations of the database.

The lethality results in cats (Diem, 1907) provide the only estimate of a NOAEL for life-threatening effects. No raw mortality data or NOAELs were provided by Gray *et al.* (1954) or NIOSH (1976). The cause of death in experimental animals from Diem (1907) and Gray *et al.* (1954) was due to pulmonary edema. Adjustment of the NOAEL (164.4 ppm for 90 minutes) to a 1 hour exposure, using a modification of Haber's equation ($C^n * T = K$; $n = 2$), yields an adjusted NOAEL of 201 ppm. Uncertainty factors of 10 each, applied to account for interspecies differences and for increased susceptibility of sensitive human individuals, yield a life-threatening level of 2 ppm (5.2 mg/m^3 ; $5.2 \times 10^3 \text{ } \mu\text{g/m}^3$). Exposure to 2 ppm would likely cause only mild symptoms of irritation in normal humans (Diem, 1907; Sackner and Ford, 1981). Until this issue can be resolved, this derivation is meant for illustrative purposes only and is not a recommended value.

NIOSH (1995) lists a (revised) IDLH of 25 ppm based on acute toxicity data in humans and animals. NIOSH states that this may be a conservative value due to the lack of relevant acute inhalation toxicity data for workers.

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ACUTE TOXICITY SUMMARY

NITROGEN DIOXIDE

CAS Registry Number: 10102-44-0

I. Acute Toxicity Summary (for a 1-hour exposure)

Inhalation reference exposure level **470 µg/m³**
Critical effect(s) increased airway reactivity in asthmatics
Hazard Index target(s) Respiratory System

II. Physical and Chemical Properties (HSDB, 1994 except as noted)

<i>Molecular formula</i>	NO ₂
<i>Molecular weight</i>	46.01
<i>Specific gravity</i>	1.448 @ 20°C (liquid)
<i>Boiling point</i>	21.15° C (70°F)
<i>Melting point</i>	-9.3° C
<i>Vapor pressure</i>	720 mm Hg @ 20°C
<i>Vapor density</i>	1.58 (air = 1)
<i>Flashpoint</i>	not applicable
<i>Explosive limits</i>	not applicable
<i>Solubility</i>	soluble in concentrated nitric and sulfuric acids; decomposes in water, forming nitric oxide and nitric acid.
<i>Odor threshold</i>	0.11-0.22 ppm
<i>Odor description</i>	similar to that of bleach (AIHA, 1989)
<i>Metabolites</i>	nitrogen dioxide and water combine to produce nitric acid in the respiratory tract
<i>Description</i>	colorless liquid, reddish brown gas
<i>Conversion factor</i>	1 ppm = 1.88 mg/m ³ @ 20°C

III. Major Uses or Sources

Nitrogen dioxide (NO₂) is used as a nitrating agent, as a component of rocket fuels, and as an intermediate in the formation of nitric acid (ACGIH, 1986). The majority of occupational exposures to NO₂ result from its presence as a by-product of nitrate decomposition, as in the reaction of nitric acid with metals or other reducing agents, various processes in which air is heated to high temperature with the formation of nitric oxide (NO), or in the exhaust of internal-combustion engines.

Major indoor sources of NO₂ include unvented gas stoves, other gas appliances, and kerosene heaters (CARB, 1992). The major outdoor sources of NO₂ emissions in California are: on-road vehicles (approximately 51%), other vehicles, locomotives, aircraft (23%), and stationary combustion sources (e.g., oil and gas production, and refining, manufacturing/industrial, and electric utilities) (26%).

IV. Acute Toxicity to Humans

Acute exposure to NO₂ has caused pulmonary edema, pneumonitis, bronchitis, and bronchiolitis obliterans (Reprotext, 1994). NO₂ is considered a relatively insoluble, reactive gas, such as phosgene and ozone. Once inhaled, it reaches the lower respiratory tract, affecting mainly the bronchioles and the adjacent alveolar spaces, where it may produce pulmonary edema within hours (Plog, 1988). Many deaths from pulmonary edema have been induced by acute inhalation of high concentrations of NO₂. Short exposures to 100-500 ppm (190-900 mg/m³) NO₂ may lead to sudden death. More characteristic is insidious, delayed pulmonary edema within hours. Finally, delayed inflammatory changes may lead to death hours or days after exposure (Plog, 1988).

A few accidental exposure studies estimated the NO₂ concentration leading to signs and symptoms of toxicity. Norwood *et al.* (1966) reported pulmonary edema in a worker who had a 30-minute exposure to NO₂ in an oxyacetylation cutting process. Recreation of the exposure conditions produced an NO₂ concentration of up to 90 ppm.

In another accidental human exposure, 3 astronauts inhaled a high concentration of NO₂ for 4 minutes and 40 seconds during reentry before the air was cleared inside the cabin (Hatton *et al.*, 1977). Postflight analysis suggested a peak cabin concentration of 750 ppm (1,530 mg/m³) at 1 atm, and an average exposure to 250 ppm (510 mg/m³). One hour after splashdown, the astronauts complained of tightness of the chest, retrosternal burning sensation, inability to inhale deeply, and a nonproductive cough. The following day, the astronauts were unable to hold their breath or perform the forced expiratory maneuvers required for pulmonary function tests (PFTs). Chest x-rays were normal on the day of exposure but on the following day the blood gases and chest x-rays were consistent with diffuse chemical pneumonitis. Recovery occurred over several days; chest roentgenograms appeared normal by the fifth day after overexposure.

In an early attempt at controlled exposure to high NO₂ concentrations, Adley (1946) reported that exposure of an unspecified number of workmen to an average concentration of 80 ppm (150 mg/m³) NO₂ for 4 minutes produced slight tightness of the chest. However, 4-minute exposure to an average concentration of 38 ppm (71 mg/m³) resulted in no reports of symptoms. Exposure to an average concentration of 210 to 352 ppm for about 3 minutes resulted in a spontaneous, dry cough and tightness of the chest. A few hours after exposure, subjects reported general malaise.

In a human inhalation study by Meyers and Hine (1961), sensory responses were recorded for 7 or 8 normal volunteers exposed to 1, 5, 13, or 25 ppm NO₂ for 5 minutes each. Eye irritation and pulmonary discomfort were not significantly different from control values, but slight to moderate nasal irritation was noted at 13 ppm (7 of 8 subjects) and 25 ppm (5 of 7 subjects). Exposure to 50 ppm NO₂ produced symptoms of severe pulmonary distress in 1 of 7 subjects resulting in termination of exposure after only 1 minute. In a 1 hour inhalation study, exposure of 5 subjects to 10 ppm NO₂ resulted in pulmonary discomfort, characterized as pharyngeal irritation in all subjects and slight to moderate nasal irritation in 3 subjects. Eye irritation was not significantly

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different from control values and no consistent changes in inspiratory reserve, expiratory reserve, or vital capacity were observed.

Nakamura (1964) exposed 13 healthy young adult volunteers to specific concentrations of NO₂ ranging from 3 to 40 ppm for 5 minutes. Two volunteers were exposed twice at different concentrations. Although airway resistance increased following exposure, no significant dose-response relationship between NO₂ concentration and increased airway resistance was observed. Subjective complaints were concentration-dependent and included bad odor, irritation of the upper airway, coughing, and unusual feeling in the lungs.

Yokoyama (1968) exposed up to 8 healthy subjects, 5 of whom were smokers, to NO₂ concentrations of 2.7, 6.2, 12.6, and 16.9 ppm for 10 minutes via mouthpiece. An average increase in pulmonary flow resistance was significant only at 16.9 ppm. The average 22% increase at this concentration occurred at the end of exposure and the highest individual increase in resistance was 78%. Other pulmonary function tests remained unchanged at all exposure levels. Irritation in the throat was noted in only 1 of 8 subjects exposed to 16.9 ppm.

Exposure of normal volunteers to 5 and 7.5 ppm NO₂ has been performed (von Nieding and Wagner, 1977; von Nieding and Wagner, 1979; von Nieding et al., 1973; Beil and Ulmer, 1976). However, these studies lacked details, both of methods and of results, which makes evaluation difficult. In the best of these studies, Von Nieding and Wagner (1977) exposed 11 healthy male volunteers in a chamber to 5 ppm NO₂ with light intermittent exercise. After 2 hours of exposure, a statistically significant 60% increase in total airway resistance (R_T) was observed relative to the pre-exposure R_T. The mean arterial oxygen partial pressure (PaO₂) decreased significantly from 89.6 to 81.6 mm Hg. R_T remained significantly elevated 1 hour following exposure while PaO₂ returned to normal. Pulmonary function data for individual subjects and subjective symptoms were not reported.

In 18 normal nonsmoking subjects exposed to filtered air or 2 ppm (4 mg/m³) NO₂ for 1 hour (Mohsenin, 1988), airway reactivity to methacholine challenge increased significantly after NO₂ exposure. However, no significant changes were noted in lung volumes, flow rates, or respiratory symptoms.

In controlled studies, exposure of asthmatics to up to 4 ppm NO₂ have not resulted in statistically significant changes in PFTs (Koenig *et al.*, 1988; Linn *et al.*, 1985a; Linn *et al.*, 1986). Exposure of subjects with chronic obstructive pulmonary disease to concentrations up to 3 ppm NO₂ have resulted in no changes (Linn *et al.*, 1985b) or marginal to equivocal changes in PFTs (Morrow and Utell, 1989).

Controlled acute exposure studies with asthmatics show an increase in airway reactivity in response to NO₂ concentrations between 0.25 and 0.50 ppm (0.47 and 0.9 mg/m³). Bauer *et al.* (1986) reported that NO₂ potentiated exercise-induced bronchospasm and airway reactivity to cold air provocation in asthmatics following exposure to 0.3 ppm (0.6 mg/m³) for 30 minutes. Exposure to NO₂ while at rest resulted in no significant change in pulmonary function. Following 10 minutes of exercise, significant reductions in FEV₁ (p<0.01) and partial expiratory

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flow rates at 60% of total lung capacity were observed. One hour after NO₂ exposure and exercise, pulmonary function returned to baseline. Mohsenin (1987) reported an increase in airway reactivity in normal subjects following exposure to 0.5 ppm (0.9 mg/m³) NO₂ for 1 hour. Other studies have reported the absence of airway reactivity in asthmatics at these concentrations (Rubinstein *et al.*, 1990; Avol *et al.*, 1988; Roger *et al.*, 1990).

Additional controlled-exposure studies of asthmatics demonstrate an increase in nonspecific airway reactivity following exposure at or below 0.25 ppm (0.47 mg/m³) NO₂. Jorres *et al.* (1990) report an increase in airway reactivity to hyperventilation of 0.75 ppm SO₂ without altering airway tone following exposure to 0.25 ppm NO₂ for 30 minutes. Kleinman *et al.* (1983) report an increase in airway reactivity in 2/3 of 31 subjects exposed to 0.2 ppm (0.4 mg/m³) NO₂ for two hours. Orehek *et al.* (1976) report increased airway reactivity in 13 of 20 subjects exposed to 0.1 ppm (0.2 mg/m³) for one hour. Other investigators report no increase in airway reactivity in asthmatics following NO₂ exposure at or below 0.25 ppm (0.47 mg/m³) (Hazucha *et al.*, 1983; Jorres *et al.*, 1991). Results from these studies suggest that a sensitive subgroup of asthmatics with increased airway reactivity following inhalation exposure to NO₂ may be present in the general population, and that they contribute to the wide range of responsiveness present among asthmatics to inhaled NO₂ (Utell, 1989).

Predisposing Conditions for Nitrogen Dioxide Toxicity

Medical: Persons with asthma and other pulmonary diseases may be more sensitive to the effects of NO₂ (Reprotext, 1994).

Chemical: There is a theoretical possibility that persons who live in heavily polluted areas, who drink water with high levels of nitrate, or who are exposed to other oxides of nitrogen, nitrates, or nitrites may be more sensitive to NO₂ because of the potential induction of methemoglobinemia (Reprotext, 1994). However, there is no empirical evidence of this effect.

V. Acute Toxicity to Laboratory Animals

Although accurate quantitative data are lacking for life-threatening exposures to NO₂ in humans, the clinical syndrome in accidental human exposure cases is similar to that seen in experimental animals exposed to high levels of NO₂ (Mauderly, 1984). The most comprehensive acute lethality study for NO₂ in experimental animals was done by Hine *et al.* (1970). Numerous exposure durations, ranging from 5 minutes to 24 hours, were examined for each concentration of NO₂, which ranged from 5 ppm to 250 ppm, in mice, rats, guinea pigs, rabbits, and dogs. At low levels of exposure up to 20 ppm, signs of irritation were minimal, and no effects on behavior were noted. At 40 ppm and above, signs of toxicity included eye irritation, lacrimation, and increased respiration followed by labored breathing. In all 5 species, 50 ppm was considered a critical concentration, below which mortality rarely occurred with exposures up to 8 hours. In animals which developed pulmonary edema there was profuse, occasionally hemorrhagic fluid discharge from the nares. Gross pathology revealed mottled, fluid-filled lungs. Some guinea pigs exhibited sudden exaggerated gasping for air, then convulsed and died. Pulmonary edema

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was not present in these animals but the vocal cords were slightly edematous, which suggested asphyxiation due to laryngeal spasm.

Because the mortality data in Hine *et al.* (1970) were not presented in conventional form by the standard LC₅₀ method (the study varied exposure duration for a given concentration), the data were normalized to a 1-hour exposure using Haber's equation ($C^n \times T = K$). The exponent "n" was determined for each species by varying the term n in a log-normal probit analysis (Crump, 1984; Crump and Howe, 1983) until the lowest chi-square value was achieved. Only exposure durations which reasonably bracketed 1 hour 20 minutes to 4 hours in length were used in the probit analysis. Exposure durations outside of this range tended to deviate from Haber's formula. The term was subsequently found to be between 3.0 and 4.0 for mice, guinea pigs, and dogs. These estimates of the exponent "n" are similar to the exponent value (n = 3.5) estimated by ten Berge *et al.* (1986) using the same data set. The data sets for rats and rabbits were heterogeneous or too weak for "n" determination.

Acute lethality determinations for the LC₅₀, maximum likelihood estimate corresponding to 5% mortality (MLE₀₅), and benchmark doses at the lower 95% confidence interval expected to produce a response rate of 5% and 1% (BC₀₅ and BC₀₁, respectively) for mice, rats, guinea pigs and dogs are shown in Table 1.

Table 1. Nitrogen Dioxide Acute Lethality Determinations (in ppm) Derived from the Data by Hine *et al.* (1970) and Normalized to 1-Hour Exposure.

Species	LC ₅₀	MLE ₀₅	BC ₀₅	BC ₀₁
Mouse	93	70	59	50
Rat ¹	106	60	47	34
Guinea Pig	83	44	28	18
Dog	125	96	62	48

¹ Only 1 hour exposure duration data were used to derive the rat lethality values.

In other lethality studies, Carson *et al.* (1962) observed 5-, 15-, 30-, and 60-minute LC₅₀'s of 416, 201, 162, and 115 ppm, respectively, in young male rats. A 15-minute LC₅₀ of 315 ppm was observed in rabbits. Higgins *et al.* (1972) determined a 5 minute LC₅₀ of 831 and 1,880 ppm in rats and mice, respectively. Hilado and Machado (1977) observed a 10-minute LC₅₀ of about 1,000 ppm in male mice. Takenaka *et al.* (1983) determined 16 hour LC₅₀'s in 9 strains of mice and 4 strains of rats. In mice, the LC₅₀'s ranged from 67 ppm to 33 ppm. In rats, the LC₅₀'s ranged from 56 ppm to 39 ppm. Takenaka *et al.* (1983) also observed a 16 hour LC₅₀ of 22 ppm (males) and 28 ppm (females) in Golden hamsters, and 62 ppm (males) and 50 ppm (females) in Hartley guinea pigs.

Steadman *et al.* (1966) exposed groups of rats, guinea pigs, rabbits, squirrel monkeys, and beagle dogs to NO₂ concentrations of 123 mg/m³ (65 ppm) and 67 mg/m³ (36 ppm) for 8 hours or more.

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Signs of eye and nose irritation were noted in all animals during the first hour of exposure to 123 mg/m³, accompanied by anorexia and lethargy. Monkeys were the most susceptible to the lethal effects of NO₂, with 3 out of 3 dying at each exposure level within the first 6.5 hours.

Henry and co-workers (1969) reported that monkeys exposed to 35-50 ppm NO₂ for 2 hours showed a marked decrease in resistance to infection when subsequently challenged with *Klebsiella pneumoniae*. Animal studies indicate that decreased host resistance to infection is influenced more by concentration of NO₂ than by duration of exposure (CARB, 1985).

Lung-only exposure of sheep to 500 ppm NO₂ for 15-20 minutes resulted in an immediate tidal volume decrease and an increase in both breathing rate and minute volume (Januskiewicz and Mayorga, 1994). Maximal lung resistance and dynamic lung compliance changes occurred at 24 hours post-exposure. Histopathologic examination of lung tissue revealed patchy edema, mild hemorrhage, and polymorphonuclear and mononuclear leukocyte infiltration. Signs of NO₂-induced toxicity were significantly attenuated when sheep were exposed to 100 ppm (Januskiewicz *et al.*, 1992), or to 500 ppm through a face mask (nose-only exposure) (Januskiewicz and Mayorga, 1994).

Species-specific sensitivity to NO₂ inhalation may exist, based, in part, on animal size or weight-specific minute ventilation (Book, 1982; Carson *et al.*, 1962; Januskiewicz and Mayorga, 1994). The evidence indicates that smaller experimental animals species, such as rodents, are more susceptible to the toxic effects of NO₂ than larger animals such as dogs, sheep, and humans (Book, 1982; Januskiewicz and Mayorga, 1994).

VI. Reproductive or Developmental Toxicity

Limited data are available on the effects of NO₂ on reproduction. Reproductive studies in animals have been done but are difficult to interpret. In one study, exposure of pregnant rats to 0.43, 0.045, or 0.018 ppm (0.81, 0.085, or 0.034 mg/m³) NO₂ resulted in an increase in intrauterine deaths, stillbirths, and certain unspecified developmental abnormalities, and in decreased birth weights (Gofmekler *et al.*, 1977); the original reference was not available for review. Tabacova *et al.* (1985) found dose-dependent neurobehavioral deviations and delays in eye opening and incisor eruption in the offspring of rats exposed to 0.5 ppm (0.9 mg/m³) NO₂ and higher. The authors suggest that the effects may be due to lipid peroxidation of the placenta. No effects in spermatogenesis, germinal cells, or interstitial testicular cells occurred in rats exposed to 1.0 ppm (2 mg/m³) NO₂ for 7 hours/day, 5 days per week, for 3 weeks (Kripke and Sherwin, 1984). No human reproductive studies of NO₂ were available at the time of this review.

VII. Derivation of Acute Reference Exposure Level and Other Severity Levels (for a 1-hour exposure)

Reference Exposure Level (protective against mild adverse effects):

0.25 ppm (470 µg/m³) (California Ambient Air Quality Standard)

<i>Study</i>	California Air Resources Board (CARB), 1992
<i>Study population</i>	sensitive humans (asthmatics)
<i>Exposure method</i>	inhalation
<i>Critical effects</i>	increase in airway reactivity
<i>LOAEL</i>	
<i>NOAEL</i>	0.25 ppm
<i>Exposure duration</i>	1 hour
<i>Extrapolated 1 hour concentration</i>	0.25 ppm
<i>LOAEL uncertainty factor</i>	1
<i>Interspecies uncertainty factor</i>	1
<i>Intraspecies uncertainty factor</i>	1
<i>Cumulative uncertainty factor</i>	1
<i>Reference Exposure Level</i>	0.25 ppm (0.47 mg/m ³ ; 470 µg/m ³)

The REL is the California Ambient Air Quality Standard.

Level Protective Against Severe Adverse Effects

No recommendation is made due to the limitations of the procedures.

The few studies that observed disabling effects on pulmonary function following NO₂ exposure did not provide reliable values. Meyers and Hine (1961) observed respiratory distress in 1 of 7 test subjects exposed to 50 ppm for 1 minute. However, this exposure is too short for consideration of a severe adverse effect level. Likewise, the disabling effects produced by accidental exposure of astronauts to high concentrations of NO₂ was too variable and too short for consideration. Hine *et al.* (1970) observed signs of compromised lung function in 5 experimental animal species exposed to greater than 40-50 ppm. However, extrapolation of the animal NOAEL (40-50 ppm) to sensitive humans using a total uncertainty factor of 100 would result in a severe adverse effect level significantly below 4 ppm. This concentration of NO₂ failed to produce symptoms of mild irritation in asthmatic subjects (Linn *et al.*, 1985a).

Level Protective Against Life-threatening Effects

No recommendation is made due to the limitations of the procedures.

Applying an uncertainty factor of 30 (3 to account for interspecies differences and 10 for increased susceptibility of sensitive human individuals) to the BC₀₅'s from Table 1 results in a life-threatening level of 1-2 ppm, for 1-hour exposure to NO₂. Probit analysis to determine the BC₀₅ from rat lethality data by Higgins *et al.* (1972) and mouse lethality data by Hilado and

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Machado (1977) also resulted in a life-threatening level of 2 ppm following adjustment of the BC₀₅'s to 1-hour exposure and application of appropriate uncertainty factors. While the benchmark dose results of 3 lethality studies in a total of 4 different experimental animal species are consistent, they result in a life-threatening level value (2 ppm) that is known to cause no symptoms of irritation or changes in pulmonary function in sensitive humans (Linn *et al.*, 1985a; Linn *et al.*, 1985b). Species-specific susceptibility comparisons of experimental animals suggest that humans are less sensitive to the toxic effects of NO₂ than smaller experimental animal species (Book, 1982; Januskiewicz and Mayorga, 1994). However, Steadman *et al.* (1966) observed that squirrel monkeys were more susceptible to the acute lethal effects of NO₂ than rodents. Until this issue can be resolved, these derivations are meant for illustrative purposes only.

NIOSH (1995) lists a (revised) IDLH for nitrogen dioxide of 20 ppm based on acute inhalation toxicity data in humans. NIOSH states that this may be a conservative value due to the lack of relevant acute toxicity data for workers exposed to concentrations above 20 ppm.

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ACUTE TOXICITY SUMMARY

OZONE

(triatomic oxygen)

CAS Registry Number: 10028-15-6

I. Acute Toxicity Summary (for a 1-hour exposure)

Inhalation reference exposure level **180 µg/m³**
Critical effect(s) eye irritation and minor changes
in lung function tests
Hazard Index target(s) Eyes; Respiratory System

II. Physical and Chemical Properties (HSDB, 1994 except as noted)

<i>Molecular formula</i>	O ₃
<i>Molecular weight</i>	48.0
<i>Specific gravity</i>	2.144 @ 0°C (gas)
<i>Boiling point</i>	-111.9°C
<i>Melting point</i>	-192.7°C
<i>Vapor pressure</i>	>760 mm Hg @ 25°C (NIOSH, 1994)
<i>Flashpoint</i>	not applicable
<i>Explosive limits</i>	not applicable
<i>Solubility</i>	insoluble in water; soluble in alkaline solvents, oils
<i>Odor threshold</i>	0.0076-0.036 ppm (AIHA, 1989)
<i>Odor description</i>	pungent
<i>Metabolites</i>	unknown
<i>Description</i>	colorless to light blue gas
<i>Conversion factor</i>	1 ppm = 1.96 mg/m ³ @ 25°C

III. Major Uses or Sources

Ozone (O₃) is produced in photochemical reactions of hydrocarbons and nitrogen oxides (CARB, 1987). Ozone is used commercially as a disinfectant for air and water. It is also used for bleaching textiles, oils, waxes, and in organic synthesis (ACGIH, 1994).

IV. Acute Toxicity to Humans

Impairment of lung function and subsequent impairment of exercise performance were measured in exercising adult athletes (age 19-30) exposed to 0.2 ppm (0.4 mg/m³) ozone for 1 hour (Gong *et al.*, 1986). A decrement in post-exercise forced expiratory volume in 1 second (FEV₁) of 21.6% was observed; a 5.6% decrease in FEV₁ was observed in athletes following a 1-hour exposure to 0.12 ppm (0.24 mg/m³) ozone with exercise. Significant reductions in peak minute

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ventilation, oxygen uptake, and tidal volume were observed in athletes exposed to 0.2 ppm ozone, but not in those exposed to 0.12 ppm.

Healthy young males (age 19-30) exposed to ozone at concentrations as low as 0.12 ppm (0.24 mg/m³) for 2.5 hours exhibited statistically significant changes in forced vital capacity (FVC), FEV₁, forced expiratory flow rates at 75% to 25% of lung volume (FEF₂₅₋₇₅), and increased coughing (McDonnell *et al.*, 1983). Statistically significant increases in specific airway resistance (S_{Raw}) and reporting of shortness of breath and pain upon deep inspiration were observed in subjects exposed to ozone at concentrations of 0.24 ppm (0.47 mg/m³) or greater. A more recent study (McDonnell *et al.*, 1991) reported decrements in FVC, FEV₁, and significant increases in S_{Raw} and respiratory symptoms in 38 healthy young men following a 6.6-hour exposure to 0.08 ppm (0.2 mg/m³) ozone involving 5 hours of exercise.

A statistically significant 3% decrease in FEV₁ was observed in male children (age 8-11) following a 2.5 hour exposure to 0.12 ppm (0.24 mg/m³) ozone with intermittent exercise (McDonnell, *et al.*, 1985). No significant increase in cough was noted as a result of ozone exposure.

A recent review (Lippmann, 1993) reports that the ozone-associated lower airway response in the normal population engaged in outdoor recreational activity is greatly underestimated by 1 to 2-hour controlled chamber exposure studies, which indicate very little or no functional decrement at 0.120 ppm (249 µg/m³) ozone. One study cited by Lippmann (1993) reported significant ozone-associated decrements in FVC, FEV₁, peak expiratory flow rate (PEFR), FEF₂₅₋₇₅, and FEV₁/FVC in healthy adults following outdoor exercise in ambient ozone concentrations of 0.021-0.124 ppm (41-243 mg/m³) for an average of 29 minutes (Spektor *et al.*, 1988). In subjects with low ventilation rates (<60 L/minute), the effects observed were about two times greater than those reported in chamber studies using comparable ventilation rates. Recent studies have confirmed that asthmatics react more severely than normal subjects to ozone (Scannell *et al.*, 1996) and that there is a wide variability in spirometric responsiveness (as measured by changes in FVC, FEV₁, and FEF₂₅₋₇₅) among individuals to ozone (Weinmann *et al.*, 1995).

Predisposing Conditions for Ozone Toxicity

Medical: Persons with preexisting respiratory conditions, such as asthma or chronic obstructive lung disease, may be more sensitive to the adverse effects of ozone exposure (CARB, 1987a). Persons doing vigorous exercise or manual labor outdoors are likely to have increased ventilation rates and to be exposed to a higher dose of ozone and thus may be at increased risk for ozone toxicity.

Chemical: Co-exposure to some aeroallergens and respiratory irritants, such as sulfur dioxide, may exacerbate the adverse respiratory effects of ozone in asthmatics (CARB, 1987a).

V. Acute Toxicity to Laboratory Animals

The 3-hour LC₅₀ values for rats, mice, guinea pigs, and rabbits are reported as 21.8 ppm, 21 ppm, 51.7 ppm, and 36 ppm (42.7, 41, 101, and 71 mg/m³) ozone, respectively (Mittler *et al.*, 1956).

A 21% increase in mortality over controls was observed in mice challenged with aerosolized streptococci concurrent with a 3-hour exposure to 0.1 ppm (0.2 mg/m³) ozone (Miller *et al.*, 1978). Mice challenged with streptococci immediately following the 3-hour ozone exposure, however, did not exhibit a significant increase in mortality.

Due to the abundance of human exposure studies, additional animal studies were not summarized here.

VI. Reproductive or Developmental Toxicity

No reports of human reproductive or developmental toxicity due to ozone were located in the literature (Shepard, 1994). Increased resorption rates were observed following exposure of pregnant rats to 1.97 ppm (3.86 mg/m³) ozone 8 hours per day on days 6-9, 9-12, or 6-15 of gestation (Kavlock *et al.*, 1979). A later study from the same laboratory reported that pregnant rats exposed to 1.0 or 1.5 ppm (2 or 2.9 mg/m³) ozone on days 17-20 of gestation had offspring which exhibited retardation of reflex development and slowing in open field behavior (Kavlock *et al.*, 1980).

Veninga (1967) reported blepharophimosis (inability to open the eye to the normal extent) and jaw anomalies in mouse fetuses following maternal exposure to 0.2 ppm (0.4 mg/m³) ozone 7 hours per day, 5 days per week. Because the original reference was not available for review, key experimental details (including the days of gestation during which exposure occurred) are not known.

Comparisons of pregnant, lactating, and virgin female rats exposed to 1 ppm (2 mg/m³) ozone for 6 hours demonstrated enhanced sensitivity to ozone-induced pulmonary inflammation in pregnant and lactating rats (Gunnison *et al.*, 1992). Pulmonary lavage fluid indicators of inflammation measured include total protein, LDH, total leukocytes, total PMN, and β -glucuronidase activity.

VII. Derivation of Acute Reference Exposure Level and Other Severity Levels (for a 1-hour exposure)

Reference Exposure Level (protective against mild adverse effects):

0.09 ppm (180 μ g/m³) (California Ambient Air Quality Standard)

<i>Study</i>	Gong <i>et al.</i> , 1986; McDonnell <i>et al.</i> , 1983; McDonnell <i>et al.</i> , 1985; California Air Resources Board (CARB), 1987a, 1987b.
<i>Study population</i>	normal adults

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<i>Exposure method</i>	inhalation in controlled exposure chambers
<i>Critical effects</i>	decrease in pulmonary function including a 10% decrease in FEV ₁
<i>LOAEL</i>	0.12 ppm (0.24 mg/m ³) ozone
<i>NOAEL</i>	not observed
<i>Exposure duration</i>	1 hour
<i>Extrapolated 1 hour concentration</i>	0.12 ppm
<i>LOAEL uncertainty factor</i>	1.3 (margin of safety)
<i>Interspecies uncertainty factor</i>	1
<i>Intraspecies uncertainty factor</i>	1
<i>Cumulative uncertainty factor</i>	1.3 (see below)
<i>Reference Exposure Level</i>	0.09 ppm (0.18 mg/m ³ ; 180 µg/m ³)

The methodology for developing California Ambient Air Quality Standards differs from that used to develop other acute RELs. The existing CAAQS is based largely upon controlled chamber studies. Inhalation of 0.12 ppm (0.24 mg/m³) ozone by normal human subjects in exposure chambers resulted in a decrease in pulmonary function including a 10% decrease in FEV₁. A margin of safety was added yielding the 1-hour standard of 0.09 ppm (0.18 mg/m³). The CAAQS was also designed to protect against eye irritation, a symptom frequently reported when the 1-hour ozone average is 0.1 ppm or greater (although the eye irritation reported may be a result of non-ozone compounds). A recent study (Spektor *et al.*, 1988) reported significant ozone-associated decrements in FVC, FEV₁, PEFR, FEF₂₅₋₇₅, and FEV₁/FVC in healthy adults following outdoor exercise in ambient ozone concentrations of 21-124 ppb (41-243 µg/m³) for an average of 29 minutes. In subjects with low ventilation rates (<60 L/minute), the effects observed were about two times greater than those reported in chamber studies using comparable ventilation rates. This new information will be considered when the CAAQS is reevaluated by OEHHA.

Level Protective Against Severe Adverse Effects

No recommendation is made due to the limitations of the database.

USEPA (1975) has identified a significant harm level of 0.6 ppm (1.2 mg/m³). USEPA states that “at this exposure-time combination [0.6 ppm (1.2 mg/m³) ozone for a 1-hour exposure], it is judged that acutely incapacitating symptoms will be experienced by significant portions of the population, especially those engaged in light to moderate exercise, and that the health status of particularly vulnerable cardiopulmonary subjects may be seriously compromised.” The key study, on which this level is based, is a study of 10 subjects who reported substernal soreness (6/10), cough (8/10), and marked shortness of breath during a 2-hour exposure to 0.75 ppm (1.5 mg/m³) ozone involving alternating 15-minute periods of exercise and rest (Bates *et al.*, 1972). The authors concluded that an ozone concentration of 0.75 ppm (1.5 mg/m³) produced serious adverse effects under conditions of mild exercise. The significant harm level is unacceptable for exposure of the general public due to the lack of a formal protocol for its derivation.

Level Protective Against Life-threatening Effects

No recommendation is made due to the limitations of the database.

The NIOSH-IDLH for ozone (NIOSH, 1995) is 10 mg/m³ (5 ppm) based on acute inhalation toxicity data in humans (Deichmann and Gerarde 1969; Kleinfeld *et al.* 1957). According to NIOSH, "Pulmonary edema developed in welders who had a severe acute exposure to an estimated 9 ppm ozone plus other air pollutants (Kleinfeld *et al.* 1957). It has been reported that on the basis of animal data, exposure at 50 ppm for 60 minutes will probably be fatal to humans (King 1963)." The derivation of this value is not clearly explained.

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