ACUTE TOXICITY SUMMARY

MERCURY (INORGANIC)

Molecular Formula	Molecular Weight	Synonyms	CAS Registry Number
$Hg°$	200.59	mercury quicksilver colloidal mercury	7439-97-6
$HgCl_2$	271.52	mercuric chloride corrosive sublimate mercuric bichloride mercury perchloride	7487-94-7
$Hg_2(NO_3)_2$	525.19	mercurous nitrate mercury protonitrate	10415-75-5
$Hg(NO_3)_2$	324.66	mercuric nitrate mercury pernitrate	10045-94-0
Hg_2O	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
                                            to metallic mercury vapor
Hazard Index target(s)   Reproductive/developmental

II.   Physical and Chemical Properties (HSDB, 1994)

Description	Hg: silver-white liquid Hg salts: white crystalline solids mercurous oxide: black powder
Density	$HgCl_2$: 5.44 g/cm³ @ 25°C HgO: 9.8 g/cm³ @ 25°C $HgSO_4$: 6.47 g/cm³
Boiling point	Hg°: 356.7°C $HgCl_2$: 302°C
Melting point	Hg°: -38.9°C $HgCl_2$: 276°C $HgHNO_3$: 70°C

	$Hg(HNO_3)_2$: 79°C
Vapor pressure	Hg: 0.002 mm Hg @ 25°C
	$HgCl_2$: 1 mm Hg @ 136°C
Flashpoint	not applicable
Explosive limits	not applicable
Solubility	Hg°: 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_2^{2+} forms are water soluble.
	Hg^{2+} forms are not water soluble.
Odor threshold	odorless
Odor description	odorless
Metabolites	methylmercury (CH_3Hg)
Conversion factor	1 ppm = 8.34 mg/m³ (Hg° 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 (Hg°) vapor is the dominant form in the atmosphere, followed by mercuric ionic species (Hg^{2+}) and methylmercury (CH_3Hg).

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 Hg° 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 Hg°. 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 insipissated 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 Hg° 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

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 Hg° 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 Hg° 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: Persons with preexisting allergies, skin conditions, chronic respiratory disease, nervous system disorders, or kidney diseases might have increased toxicity (Reprotext, 1999).

Chemical: Persons exposed to other neurotoxicants might have increased sensitivity (Reprotext, 1999).

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 LD$_{50}$ 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

Study	Danielsson *et al*., 1993
Study population	groups of 12 pregnant rats
Exposure method	inhalation of metallic mercury vapors
Critical effects	CNS disturbances in offspring
LOAEL	1.8 mg/m³
NOAEL	not observed
Exposure duration	1 hour per day
Extrapolated 1 hour concentration	1.8 mg/m³
LOAEL uncertainty factor	10
Interspecies uncertainty factor	10
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	1,000
Reference Exposure Level	0.0018 mg/m³ (1.8 µg/m³)

Maternal rats exposed by inhalation to 1.8 mg/m³ of metallic mercury vapor 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. Since mercury salts have no significant vapor pressure under normal atmospheric conditions, they would only be of concern as hazards if aerosolized in aqueous solution or burned. This REL is developed for metallic mercury vapor and would be an overestimate of the REL for mercury salts.

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.

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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)

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

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

Description	colorless liquid
Molecular formula	CH_3OH
Molecular weight	32.04
Density	0.7915 g/cm³ @ 20°C
Boiling point	64.5°C
Melting point	-97.8°C
Vapor pressure	92 mm Hg @ 20°C
Flashpoint	12°C, closed cup
Explosive limits	lower = 7.3%
	upper = 36%
Solubility	methanol is miscible with water, ethanol, ether and many other organic solvents
Odor threshold	160 ppm (geometric mean) (AIHA, 1989)
Odor description	sour/sweet (AIHA, 1989)
Metabolites	metabolized to formaldehyde, then formate
Conversion factor	1 ppm = 1.31 mg/m³ @ 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, 1999).

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, 1999). There is a great 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
(Reprotext, 1999).

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.

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)

Study	Cook *et al.*, 1991
Study population	twelve healthy male volunteers
Exposure method	inhalation of 192 ppm (250 mg/m³)
Critical effects	subtle impairment in the performance of complicated tasks
LOAEL	not observed
NOAEL	192 ppm
Exposure duration	75 minutes
Extrapolated 1 hour concentration	214 ppm (192^2 ppm * 1.25 h = C^2 * 1 h) (see Table 12 for information on "n")
LOAEL uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	10
Reference Exposure Level	21 ppm (28 mg/m³; 28,000 μg/m³)

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 MLE_{01} and BC_{01} for cervical ribs were 302 ppm (393 mg/m³) and 58 ppm (75 mg/m³), respectively. The MLE_{05} and BC_{05} 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 BC_{05} 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.

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

The 7-hour value was used as the basis for the level protective against severe adverse effects. The resulting level protective against severe adverse effects is 10 ppm (13 mg/m³), and is designed for a 7-hour exposure. 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 LC_{Lo} 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 (7,860 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 70-kg 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 6,000 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)

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

II.   Physical and Chemical Properties (HSDB, 1994)

Description	colorless gas
Molecular formula	CH_3Br
Molecular weight	94.95
Density	3.88 g/L @ 25°C
Boiling point	3.6°C
Melting point	-93.7°C
Vapor pressure	1,420 mm Hg @ 20°C
Flashpoint	unknown
Explosive limits	unknown
Solubility	soluble in ethanol, benzene, carbon disulfide, and 1.75% (w/w) in water
Odor threshold	20.6 ppm
Odor description	sweetish odor
Metabolites	methanol, bromide, 5-methylcysteine
Conversion factor	1 ppm = 3.89 mg/m³ @ 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).

During a two-week manufacturing operation, 90 persons were exposed to concentrations of methyl bromide generally less than 35 ppm (136 mg/m^3) (Watrous, 1942). Toxic symptoms developed sometime during the workshift, for example, following a few hours of exposure. In others, the symptoms were delayed and did not develop until several hours following the shift. The symptoms occurred in 33 of the 90 workers and were described as mild systemic symptoms primarily of anorexia, nausea and headache. Anorexia (reported by 25 of the 90 workers) was a common symptom and in some cases lasted for a week or more post-exposure, but without marked weight-loss. In some cases, the symptoms progressed to vomiting. Headache was a fairly common symptom (16 of 90) which disappeared when exposure ceased. While exposure was measured in a crude fashion using a "Frigidaire Leak Detector" (measures halides by color of flame), extensive monitoring was conducted throughout the manufacturing operation. In general, concentrations were at or below the limit of detection of 35 ppm.

A study by Garnier et al (1996) found that two workers similarly exposed to methyl bromide (about 17,000 mg/m3) exhibited substantially different symptoms. Glutathione-s-transferase (GsT) was measured in the erythrocytes of both patients. The patient with severe poisoning possessed GsT and was therefore a conjugator. The second patient who exhibited only mild symptoms lacked measurable GsT activity in the erythrocytes and was therefore classed as a nonconjugator. The genetic polymorphism of GsT is not restricted to the erythrocytes. Conjugators appear to be homozygous or heterozygous bearers of the gene for GsT. As cited by

Garnier et al (1996), the gene is lacking in 20.4 % of whites, 21.8% of African-Americans, 64.6% of Chinese-Americans, 60.2% of Korean-Americans, and 9.7% of Mexican-Americans. Thus, conjugation of methyl bromide with glutathione may be a toxifying step for neurotoxicity and the ability to conjugate may reflect susceptibility to neurotoxicity. Conjugation apparently protects against the cytogenetic effects of methyl bromide (Hallier et al (1993). These latter investigators note that about one-quarter of the human population does not possess GsT activity in erythrocytes, and that this enzyme is not found in erythrocytes of laboratory animals (rats and mice). For this reason, studies in laboratory rodents may underestimate the neurotoxicity of methyl bromide.

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). In addition, a wide variability in response to methyl bromide in the human population is suggested by the studies of Hallier et al (1993) and Garnier et al (1996), due to the impact of the polymorphisms for glutathione-s-transferase in the population. People with high glutathione-s-transferase activity in eruthrocytes may be more sensitive to the neurotoxic effects of methyl bromide due to metabolism to a neurotoxic metabolite than those with low to no levels of this enzyme in the erythrocytes.

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 LC_{50} in rats was 2,828 ppm (11,000 mg/m³) (Bakhishev, 1973). An 8-hour LC_{50} 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 LC_{50} 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 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 premating 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)

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

Study	Watrous, 1942
Study population	humans, 90 workers
Exposure method	acute inhalation of 35 ppm
Critical effects	anorexia, nausea, headache
LOAEL	35 ppm
NOAEL	not available
Exposure duration	2 hours
Extrapolated 1 hour concentration	59 ppm
	$C^{1.33}$ (2 hr) = $C^{1.33}$ (1 hr)
LOAEL uncertainty factor	6
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	60
Reference Exposure Level	1 ppm (3.9 mg/m³; 3,900 µg/m³)

The evaluation by Watrous (1942) of 90 workers indicated that symptoms developed during the workshift. We thus assumed a 2 hour exposure was sufficient to cause the symptoms to occur. Using the value for the exponent "n" in the modified Haber's Law equation $C^n \times T = K$ of 1.33, derived by Zwart et al. (1992) from the data of Irish et al. (1940), we extrapolated to a one-hour LOAEL of 59 ppm. Applying an uncertainty factor of 6 for extrapolation of a LOAEL to a NOAEL for mild adverse effects, and an additional uncertainty factor of 10 for intraindividual variability yields an acute REL of 1 ppm.

Level Protective Against Severe Adverse Effects

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. Applying the value of 1.33 for the exponent "n" in the modified Haber's equation yields a one-hour concentration of 445 ppm. Dividing by a cumulative uncertainty factor of 100 (10 for interspecies and 10 for intraindividual variability) yields a level protective against severe adverse effects of 4.45 ppm.

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 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. Extrapolation to a one-hour concentration using modified Haber's Law and an exponent of 1.33, yields a one-hour concentration of 1157 ppm. Using an uncertainty factor of 100 for interspecies and intraspecies extrapolation, the level protective against life-threatening effects is 115 ppm (447 mg/m³).

Comparison with studies in mice

By using data from an LC_{50} 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 (BC_{05}) was 747 ppm (2,906 mg/m³). An uncertainty factor of 3 to account for interspecies variability since the BC_{05} 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 BC_{05}.

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

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)
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)

Description	colorless liquid
Molecular formula	$C_2H_3Cl_3$
Molecular weight	133.42
Density	1.3376 g/cm^3 @ 20°C
Boiling point	74.1°C
Melting point	-30.4°C
Vapor pressure	127 mm Hg @ 25°C
Flashpoint	not applicable
Explosive limits	upper = 10.5%
	lower = 8.0%
Solubility	soluble in acetone, benzene, methanol, carbon tetrachloride
Odor threshold	390 ppm (geometric mean) (AIHA, 1989)
Odor description	sweet, chloroform-like odor
Metabolites	trichloroethanol, trichloroacetic acid (ACGIH, 1991)
Conversion factor	1 ppm = 5.46 mg/m³ @ 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).

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: Persons with preexisting eye, skin, respiratory, liver or cardiovascular disease may have increased sensitivity. Those persons using epinephrine-containing bronchodilators may be at greater risk of developing cardiac arrhythmias when exposed to methyl chloroform (Reprotext, 1999).

Chemical: Alcohol use concurrent with methyl chloroform exposure has been shown to potentiate methyl chloroform toxicity in rats (Reprotext, 1999).

V.   Acute Toxicity to Laboratory Animals

A 1-hour LC_{50} of 18,400 ppm (1 x 10^5 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 10^4 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 (ET_{50}) is reported as 16.3 minutes. The duration of exposure lethal to 50% of the test population (LT_{50}) 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).

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, 1999). 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

Study	Gamberale and Hultengren, 1973
Study population	twelve human volunteers
Exposure method	inhalation of methyl chloroform
Critical effects	reduced performance in manual dexterity, perceptual speed, and reaction time
LOAEL	350 ppm
NOAEL	250 ppm
Exposure duration	30-minutes (see Table 12 for information on *"n"*)
Extrapolated 1 hour concentration	125 ppm (250^1ppm * 0.5 h = C^1 * 1 h)
LOAEL uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	10
Reference Exposure Level	12.5 ppm (68 mg/m³; 68,000 µg/m³)

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   **13,000 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)

Description   colorless liquid
Molecular formula C_4H_8O
Molecular weight   72.10
Density   0.805 g/cm^3 @ 20°C
Boiling point   79.6°C
Melting point   -86.3°C
Vapor pressure   77.5 mm Hg @ 20°C
Flashpoint   -9°C (closed cup)
Explosive limits   1.4% - 11.4%
Solubility   soluble in alcohol, ether, acetone benzene and water
Odor threshold   16 ppm (geometric mean) range = 2-85 ppm (AIHA, 1989)
Odor description   sweet, sharp odor (AIHA, 1989)
Metabolites   2-butanol, 2,3-butanediol (NIOSH, 1978)
Conversion factor   1 ppm = 2.94 mg/m³ @ 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.

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 preexisting eye or neurologic or skin or respiratory conditions may be more sensitive to the toxic effects of MEK (Reprotext, 1999).

Chemical: Persons exposed to isobutanol may be more sensitive to MEK exposure because MEK is a metabolite of isobutanol (Reprotext, 1999). 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 RD_{50} 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 LC_{50} in rats to be 23.5 mg/l (7,993 ppm). A 2-hour LC_{50} 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 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):   13,000 µg/m³

Study	Nakaaki (1974)
Study population	4 healthy human volunteers
Exposure methods	inhalation chamber
Critical effects	subjective reports of eye, nose, and throat irritation; lacrimation and sneezing
LOAEL	270 ppm
NOAEL	not reported
Exposure duration	2 hours
Extrapolated 1-hour concentration	270 ppm (not extrapolated; see below)
LOAEL uncertainty factor	6 (mild irritation)
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	60
Reference Exposure Level	4.5 ppm (13 mg/m³; 13,000 µg/m³)

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 used as the basis for the level protective against severe adverse effects with no time extrapolation. 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 11 ppm (32 mg/m³) for 7-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, LC_{50} 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 LC_{50}, MLE_{05} (maximum likelihood estimate, corresponding to 5% mortality), BC_{05}, and BC_{01} (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 BC_{05} was determined to be 7,062 ppm (see Table 1). The BC_{05} 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 duration greater than 1 hour to 1 hour exposure). The resulting concentration at the BC_{05} for 1 hour exposure was 14,124 ppm. An uncertainty factor of 3 was applied to account for interspecies differences because the BC_{05} 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.

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

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.

VIII.   References

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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	**14,000 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)

Description	colorless liquid
Molecular formula	CH_2Cl_2
Molecular weight	84.93
Density	1.32 g/cm^3 @ 20°C (ACGIH, 1991)
Boiling point	39.75°C
Melting point	-95.1°C (ACGIH, 1991)
Vapor pressure	400 mm Hg @ 24.1°C
Flashpoint	unknown
Explosive limits	upper = 66.4%
	lower = 15.5%
Solubility	miscible with most organic solvents, slightly soluble in water (ACGIH, 1991)
Odor threshold	160 ppm (geometric mean) (AIHA, 1989)
Odor description	sweet, pleasant, chloroform-like odor
Metabolites	carbon monoxide (Reprotext, 1999)
Conversion factor	1 ppm = 3.47 mg/m³ @ 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).

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. 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 due to the greater affinity of fetal hemoglobin for CO. Persons with pre-existing cardiovascular disease might have increased sensitivity (Reprotext, 1999).

Chemical: Tobacco smokers typically have chronically elevated COHb levels and may not be able to tolerate higher levels of CO resulting from methylene chloride exposure.

V. Acute Toxicity to Laboratory Animals

The 20-minute LC_{50} for mice is 27,000 ppm (94,000 mg/m³) MC (Aviado *et al.*, 1977). The 6-hour LC_{50} 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): 4 ppm (14,000 µg/m³)

Study	Putz *et al*., 1976
Study population	twelve healthy adult volunteers
Exposure method	inhalation of 195 ppm methylene chloride
Critical effects	impaired performance on dual-task and auditory vigilance tests
LOAEL	195 ppm
NOAEL (LOEL)	not observed
Exposure duration	90 minutes
Extrapolated 1 hour concentration	240 ppm (195^2 ppm* 1.5 h = C^2 * 1 h) (see Table 12 for information on *"n"*)
LOAEL uncertainty factor	6
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	60
Reference Exposure Level	4 ppm (14 mg/m³; 14,000 µg/m³)

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. . The 90-minute exposure to 195 ppm MC is a LOAEL. An uncertainty factor of 6 was applied to the LOAEL to develop a NOAEL and a 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 when there is a sufficent database to derive 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_3S_2	240.19	nickel subsulfide trinickel disulfide heazlewoodite	12035-72-2

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

Inhalation reference exposure level **6 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)

Description   Ni metal: silvery metal
      NiO: black crystals
      $NiCl_2$: yellow deliquescent crystals (U.S.EPA, 1985)
Density   8.9 g/cm^3 (Ni)
Boiling point   2730°C (Ni)
Melting point   1455°C (Ni); 1030°C ($NiCl_2$)
Vapor pressure   not applicable for dust
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   odorless
Metabolites Ni^{2+}

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 (U.S.EPA, 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 (U.S.EPA, 1985). Nickel is also used in electroplating baths, batteries, textile dyes, and catalysts (U.S.EPA, 1985). Nickel dust or powder is flammable (CDTSC, 1985). Nickel carbonyl also is airborne. However, because of its unique toxicity relative to the inorganic nickel compounds, this REL is not applicable to nickel carbonyl.

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 µg Ni/m³, range = 70-1,100 µg Ni/m³) 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/m³ 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, 1999). Additionally, a review of the literature on nickel toxicity showed that Ni^{2+} causes vasoconstriction in animals and humans which may potentiate the effects of a primary ischemic lesion in the cardiovascular system (U.S.EPA, 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 Ni_3S_2/m^3, 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 Ni_3S_2/m^3, and fibrosis in mice exposed to 5 mg Ni_3S_2/m^3. Atrophy of lymphoid tissues, including spleen, thymus, and bronchial lymph nodes, was observed in mice and rats exposed to 5 or 10 mg Ni_3S_2/m^3.

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/m^3 as $NiCl_2$ 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 $NiCl_2$ (Graham *et al*., 1975). Haley *et al*. (1987) showed that male cynomolgus monkeys, exposed to intratracheal Ni_3S_2 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 Ni_3S_2 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 <u>in</u> <u>vivo</u> was suppressed in two strains of mice exposed to intramuscular injections of 18.3 mg Ni/kg as $NiCl_2$ 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 $NiCl_2$ or $NiSO_4$ were significantly more susceptible to mortality from streptococcal bacterial infection. The concentrations of nickel that showed these effects were 499 µg Ni/m^3 ($NiCl_2$) and 455 µg Ni/m^3 ($NiSO_4$). No significant change in mortality was seen with exposure to 369 µg Ni/m^3 as $NiCl_2$.

Nickel distributes preferentially to the lungs and kidneys following intratracheal administration of $NiCl_2$ to rats (Carvalho and Ziemer, 1982). The electrophilic Ni^{2+} ion is reported to be the causative agent of nephrotoxicity in rats; it binds to intracellular nucleophiles in kidney tissue

such as guanine, adenine, and glutathione 2 hours following intraperitoneal exposure to 10 mg Ni/kg as $NiCO_3$ (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 Ni^{2+} as $NiCl_2$ (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 $NiCl_2$ 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 anopthalmia, cystic lungs, and hydronephrosis (Sunderman *et al.*, 1983). Temporary hyperglycemia was seen in pregnant rats exposed intraperitoneally to $NiCl_2$ 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 Ni_3S_2 (Hoey, 1966). Benson *et al.* (1987) showed that mice and rats exposed to 5 or 10 mg Ni_3S_2/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):   6 μg Ni/m³

Study	Cirla *et al.*, 1985
Study population	7 volunteer metal plating workers with occupational asthma
Exposure method	inhalation of 0.3 mg/m³ NiSO₄·6H₂O (67 μg Ni/m³)
Critical effects	significant (> 15%) decrease in FEV_1
LOAEL	67 μg Ni/m³
NOAEL	not observed
Exposure duration	30 minutes
Extrapolated 1 hour concentration	33 μg Ni/m³ ($(67$ μg Ni/m³$)^1$ * 0.5 h = C^1 * 1 h) (see Table 12 for information on *"n"*)
LOAEL uncertainty factor	6

Interspecies uncertainty factor	1
Intraspecies uncertainty factor	1
Cumulative uncertainty factor	6
Reference Exposure Level	6 μg Ni/m³

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 Cirla *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. The REL specifically does not apply to nickel carbonyl, which releases both nickel and carbon monoxide.

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)

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

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

Description   colorless or yellow liquid
Molecular formula HNO_3
Molecular weight   63.02
Density   1.50269 g/cm^3 @ 25°C
Boiling point   83° C with decomposition
Melting point   -41.59°C
Vapor pressure   62 mm Hg @ 25°C
Flashpoint   not applicable
Explosive limits   not applicable
Solubility   miscible in water
Odor threshold   0.27 ppm (AIHA, 1989)
Odor description   choking odor
Metabolites   oxides of nitrogen, particularly NO_2 and NO
                          (ACGIH, 1991)
Conversion factor   1 ppm = 2.58 mg/m³ @ 25°C

III.   Major Uses or Sources

Nitric acid (HNO_3) 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. HNO_3 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 NO_2 (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 NO_2 content in WFNA and RFNA are about 0.5 and 14%, respectively. Decomposition of HNO_3 releases nitrogen dioxide (NO_2) and nitric oxide (NO). In practice, HNO_3 is usually found in conjunction with NO_2 which appears to be more hazardous (ACGIH, 1991).

IV.   Acute Toxicity to Humans

HNO_3 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 HNO_3 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 (NO_2) 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 NO_2 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) HNO_3 via mouthpiece for 40 minutes, including 10 minutes of moderate exercise, exhibited a 4% decrease in FEV_1 (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 HNO_3, even though total exercise time during exposure was increased (Koenig, 1989b). The author cautioned that the lack of response to HNO_3 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) HNO_3 (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 FEV_1 decrement of $\geq$ 10% of the 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 FEV_1, 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 FEV_1 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/m^3 (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 preexisting eye, skin, or respiratory conditions including underlying cardiopulmonary disease may be more sensitive to the irritative effects of nitric acid. Persons with preexisting disorders of the blood which result in decreased oxygen carrying capacity such as anemia and those with liver or kidney disorders might have increa sed sensitivity (Reprotext, 1999).

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 HNO_3 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 LC_{50} 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 LC_{50} for white fuming nitric acid was estimated to be 244 ppm. However, these LC_{50}'s represent only the concentration of NO_2 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 NO_2 with a post-exposure observation period of 3 days. Similar lethality tests conducted with NO_2 indicated that the primary toxic constituent of red and white fuming nitric acid was NO_2, 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 LC_{50}'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 NO_2 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 LC_{50} values presented in Gray *et al*. (1954). The LC_{50} for NO_2 gas (174 ppm) was below the LC_{50} 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 NO_2 under acute exposure conditions.

Table 1.   Thirty minute LC_{50}s of male rats exposed to nitric acid (red fuming and white fuming) and NO_2[1].

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 HNO_3 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 HNO_3 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)

Study	Koenig *et al*., 1989a
Study population	9 adolescent asthmatics
Exposure method	inhalation of 0.05 ppm for 40 minutes with 10 minutes of moderate exercise
Critical effects	decrease in FEV_1 and increase in total respiratory resistance
LOAEL	not observed
NOAEL	0.05 ppm
Exposure duration	40 minutes
Extrapolated 1 hour concentration	0.033 ppm (0.05^1ppm * 2/3 h= C^1 * 1 h) (see Table 12 for information on "n")
LOAEL uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	1
Cumulative uncertainty factor	1
Reference Exposure Level	0.033 ppm (0.086 mg/m³; 86 μg/m³)

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/m³; 5.2×10^3 µg/m³). 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.

VIII.   References

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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)

Description	colorless liquid, reddish brown gas
Molecular formula	NO_2
Molecular weight	46.01
Density	1.448 g/cm^3 @ 20°C (liquid)
	1.88 g/L @ 25°C (gas)
Boiling point	21.15° C (70°F)
Melting point	-9.3° C
Vapor pressure	720 mm Hg @ 20°C
Flashpoint	not applicable
Explosive limits	not applicable
Solubility	soluble in concentrated nitric and sulfuric acids; decomposes in water, forming nitric oxide and nitric acid.
Odor threshold	0.11-0.22 ppm
Odor description	similar to that of bleach (AIHA, 1989)
Metabolites	nitrogen dioxide and water combine to produce nitric acid in the respiratory tract
Conversion factor	1 ppm = 1.88 mg/m³ @ 20°C

III.   Major Uses or Sources

Nitrogen dioxide (NO_2) 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 NO_2 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 NO_2 include unvented gas stoves, other gas appliances, and kerosene heaters (CARB, 1992). The major outdoor sources of NO_2 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 NO_2 has caused pulmonary edema, pneumonitis, bronchitis, and bronchiolitis obliterans (Reprotext, 1999). NO_2 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 NO_2. Short exposures to 100-500 ppm (190-900 mg/m³) NO_2 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 NO_2 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 NO_2 in an oxyacetylation cutting process. Recreation of the exposure conditions produced an NO_2 concentration of up to 90 ppm.

In another accidental human exposure, 3 astronauts inhaled a high concentration of NO_2 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 NO_2 concentrations, Adley (1946) reported that exposure of an unspecified number of workmen to an average concentration of 80 ppm (150 mg/m³) NO_2 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 NO_2 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 NO_2 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 NO_2 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 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 NO_2 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 NO_2 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 NO_2 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 NO_2 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 NO_2 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 (PaO_2) decreased significantly from 89.6 to 81.6 mm Hg. R_T remained significantly elevated 1 hour following exposure while PaO_2 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) NO_2 for 1 hour (Mohsenin, 1988), airway reactivity to methacholine challenge increased significantly after NO_2 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 NO_2 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 NO_2 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 NO_2 concentrations between 0.25 and 0.50 ppm (0.47 and 0.9 mg/m³). Bauer *et al.* (1986) reported that NO_2 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 NO_2 while at rest resulted in no significant change in pulmonary function. Following 10 minutes of exercise, significant reductions in FEV_1 (p<0.01) and partial expiratory flow rates at 60% of total lung capacity were observed. One hour after NO_2 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) NO_2 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) NO_2. Jorres *et al*. (1990) report an increase in airway reactivity to hyperventilation of 0.75 ppm SO_2 without altering airway tone following exposure to 0.25 ppm NO_2 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) NO_2 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 NO_2 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 NO_2 may be present in the general population, and that they contribute to the wide range of responsiveness present among asthmatics to inhaled NO_2 (Utell, 1989).

Predisposing Conditions for Nitrogen Dioxide Toxicity

Medical: Persons with asthma and other preexisting pulmonary diseases, especially RADS, may be more sensitive to the effects of NO_2 (Reprotext, 1999).

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 NO_2 because of the potential induction of methemoglobinemia (Reprotext , 1999). 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 NO_2 in humans, the clinical syndrome in accidental human exposure cases is similar to that seen in experimental animals exposed to high levels of NO_2 (Mauderly, 1984). The most comprehensive acute lethality study for NO_2 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 NO_2, 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 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 LC_{50} 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 LC_{50}, maximum likelihood estimate corresponding to 5% mortality (MLE_{05}), and benchmark doses at the lower 95% confidence interval expected to produce a response rate of 5% and 1% (BC_{05} and BC_{01}, 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 LC_{50}'s of 416, 201, 162, and 115 ppm, respectively, in young male rats. A 15-minute LC_{50} of 315 ppm was observed in rabbits. Higgins *et al*. (1972) determined a 5 minute LC_{50} of 831 and 1,880 ppm in rats and mice, respectively. Hilado and Machado (1977) observed a 10-minute LC_{50} of about 1,000 ppm in male mice. Takenaka *et al*. (1983) determined 16 hour LC_{50}'s in 9 strains of mice and 4 strains of rats. In mice, the LC_{50}'s ranged from 67 ppm to 33 ppm. In rats, the LC_{50}'s ranged from 56 ppm to 39 ppm. Takenaka *et al*. (1983) also observed a 16 hour LC_{50} 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 NO_2 concentrations of 123 mg/m³ (65 ppm) and 67 mg/m³ (36 ppm) for 8 hours or more. 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 NO_2, 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 NO_2 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 NO_2 than by duration of exposure (CARB, 1985).

Lung-only exposure of sheep to 500 ppm NO_2 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 NO_2-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 NO_2 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 NO_2 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 NO_2 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) NO_2 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) NO_2 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) NO_2 for 7 hours/day, 5 days per week, for 3 weeks (Kripke and Sherwin, 1984). No human reproductive studies of NO_2 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)

Study	California Air Resources Board (CARB), 1992
Study population	sensitive humans (asthmatics)
Exposure method	inhalation
Critical effects	increase in airway reactivity
LOAEL	
NOAEL	0.25 ppm
Exposure duration	1 hour
Extrapolated 1 hour concentration	0.25 ppm
LOAEL uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	1
Cumulative uncertainty factor	1
Reference Exposure Level	0.25 ppm (0.47 mg/m³; 470 µg/m³)

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 NO_2 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 NO_2 were 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 NO_2 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 BC_{05}'s from Table 1 results in a life-threatening level of 1-2 ppm, for 1-hour exposure to NO_2. Probit analysis to determine the BC_{05} from rat lethality data by Higgins *et al*. (1972) and mouse lethality data by Hilado and Machado (1977) also resulted in a life-threatening level of 2 ppm following adjustment of the

BC_{05}'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 NO_2 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 NO_2 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.

VIII. References

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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)

Description	colorless to light blue gas
Molecular formula	O_3
Molecular weight	48.0
Density	2.144 g/L @ 0°C (gas)
Boiling point	-111.9°C
Melting point	-192.7°C
Vapor pressure	>760 mm Hg @ 25°C (NIOSH, 1994)
Flashpoint	not applicable
Explosive limits	not applicable
Solubility	insoluble in water; soluble in alkaline solvents, oils
Odor threshold	0.0076-0.036 ppm (15-71 μg/m³) (AIHA, 1989)
Odor description	pungent
Metabolites	unknown
Conversion factor	1 ppm = 1.96 mg/m³ @ 25°C

III.   Major Uses or Sources

Ozone is a natural (non-anthropogenic) constituent of the atmosphere with a level between 0.01 and 0.04 ppm. Ozone (O_3) is produced in photochemical reactions of hydrocarbons and nitrogen oxides in the engines of motor vehicles (CARB, 1987) and by certain welding operations. 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, 1991).

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 (FEV_1) of 21.6% was observed; a 5.6% decrease in FEV_1 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 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), FEV_1, forced expiratory flow rates at 75% to 25% of lung volume (FEF_{25-75}), and increased coughing (McDonnell *et al*., 1983). Statistically significant increases in specific airway resistance (SRaw) 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, FEV_1, and significant increases in SRaw 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 FEV_1 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 review by Lippmann (1993) reported 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, FEV_1, peak expiratory flow rate (PEFR), FEF_{25-75}, and FEV_1/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, FEV_1, and FEF_{25-75}) 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 LC_{50} 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 µg/m³)
(California Ambient Air Quality Standard)

Study	Gong *et al*., 1986; McDonnell *et al*., 1983; McDonnell *et al*., 1985; California Air Resources Board (CARB), 1987a, 1987b.
Study population	normal adults
Exposure method	inhalation in controlled exposure chambers
Critical effects	decrease in pulmonary function including a 10% decrease in FEV_1
LOAEL	0.12 ppm (0.24 mg/m³) ozone
NOAEL	not observed
Exposure duration	1 hour
Extrapolated 1 hour concentration	0.12 ppm
LOAEL uncertainty factor	1.3 (margin of safety)
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	1
Cumulative uncertainty factor	1.3 (see below)
Reference Exposure Level	0.09 ppm (0.18 mg/m³; 180 µg/m³)

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 FEV_1. 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, FEV_1, PEFR, FEF_{25-75}, and FEV_1/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.

U.S.EPA (1975) has identified a significant harm level of 0.6 ppm (1.2 mg/m³). U.S.EPA 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 choice of the significant harm level is unacceptable as a level protective against severe health effects for exposure of the general public due to the lack of the presentation of a formal protocol for its derivation by U.S.EPA (1975).

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.

VIII.   References

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