CHRONIC TOXICITY SUMMARY

MALEIC ANHYDRIDE

(2,5-furandione; cis-butenedioic anhydride; toxilic anhydride; maleic andride)

CAS Registry Number: 108-31-6

I. Chronic Toxicity Summary

Inhalation reference exposure level	**0.7 µg/m^3** (2.5 ppb**)**
Critical effect(s)	Neutrophilic infiltration of the nasal epithelium; irritation of the respiratory system in rats, hamsters and monkeys
Hazard index target(s)	Respiratory system

II. Chemical Property Summary (HSDB, 1995)

Description	Colorless or white solid
Molecular formula	$C_4H_2O_3$
Molecular weight	98.06 g/mol
Boiling point	202°C
Melting point	52.8°C
Vapor pressure	0.1 torr @ 25°C (AIHA, 1970)
Solubility	Soluble in water, ether, acetate, chloroform, dioxane; @ 25°C, 227 g/100 g acetone, 112 g/100 g ethyl acetate, 52.5 g/100 g chloroform, 50 g/100 g benzene, 23.4 g/100 g toluene, 19.4 g/100 g o-xylene, 0.6 g/100 g CCl_4, 0.25 g/100 g ligroin
Conversion factor	4.0 µg/m^3 per ppb at 25ºC

III. Major Uses and Sources

Maleic anhydride is used as a chemical intermediate in the synthesis of fumaric and tartaric acid, certain agricultural chemicals, resins in numerous products, dye intermediates, and pharmaceuticals (HSDB, 1995). It is also used as a co-monomer for unsaturated polyester resins, an ingredient in bonding agents used to manufacture plywood, a corrosion inhibitor, and a preservative in oils and fats. The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 7366 pounds of maleic anhydride (CARB, 2000).

IV. Effects of Human Exposure

In many occupational situations workers are exposed to mixtures of acid anhydrides, including maleic anhydride, phthalic anhydride, and trimellitic anhydride. For example, Barker *et al.* (1998) studied a cohort of 506 workers exposed to these anhydrides. In one factory, workers were exposed only to trimellitic anhydride, which has the lowest acceptable occupational exposure limit (40 $\mu g/m^3$) of the three anhydrides. In that factory there was an increased prevalence of sensitization to acid anhydride and work related respiratory symptoms with increasing full shift exposure even extending down to levels below the current occupational standard. However, none of the workplaces had exposure only to maleic anhydride and a dose-response relationship was not seen with mixed exposures.

The following reports involve exposure only to maleic anhydride.

There are several case reports describing asthmatic responses possibly resulting from exposure to maleic anhydride. An individual showed an acute asthmatic reaction after exposure to dust containing maleic anhydride (Lee *et al.*, 1991). Workplace concentrations of maleic anhydride were 0.83 mg/m^3 in the inspirable particulate mass and 0.17 mg/m^3 in the respirable particulate mass. Bronchial provocation testing was performed with phthalic anhydride, lactose, and maleic anhydride. Exposure of this individual to maleic anhydride (by bronchial provocation testing) at 0.83 mg/m^3 and 0.09 mg/m^3 in inspirable and respirable particulate mass, respectively, showed a response of cough, rhinitis, and tearing within two minutes. Within 30 minutes, rales developed in both lungs and peak flow rate decreased 55%.

An individual occupationally exposed to maleic anhydride developed wheezing and dyspnea upon exposure (Gannon *et al.*, 1992). After a period without exposure, two re-exposures both resulted in episodes of severe hemolytic anemia. There was no evidence of pulmonary hemorrhage. Radioallergosorbent testing showed specific IgE antibodies against human serum albumin conjugates with maleic anhydride, phthalic anhydride, and trimellitic anhydride, but not with tetrachlorphthalic anhydride. A critique of the Gannon *et al.* (1992) study by Jackson and Jones (1993) questions the relationship of maleic anhydride exposure to the onset of the anemia, since there were extended periods of exposure to maleic anhydride before symptoms appeared.

Another case report described occupational asthma due to exposure to maleic anhydride (Guerin *et al.*, 1980).

Humans exposed to maleic anhydride showed respiratory tract and eye irritation at concentrations of 0.25 to 0.38 ppm (1 to 1.6 mg/m^3) maleic anhydride (Grigor'eva, 1964). No irritation was reported at 0.22 ppm maleic anhydride.

V. Effects of Animal Exposure

Short *et al.* (1988) chronically exposed CD rats (15/sex/group), Engle hamsters (15/sex/group), and rhesus monkeys (3/sex/group) to maleic anhydride by inhalation. Four groups of each species were exposed to concentrations of 0, 1.1, 3.3, or 9.8 mg/m^3 maleic anhydride for 6

hours/day, 5 days/week, for 6 months in stainless steel and glass inhalation chambers. Solid maleic anhydride was heated to 53°C to generate vapors, which were then mixed with a stream of nitrogen. Chamber target levels were monitored by gas chromatography as total maleic (maleic anhydride plus maleic acid). No exposure-related increase in mortality occurred. Of the species examined, only rats showed significant changes in body weight during the course of the experiment, with reductions among males in the high-dose groups after exposure day 40 and a transient weight reduction from days 78-127 in the mid-dose group. All species exposed to any level of maleic anhydride showed signs of irritation of the nose and eyes, with nasal discharge, dyspnea, and sneezing reported frequently. No exposure-related eye abnormalities were reported. The severity of symptoms was reported to increase with increased dose. No dose-related effects were observed in hematological parameters, clinical chemistry, or urinalysis. No effects on pulmonary function in monkeys were observed. Dose-related increases in the incidence of hyperplastic change in the nasal epithelium occurred in rats in all exposed groups, and in hamsters in the mid- and high-dose groups. Neutrophilic infiltration of the epithelium of the nasal tissue was observed in all species examined at all exposure levels. All changes in the nasal tissues were judged to be reversible. The only other significant histopathological observation was slight hemosiderin pigmentation in the spleens of female rats in the high-dose group.

Incidence of epithelial hyperplasia of the nasal mucosa in animals from Short *et al*. (1988)

Maleic anhydride (mg/m^3)	0	0	1.1	1.1	3.3	3.3	9.8	9.8
Pathology grade	Trace	Mild	Trace	Mild	Trace	Mild	Trace	Mild
Rat								
Male	0/15	0/15	2/15	6/15	1/15	14/15	0/15	12/15
Female	0/15	0/15	6/15	5/15	4/15	10/15	0/15	14/15
Combined		0/30		11/30		24/30		26/30
Hamster								
Male	0/15	0/15	0/15	0/15	0/15	5/15	0/15	8/15
Female	0/15	0/15	0/15	0/15	4/15	4/15	1/15	4/15
Combined		0/30		0/30		9/30		12/30
Monkey								
Male	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
Female	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
Combined		0/6		0/6		0/6		0/6

The teratogenicity and multigeneration reproductive toxicity of maleic anhydride were also investigated (Short *et al.*, 1986). To evaluate teratogenicity, pregnant CD rats were treated orally with maleic anhydride in corn oil at concentrations of 0, 30, 90, or 140 mg/kg-day from gestational days 6-15. Animals were necropsied on gestational day 20. No statistically significant dose-related effects were observed in maternal weight gain, implantation, fetal viability, post-implantation loss, fetal weight, or malformations. Groups of 10 male rats and 20 female rats/group (F_0 animals) were orally treated with 0, 20, 55, or 150 mg/kg-day maleic anhydride in corn oil to study multigeneration reproductive toxicity. Animals within the same dose group were bred together after 80 days of treatment to produce two F_1 generation animals (F_{1a} and F_{1b}) and animals from the F_1 generation were interbred to produce two F_2 generation animals (F_{2a} and F_{2b}). A significant increase in mortality was observed among both F_0 and F_1

generation animals in the high-dose group. Total body weight was significantly reduced in animals in the high-dose group at Week 11 of exposure for the F_0 generation males and females and at Week 30 of exposure in the F_1 generation males. No consistent pattern of dose- or treatment-related effect on fertility, litter size, or pup survival was observed. Examination of F_0 animals showed necrosis of the renal cortex in the high-dose group (60% of males and 15% of females). Absolute kidney weights were significantly increased in F_1 females in the low- and mid-dose groups, although there was no histological correlate. No changes in organ weight or histology were observed in the F_2 generation animals.

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Short *et al.*, 1988
Study population	Rats (15/sex/group), hamsters (15/sex/group), monkeys (3/sex/group)
Exposure method	Discontinuous inhalation exposure (0, 1.1, 3.3, or 9.8 mg/m^3)
Critical effects	Neutrophilic infiltration of the nasal epithelium; epithelial hyperplasia; respiratory irritation
LOAEL	1.1 mg/m^3
NOAEL	Not observed in rats
BMC_{05}	0.12 mg/m^3 for mild epithelial hyperplasia in rats (males and females combined)
Exposure continuity	6 hr/day, 5 days/week
Exposure duration	6 months
Average experimental exposure	21 µg/m^3 for the BMC_{05} (0.12 x 6/24 x 5/7 x 1000)
Human equivalent concentration	21 µg/m^3 for the BMC_{05} (Due to the lack of aerosol particle size data for the critical study, a human equivalent concentration could not be developed using recommended methods of inhalation dosimetry.)
LOAEL uncertainty factor	not needed in benchmark approach
Subchronic uncertainty factor	1
Interspecies uncertainty factor	3 (see below)
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	30
Inhalation reference exposure level	0.7 µg/m^3 0.2 ppb)

Short *et al.* (1988) examined the toxicity of maleic anhydride to rats, hamsters, and monkeys by the inhalation route of exposure. Dose- and exposure related effects, although mild and reversible, were observed at all exposure levels. Specifically, exposure to maleic anhydride vapors resulted in hyperplastic change in the nasal epithelium of rats and hamsters (obligate nose breathers). Neutrophilic infiltration of the nasal epithelium was observed in all three species at all levels of exposure. All species also showed signs of irritation at all exposure levels. The observation that acute maleic anhydride is a strong respiratory irritant to humans (ACGIH, 1992)

suggests that this is a valid endpoint of toxicity to humans as well. Human exposure at levels as low as ~1 mg/m^3 appears to trigger acute asthmatic reactions in sensitive individuals (Lee *et al.*, 1991). The histological changes observed by Short *et al*. occurring as a result of inhalation exposure to a known strong irritant such as maleic anhydride are considered to be the adverse effect of repetitive acute exposures, rather than a chronic response, in the development of the REL.

The chronic REL was developed using the benchmark approach. The gamma model in the U.S. EPA's BMDS software yielded a BMC_{05} of 0.12 mg/m3 for mild epithelial hyperplasia in male and female rats combined. Because of the similarities among species and the inclusion of monkeys in the study, an interspecies uncertainty factor of 3, rather than 10, was used. Although there is no evidence of a toxic response similar to the development of asthma in animals, the 1.1 mg/m^3 LOAEL from the animal studies of Short *et al.* (1988) results in a REL of 0.7 $\mu g/m^3$ which should protect asthmatics from maleic and other anhydrides.

VII. Data Strengths and Limitations for Development of the REL

The major strengths of the REL for maleic anhydride are the availability of multiple-species, multiple-dose subchronic inhalation studies, and the observation of a mild effect LOAEL. The major uncertainties are the lack of human data and the lack of a NOAEL observation.

VIII. Potential for Differential Impacts on Children's Health

Minimal teratogenic and reproductive adverse effects were seen at the lowest oral dose of maleic anhydride (20 mg/kg-day), given to rats during gestation (Short et al., 1986). This dose is equivalent to a person inhaling 70 mg/m^3. Thus the chronic REL of 0.7 $\mu g/m^3$ should protect children. Maleic anhydride is a respiratory irritant and an inducer of asthma. Exacerbation of asthma has a more severe impact on children than on adults. However, there is no direct evidence in the literature to quantify a differential effect of maleic anhydride in children.

IX. References

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CHRONIC TOXICITY SUMMARY

METHYL ISOCYANATE

(MIC, CH_3-N=C=O)

CAS Registry Number: 624-83-9

I. Chronic Toxicity Summary

Inhalation reference exposure level	**1 µg/m^3** (0.5 ppb)
Critical effects(s)	Decreased weight gain and lung pathology at cessation of exposure in rats
Hazard index target(s)	Respiratory system; reproductive system

II. Chemical Property Summary (HSDB, 1995; CRC, 1994)

Description	Colorless liquid
Molecular formula	C_2H_3NO
Molecular weight	57.06 g/mol
Boiling point	39.5°C
Melting point	–45°C
Vapor pressure	348 torr @ 20°C, 600 torr @ 30°C (Varma and Guest, 1993)
Solubility	10 percent in water @ 15°C
Conversion factor	2.3 µg/m^3 per ppb at 25°C

III. Major Uses and Sources (Dave, 1985; U.S. EPA, 1986; HSDB, 1995)

Methylisocyanate (MIC) is prepared industrially by reacting methylamine with phosgene, oxidizing monomethylformamide at high temperatures (≥ 550°C), or heating metal methylisocyanates. Because of its high reactivity, MIC is used as an intermediate in organic synthesis, most notably in the production of carbamate based pesticides. Tobacco smoke from some brands of cigarettes also contains MIC (about 4 µg per cigarette). Workers exposed to the MIC 8-hour threshold limit value of 0.02 ppm (46 µg/m^3) are exposed to approximately 460 µg MIC in a workday. Based on the most recent inventory, the annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California were negligible (CARB, 2000). This does not include estimates of emissions of breakdown products from the use of metam sodium in agricultural applications. Use of metam sodium averaged 15,400,000 pounds/year from 1995 to 1999.

IV. Effects of Human Exposure

Although occupational exposures to MIC have been documented (Varma, 1986), few known exposures to the general public have occurred. A major exposure occurred in Bhopal, India in December 1984. Because of the sudden, short-term release (30-45 minutes), no measurements occurred, but the air concentration was estimated as 13 ppm (Dave, 1985) to 100 ppm (Varma, 1986).

The chemical identity of the ultimate toxicant has not been unequivocally determined and may consist of more than one chemical species. Although the chemistry of MIC suggests that hydrolysis to methylamine and dimethylurea is rapid, such hydrolysis in moist air is probably slow, and the reaction with photochemically produced hydroxyl radical is also slow (chemical $T_{1/2}$ about 3 months) (U.S. EPA, 1986). Brown *et al.* (1987) have shown that the alkylisocyanates (e.g., MIC) are relatively resistant (compared to the arylisocyanates) to hydrolysis in water. Hence, despite the high water reactivity of MIC, this compound could possibly persist in the environment for many days after an initial release.

Within 5 days of the initial exposure to MIC at Bhopal, more than 2,000 deaths occurred (Dave, 1985), while 4,000 more deaths were documented during the following decade (Lepkowski, 1994). The initial symptoms among the population living near the MIC plant were irritation and difficulty in breathing (Varma, 1986). Blindness occurred in more than 10,000 exposed persons but later resolved in most cases (Andersson *et al.*, 1990). The acute damage that led to death was mainly to the respiratory system, most likely pulmonary edema, bronchospasm, and electrolyte imbalance (Varma, 1986). However extrapulmonary damage, including tissue anoxia, gastrointestinal symptoms, and muscular weakness, were also observed (Dave, 1985). Within a year of the exposure, survivors continued to exhibit damage to the lung and eyes. Fibrosis of the lungs was seen in 30 percent of this group (Dave, 1985).

Reproductive toxicity was observed among women exposed to MIC in Bhopal. Varma (1987) reported 43 percent unsuccessful pregnancies among 865 women who were pregnant at the time of the MIC release. Among the live births, 14 percent of the infants died within 30 days, whereas a death rate of only 3 percent for the same interval was recorded 2 years prior to the release. Bhandari *et al.* (1990) reported increased spontaneous abortions and neonatal deaths among exposed women who were pregnant at the time of exposure compared to a control group in another city. In the latter study, stillbirths and congenital malformations were similar in the exposed and non-exposed groups.

Non-reproductive, non-pulmonary responses were evident in a group of exposed Bhopal residents, 3-years following exposure to the MIC vapors. Loss of vision and loss of visual acuity were more prominent among exposed residents than among unexposed people, and the losses appeared to be dose-dependent (Andersson *et al.*, 1990). In this study, the surrogate for dose was extent of early deaths in a housing cluster. Similarly, cataracts were reported more often among the exposed than among the unexposed group.

The lesions associated with lung damage may be expressed as pulmonary edema for immediate effects (Varma, 1986), and lesions associated with the bronchoalveolar area for long-term effects

(Dave, 1985, Varma, 1986). Vijayan *et al.* (1995) studied cellular components of bronchoalveolar lavage (BAL) and pulmonary function in Bhopal patients 1.3, 2.7, and 5.1 years after exposure to MIC. All had lived within 3-miles of the factory and all experienced acute respiratory and ophthalmic symptoms on the day of exposure. All were experiencing continued respiratory symptoms. Among the exposed people, decrements in forced vital capacity and forced expiratory volume (at 1-minute) were observed. In general, the decrements ranged from 12 - 21 percent of predicted values, whereas the control group exhibited decrements of 2 - 4 percent of the expected values. Analysis of the BAL revealed increases in total cells (all exposed groups), increased absolute numbers of macrophages (all exposure groups), decreased percentage of lymphocytes (2.7 and 5.1 year groups), and increased numbers and percentage of neutrophils (5.1 year group). These cell types are involved, through the secretion of various factors, in inflammatory and immunologic processes in the lung (Reiser and Last, 1986). The Vijayan *et al.* (1995) study thus suggests long term damage to lung parenchyma among people who survived the initial acute effects of MIC exposure.

In summary, humans exposed acutely by inhalation to MIC may experience long-term (as well as immediate) damage to pulmonary and extrapulmonary systems. The lung is probably the critical target organ for long-term effects from acute exposure, although adverse effects on other organs (e.g., eye, reproductive, and gastrointestinal) also exist. The late responses to the acute exposure suggest an immunological component, which could involve several systems including lung, eye, liver, and kidney. The chemical identity of the ultimate toxicant is unknown and may be more than one compound.

Avashia *et al*. (1996) assessed pulmonary effects from long-term, low-level MIC for more than 400 workers at a large chemical facility. Serial pulmonary function data, cigarette smoking histories, and industrial-hygiene measurements were available. Jobs were classified according to level of MIC exposure as none, low, moderate or high. Where work records were incomplete, exposures were based on the ratings of supervisors and coworkers. The frequency of pulmonary impairment was evaluated for the assumed four levels of exposure. No specific or consistent pulmonary impairment was evident. Unfortunately the report gave no quantitative classification of low, moderate or high MIC levels.

V. Effects of Animal Exposure

Experimental animal studies have been designed to address the experiences of the victims of the Bhopal disaster, in which the exposure has been described as acute because of the short duration (30-45 min). No studies were found that described exposure duration greater than 10 days. However, a chronic component to MIC exposure may exist as a result of slower rates of hydrolysis in air (compared to water), the presence of carbamylated hemoglobin in MIC-exposed people, and the change from edematous to inflammatory and/or fibrotic lesions with time. Further, a glutathione-dependent reversible MIC transport system has been suggested in experimental animals (see below).

MIC is absorbed through the respiratory tract and distributed to non-respiratory organs in experimental animals. In an acute (30 min) inhalation exposure to a dose of ^{14}C-MIC (labeled in

the isocyanate moiety) equivalent to one-LC_{50} (23 mg/L), rats accumulated protein-bound radioactivity (including carbamylated proteins) in brain, liver, kidney, and lung, but not in blood (Bhattacharya *et al.*, 1988). Ferguson *et al.* (1988) exposed guinea pigs by inhalation to 0.47 ppm ^{14}C-MIC (methyl group) for 6-hours. At the end of exposure, the label was found in arterial and venous blood, bile, and urine. At 2.7 days post-exposure, the label decreased to 2-7 percent. MIC was retained in the nasal-laryngeal area of the guinea pigs.

MIC, like reactive isocyanates in general, can react with biological molecules containing amino, alcohol, or sulfhydryl groups, as well as with water. While hydrolysis in an aqueous environment, such as the lung, is theoretically possible, measurements show that alkyl isocyanates are relatively resistant (compared to arylisocyanates) to such hydrolysis (Brown *et al.* 1987). The absence of a role for MIC hydrolytic products, methylamine (MA) or dimethylurea (DMU), is also suggested by the work of Jeevaratnam and Sriramachari (1994) and Sriramachari *et al*. (1994). Inhalation (30 min) or subcutaneous exposure of rats to either hydrolytic product at levels equivalent to the LC_{50} or LD_{50} did not result in death. Similarly, neither methylamine nor dimethylurea duplicated the acute effects of respiratory necrosis and congestion. However, exposure to these hydrolytic products did lead to interstitial pneumonitis, an observation that suggests MA and/or DMU could lead to subsequent inflammatory responses if sufficient amounts are present.

A role for methylamine in reproductive/developmental toxicity was investigated by Guest and Varma (1991). In a mouse study, pregnant dams were exposed to varying doses (intraperitoneal) of methylamine (as well as the di- and trimethyl compounds). Reproductive toxicity was not observed for methylamines. However, in cultured embryo experiments, decrements in crown-rump length, yolk-sac diameter, head length, and embryo survival were observed. The concentrations were high (>0.75 mM) and the interpretation of the biological activity of methylamine in terms of inhalation exposure is difficult.

MIC is a carbamylating intermediate; this is the basis for its use in the manufacture of carbamate based pesticides. In the same way, MIC should react with the appropriate functional groups of proteins, peptides, and nucleic acids. However, i*n vitro* studies with cholinesterases show that such a reaction is not efficient (Brown *et al.*, 1987), an observation which may be explained by the presence of protonated amino groups at physiological pH (Baillie and Slatter, 1991).

A transport system for MIC via reduced glutathione (GSH) has been suggested by the discovery of the MIC-adduct, S-(N-methylcarbamoyl)glutathione (SMG), in the bile and the MIC-adduct of N-acetylcysteine (mercapturic acid, AMCC) in the urine of rats exposed to MIC by non-inhalation routes (Pearson *et al.*, 1990; Slatter *et al.*, 1991). The reaction of MIC with GSH and with cysteine is reversible, and can provide a source of free MIC in the tissues (Baille and Slatter, 1991). Similar studies in experimental animals exposed to MIC by inhalation have not been reported. However, humans exposed by inhalation to N,N-dimethylformamide (H-C-(=O)-$N(CH_3)_2$) excrete AMCC in urine (Mraz and Nohova, 1992). Hence a reversible MIC-transport system in animals, including humans, is possible, and the presence of high levels of GSH in human lavage fluid (Cantin *et al.*, 1987) would permit the initiation of this mechanism.

The toxicity of the adduct SMG was tested in mouse embryo culture (Guest *et al.*, 1992). Mouse embryos, at day 8 of gestation in vivo, were removed from their dams and cultured in the presence (and absence) of SMG. Dose-dependent (0.25 - 2 mM) decrements were observed for yolk sac diameter, crown-rump length, somite number, and protein content. Delayed DNA synthesis in the embryos and in yolk-sacs occurred in the presence of 0.25 mM SMG. Similar to the results obtained with methylamine, the SMG concentrations were high and the exposures were not by inhalation. However, the data show that a MIC metabolite, SMG, has toxic properties. In the presence of GSH (1 or 3 mM), the extent of the SMG-dependent toxicities was decreased. Such data demonstrate the reversibility of the binding between MIC and GSH.

Three inhalation studies were identified in which experimental animals were exposed to more than one dose of MIC. Among these studies, two used exposure durations for more than one day (Dodd and Fowler, 1986; Mitsumori *et al.*, 1987). Rats and mice were exposed by inhalation to 0, 1.1, and 2.8 (female) or 3.0 (male) ppm MIC for 6 hr/day for a total of 4 days, and then followed during a 91-day post-exposure interval (Mitsumori *et al.*, 1987). Among the rats, post-exposure deaths occurred by 49 days (male) and 14 days (female) at the high dose. Among the mice, only 1 male mouse died at 16 days post-exposure. Reduced weight gain was observed among the female and male rats in the high dose group, prior to death, although the absolute weights were not different from the unexposed rats one day before the end of exposure. Among the mice, a slowed weight gain was observed at 3- and 6-days post exposure (male) and 1 day post exposure (female) at the high dose, but normal weight gain returned by 1 week following cessation of exposure. At 7 days post-exposure, microscopic changes were observed in the respiratory system among the high dose rats of both sexes. Between 8- and 27 days post-exposure, increased lesions in the respiratory tract and also in liver, thymus, spleen, heart, and brain were observed at the high dose. Similar lesions were not observed in rats exposed to 1.1 ppm MIC and followed to the 8-27 day post-exposure. Among survivors, the incidence of lesions decreased to control values by 91 days. Among the mice, treatment related changes in the respiratory tract were observed at the high dose at 7 days post-exposure. Between 28 and 91 days, the lesions associated with the upper respiratory tract disappeared, whereas those associated with the major bronchi remained, although somewhat attenuated. These data suggest that the rat is more sensitive than the mouse to the effects of MIC. A LOAEL of 2.9 ppm is indicated, based on post-exposure decreased weight gain and respiratory tract changes in rats.

Dodd and Fowler (1986) exposed rats to 0, 0.15, 0.6, and 3.1 ppm MIC for two 4-day sessions at 6-hours/day and examined the animals within 1-day following exposure. The 2-cycle exposure included a 2-day recess from exposure. No deaths occurred at any MIC concentration during the exposure. Lesser weight gain occurred for rats in the 3.1 ppm groups, whereas weight among the rats in the 0.15 and 0.6 ppm MIC groups was indistinguishable from the air-exposed control animals. On exposure days 3 and 8, mean food consumption values in the high dose group were below those for the non-exposed group. At the time of termination, male rats exposed to 3.1 ppm MIC exhibited a 38 percent increase in hemoglobin concentration and a 26 percent decrease ($p<0.001$) in oxygen saturation, compared to the unexposed rats ($p<0.001$). Such changes were not observed for the female rats exposed to 3.1 ppm or for rats of either sex exposed to 0.15 or 0.6 ppm MIC. Absolute lung weights increased ($p<0.001$) in both sexes after exposure to 3.1 ppm, compared to the control rats. Decreases in liver, kidney and testes absolute weights were observed in this exposure group, but the authors interpreted these data as a reflection of the body

weight losses. No weight changes were observed in rats exposed to 0.15 or 0.60 ppm MIC. Gross and microscopic lesions were observed in rats (female and male) exposed to 3.1 ppm, but not in rats exposed to 0, 0.15, or 0.6 ppm MIC. The microscopic lesions occurred in the respiratory tract and consisted of inflammation, epithelial necrosis, squamous metaplasia, and epithelial hyperplasia. These lesions extended into the bronchioles. These data suggest a NOAEL of 0.6 ppm MIC, based on weight gain loss, absolute lung weight, and lung histopathology in rats, immediately following cessation of exposure.

Post-exposure changes in lung pathology also occurred in the rats surviving 3.1 ppm in the Dodd and Fowler (1986) study. The early lesions associated with inflammation, epithelial necrosis, squamous metaplasia, and epithelial hyperplasia extending to the bronchioles either decreased in severity or receded toward the upper respiratory tract by 85-days post-exposure. In males, the intraluminal and submucosal fibroplasia changed in appearance during this interval, due in part to the maturation of fibrous tissue. Mucous plugs were also seen in the terminal bronchioles and alveoli in some rats. The importance of this observation is the progressive character of MIC induced lung disease. Such progression may be difficult to follow at lower doses, if the times involved are of insufficient duration.

Sethi *et al.* (1989) exposed rats by inhalation to 0, 0.21, 0.26, and 0.35 ppm MIC for 6 days at 0.5 hr/day. Statistical evaluation was not presented. No post-exposure deaths were reported, although lethality was recorded for rats exposed to 3.5 and 35 ppm for only 10 minutes. Following the 0.5 hr $\times$ 6-day exposure, the weight gain declined in proportion to the exposure dose. At the lowest dose (0.21 ppm) the weight gain was 111 g after 91 days post-exposure, compared to a weight gain of 218 g during the same interval among the non-exposed rats. The absolute weights of the rats at the end of the exposure were not given. According to the narrative, inflammatory lesions of bronchopulmonary tissue were present; their extent increased with dose. A dose-response increase in markers of lung infection was present and suggests that the MIC exposed rats were more prone to infectious agents than were the unexposed animals. Non-specific lesions in liver and kidneys were also observed and appeared to be dose dependent, but the authors suggested that these effects could be a result of the lung infections.

Fetotoxicity was observed in two experimental animal studies (Schwetz *et al.*, 1987; Varma, 1987). Among female mice exposed to 0, 1, or 3 ppm MIC during gestation days 14 - 17 for 6 hr/day, an increased incidence of fetal deaths was observed at 1 ppm (Schwetz *et al.*, 1987). At 3 ppm, the average number of pups/litter decreased relative to the air-exposed controls. The dams were unaffected in terms of survival, body weight, or length of gestation. Non-gestational exposure (6 hr/day, 4 days) did not affect the number of pregnancies or the live litter sizes, suggesting that the fetotoxic effect may be specific to the female reproductive tract rather than a general attribute of systemic toxicity. Similarly, female mice exposed for 3 hours on gestation day 8 to 0, 2, 6, 9 or 15 ppm MIC gave birth to pups with decreased body weights at the lowest dose, although a good dose-response was not observed (Varma, 1987). At 9 or 15 ppm MIC, the surviving dams lost 75 - 80 percent of their fetuses. Maternal mortality and decreased skeletal lengths were also observed at 9 and 15 ppm. A distinction between maternally induced fetotoxicity and a direct effect on fetal health could not be made. Because the inhalation exposure to the dams occurred for only 3 hrs on one day, a chronic LOAEL is not suggested. Exposure of male rats to one dose of 3.2 mg/L for 8 minutes resulted in a 21 percent fertility rate

among the cohabited female rats within the day 8-14 period post-exposure compared to a fertility rate of 40% for controls; however, the rates increased after 15 days post-exposure (Agarwal and Bose, 1992). There was no evidence of fetotoxicity among the dams impregnated by the MIC-exposed male rats. Exposure of male and female mice to 0, 1, or 3 ppm MIC did not result in altered body weights, fertility, or litter size (Schwetz *et al*, 1987). The results suggest that exposures to MIC at doses that are not toxic to adult male or female (pregestational) mice or rats do not result in adverse reproductive outcomes.

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Dodd and Fowler (1986)
Study populations	F344 rats
Exposure method	Inhalation (0, 0.15, 0.6, or 3.1 ppm)
Critical effects	Decreased weight gain and lung pathology immediately after cessation of exposure
LOAEL	3.1 ppm
NOAEL	0.6 ppm
Exposure continuity	6 hours/day, 8 days/10 day experiment (2-cycles, with one 2-day recess from exposure)
Exposure duration	10 days
Average experimental exposure	0.12 ppm for the NOAEL group (0.6 x 8/10 x 6/24)
Human equivalent factor	0.15 ppm for the NOAEL group (gas with pulmonary respiratory effects, RGDR = 1.23, based on BW = 152 g, MV = 0.12 L/min, SA = 225 cm^2)
LOAEL uncertainty factor	1
Subchronic uncertainty factor	10
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	300
Inhalation reference exposure level	0.5 ppb (1 µg/m^3)

Although the exposure was for only 10 days, the Dodd and Fowler (1986) study includes the longest exposure duration of the available investigations and also uses some of the lower exposure levels (down to 0.15 ppm). The microscopic findings of the respiratory tract were statistically analyzed, although an observation of the tabulated data at the four doses (0, 0.15, 0.6, and 3.1 ppm) clearly shows a NOAEL of 0.6 ppm. Other endpoints with the same NOAEL were increased hemoglobin and increased absolute lung weights. The symptomatic ramifications of the increased hemoglobin are unknown, although similar increases were reported for humans exposed to MIC in Bhopal (Srivastava *et al.*, 1988). The lung weight gain may be a reflection of the pathological changes seen in the microscopic studies.

Decreased body weight gain was also seen in the experimental 4 day rat inhalation study of Mitsumori *et al.* (1987) (NOAEL = 1.1 ppm), except that the decrease in the latter study did not

occur until 1 and 3 days (female and male, respectively) post-exposure. The apparent discrepancy could be explained, in part, on the basis of the length of exposure, which was twice as long in the Dodd and Fowler (1986) study. However, the weight gain loss in the Dodd and Fowler (1986) study was initiated within one day of the start of exposure.

The MIC chronic REL of 0.5 ppb is based on endpoints observed within 1 day of cessation of exposure. Post-exposure evaluation showed that, at a higher exposure level (3.1 ppm), progressive changes, including death, occurred. Post-exposure observations, however, were not reported at the 0.15 and 0.6 ppm MIC levels. The attribute of delayed MIC inhalation toxicity has also been observed in other experimental animals studies (Dodd and Fowler, 1986, Mitsumori *et al.*, 1987). In the case of the human MIC exposure in Bhopal, India, death did not occur during the immediate 30 - 45 minute exposure, but exhibited a lag phase. A few deaths occurred during the first few hours, the maximum occurred at 2 - 3 days, and by the end of a week about 2500 deaths were documented (Dave, 1985; Varma, 1986; Varma and Guest , 1993), although Varma (1986) suggests that the immediate number may be closer to 5,000. One report suggests that during the intervening decade as many as 6,000 deaths may be attributed to the initial exposure in Bhopal (Lepkowski, 1994). Such information suggests that the presence of an adverse effect at the NOAEL of 0.6 ppm (Dodd and Fowler, 1986) might be possible if the rats were observed during an extended post-exposure interval. Experimental evidence is needed to test this hypothesis.

Only one study was identified in which post-exposure observations were made on experimental animals exposed subchronically by inhalation to multiple doses of MIC. Mitsumori *et al.* (1987) exposed rats to 0, 1.1, and 2.8 (females) or 3.0 (males) ppm MIC for 6 hr/day for 4 days and observed the rats for 91 days. No deaths and no weight gain loss (in contrast to Dodd and Fowler, 1986) were present until the post-exposure period and were mainly observed in animals exposed at the high dose. Using a NOAEL of 1.1 ppm MIC, a chronic REL of 1.1 ppb (2.6 $\mu g/m^3$) was derived. The REL based on the Mitsumori *et al.* (1987) study is similar to the REL based on immediate effects (Dodd and Fowler, 1986), and may indicate that the time of occurrence of exposure related effects may not be as important as the MIC air concentration.

VII. Data Strengths and Limitations for Development of the REL

The strengths of the inhalation REL for MIC include the availability of controlled exposure inhalation studies in multiple species at multiple exposure concentrations and with adequate histopathogical analysis and the observation of a NOAEL. Major areas of uncertainty are the lack of adequate human exposure data and the lack of chronic inhalation exposure studies.

VIII. Potential for Differential Impacts on Children's Health

Since exposures to MIC at levels that are not toxic to adult male or female (pregestational) mice or rats do not result in adverse reproductive outcomes, the chronic REL of 1 $\mu g/m^3$ should adequately protect infants and children. MIC is a respiratory irritant and the developing respiratory system is more sensitive than that of adults. However, there is no direct evidence in

the literature to quantify a differential effect of MIC on the respiratory system of infants and children.

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CHRONIC TOXICITY SUMMARY

4,4¢-METHYLENE DIANILINE

(MDA; 4,4'-diaminodiphenylmethane; 4,4'-diphenylmethanediamine; DAPM; dianilinemethane)

CAS Registry Number: 101-77-9

I. Chronic Toxicity Summary

Inhalation reference exposure level	**20 µg/m^3** (2 ppb)
Critical effect(s)	Ocular toxicity to the retinas of guinea pigs
Hazard index target(s)	Eyes; alimentary system (hepatotoxicity)

II. Chemical Property Summary (HSDB, 1995; CRC, 1994)

Description	Colorless to pale yellow flakes; tan
Molecular formula	$C_{13}H_{14}N_2$
Molecular weight	198.3 g/mol
Boiling point	398-399°C
Melting point	92.5°C
Vapor pressure	1 torr @ 197°C
Solubility	Soluble in alcohol, benzene, ether; 273 g/100 g acetone; 0.1 g/100 g water @ 25°C
Conversion factor	8.1 µg/m^3 per ppb at 25ºC

III. Major Uses and Sources

4,4'-Methylene dianiline (MDA) is synthesized by the reaction of aniline with formaldehyde. MDA's major uses are as a chemical intermediate in the synthesis of certain isocyanates and polyurethane polymers, as a corrosion inhibitor, in the preparation of azo dyes, as a rubber preservative, and in the curing of epoxy resins and neoprene (HSDB, 1995; ACGIH, 1992). The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 1133 pounds of MDA (and its dichloride) (CARB, 2000).

IV. Effects of Human Exposure

Several cases of human exposure to MDA have identified the compound as a hepatotoxicant which produces cholestatic jaundice (Kopelman *et al.*, 1966; McGill and Motto, 1974; Williams *et al.*, 1974; Bastian, 1984). Bastian (1984) described cases of acute hepatic illness in four workers exposed from laying floors using an epoxy resin base, which contained MDA as a curing agent. The workers were exposed via fumes and dusts in the air as well from hand

contact with powder and had worked with epoxy resins for periods ranging from one to 12 years. The level of exposure was not quantified. The workers initially reported to the hospital with symptoms of abdominal pain three days after the most recent exposure and all were discharged within four days. Two workers continued to show severe symptoms five days after the onset, with abdominal pain, jaundice, a tender liver, nausea, dyspnea, and muscular pain. Plasma bilirubin, alkaline phosphatase, and aspartate aminotransferase levels were elevated. Some symptoms did not subside until two months after the onset. One worker, after another exposure, experienced nausea, abdominal pain, and muscular pain. A second worker reported further symptoms of headache, tiredness, and decreased libido.

Williams *et al.* (1974) reported symptoms in 6 of approximately 300 workers exposed to MDA by surface coating concrete walls with epoxy resins. Exposure probably occurred by inhalation, ingestion, and skin contact as a result of mixing powder containing MDA. Symptoms of clinical hepatitis in the 6 workers appeared two days to two weeks after beginning work; five of the six had elevated bilirubin levels, and one liver biopsy showed bile stasis. All the workers recovered completely after an unspecified time.

McGill and Motto (1974) described hepatitis among 13 men who, over the course of 6 years, were occupationally exposed to MDA in the blending of epoxy resins used in the manufacture of insulating material. Among the 13 patients showing symptoms, all reported weakness, jaundice, and dark urine; 11 reported abdominal pain, nausea or vomiting, and anorexia; and over half reported fever, chills and/or headache. All the workers recovered within a 10 week period. After the first cases of hepatitis occurred, air sampling showed initial levels of MDA to be 0.1 ppm in the work area. After additional cases of hepatitis occurred, measures were taken to reduce worker exposure, and air levels were reduced to as low as 0.0064 ppm. The authors concluded that percutaneous absorption was the likely major route of exposure in light of the fact that cases occurred in spite of measures taken to reduce air levels and there was evidence that significant hand contact with the compound occurred during the workday. Since the symptoms appeared within one to 18 days after "working intensively" with the compound and exposure routes were not clearly established, quantitation of exposure levels was considered difficult.

The most well-known incident of MDA toxicity to humans resulted from ingestion of bread made with flour contaminated with MDA during transport (Kopelman *et al.*, 1966a). Eighty-four persons showed symptoms of abdominal pain and some degree of jaundice. All patients had elevated serum alkaline phosphatase and glutamic oxaloacetic transaminase levels. Seventeen had serum bilirubin levels over 5 mg/100 ml. Liver biopsy was performed on 8 persons and evaluated in a separate study (Kopelman *et al.*, 1966b). The primary finding was an unusual lesion described during the early course of the disease as portal zone cholangitis and later as centrilobular cholestasis with necrosis. The initial study reported that all but 2 patients had complete recovery within several weeks. However, a two year follow-up study of 14 individuals showed that 10 still had symptoms of some severity 7 to 23 months after initial onset including food intolerance, gastrointestinal disturbances, fatigue, and visual disturbances (Kopelman, 1968).

Human effects other than hepatotoxicity have been described including several cases of contact dermatitis and skin sensitization (LeVine, 1983; Van Joost *et al.*, 1987; de Pablo *et al.*, 1992;

Bruynzeel and van der Wegen-Keijser, 1993). A case report of a man exposed to MDA with potassium carbonate and γ-butyrolactone by accidental ingestion has been described (Roy *et al.*, 1985). In addition to hepatitis and abnormal liver function, which persisted over 18 months, the patient developed a progressively worsening retinopathy described as a "malfunction of the retinal pigment epithelium" accompanied by diminished visual acuity. The patient improved after approximately 3 months, but after examination at 18 months had not completely recovered.

Another report described the development of acute cardiomyopathy in addition to hepatitis in a worker exposed to a large quantity of MDA dust as the result of air filtration malfunction (Brooks *et al.*, 1979). The patient showed an abnormal ECG and an elevated cardiac LDH isoenzyme profile, which returned to normal within one month of onset.

V. Effects of Animal Exposure

The carcinogenicity of MDA was investigated in F344/N rats and B6C3F$_1$ mice (50/sex/dose group) administered in the drinking water at concentrations of 0, 150, and 300 ppm MDA (dihydrochloride) for 103 weeks (Lamb *et al.*, 1986). A 14-day range finding study was also conducted with 5 animal/sex/species/dose group, with exposure levels of 0, 200, 400, 800, 1600, and 3200 ppm MDA. A 13-week subchronic study was conducted with 10 animals/sex/species/dose group and exposure levels of 0, 25 (mice), 50, 100, 200, 400, and 800 (rats) ppm MDA. Using body weight and drinking water values from the study, low and high daily doses in the chronic study were calculated to be 9 and 16 mg/kg-day for male rats, 10 and 19 for female rats, 25 and 57 for male mice, and 19 and 43 for female mice. In the chronic study, survival was reduced among male mice treated with 300 ppm MDA. Final mean body weights were reduced in the 300 ppm dose group of female rats (-9%), male mice (-13%), and female mice (-16%). Among rats, non-cancer effects included follicular cysts and follicular-cell hyperplasia of the thyroid (significantly increased incidence in high-dose females; $p<0.05$ by Fisher's exact test). In the liver, the incidence of fatty and focal cellular change was elevated in low-dose male and female rats and also in high dose male rats. Incidence of unspecified dilatation of the liver was also elevated in high-dose male rats. Increased incidence of kidney mineralization was found in male rats treated with 300 ppm MDA. Among mice, incidence of liver degeneration was elevated in males in both treatment groups and females in the high-dose group ($p<0.01$ by Fisher's exact test). Incidence of kidney nephropathy was increased in male and female mice in both treatment groups and mineralization of the renal papilla was increased in both sexes in the high-dose group ($p<0.01$). From the 13-week study, the authors noted thyroid and bile duct effects in rats at 800 ppm MDA in water and in mice at 400 ppm MDA in water.

Albino and pigmented guinea pigs were exposed to aerosols of methylene dianiline in polyethylene glycol 200 (PEG) in nose-only exposure chambers (Leong *et al.*, 1987). Animals (8 of each strain) were exposed to a time-weighted average aerosol concentration of 0.44 g MDA/m^3 in air for 4 hours/day, 5 days/week for 2 weeks. Eight control animals were neither exposed to aerosol nor placed in the exposure chamber. Two weeks after the exposure period, animals were evaluated for dermal sensitization and irritation by challenge with 0.05 ml of 0, 2, 20, and 200 mg MDA/ml in PEG for up to 24 hours. No evidence of dermal irritation or

sensitivity was found. Subsequently, the animals were also examined for pulmonary sensitization by challenge with aerosols containing 0.01 and 0.05 ml of 200 mg MDA/ml PEG. Lung insufflation pressures were measured as an indication of changes in lung distensibility. No evidence of pulmonary sensitization was found. After the pulmonary challenge, the animals were examined histopathologically, with emphasis on eye, lung, liver, and kidney toxicity. Ocular toxicity ranging from mild to more severe was observed in all MDA-treated animals, but in none of the control animals. Pigmented animals did not differ in sensitivity or effect compared to albino animals. Mild lesions were described as "retraction and thickening of the outer segments of the photoreceptor cells" while more severe effects included swelling "through the inner segments of the photoreceptor cells to the outer nuclear layer." Some evidence of inflammatory cell infiltration was also noted and the pigmented epithelial layer was also degenerated. The authors conclude that the effects were attributable to MDA because no retinal lesions have been associated with exposure to the PEG vehicle. Furthermore, the inhalation exposures to MDA are the likely cause rather than the dermal and lung sensitization study exposures because these subsequent studies were conducted on control as well as treated animals. Pulmonary granulomas consisting of "an aggregate of macrophages surrounded by a thin mantle of lymphocytes" were found in 7 of the 16 MDA-exposed animals and one of the 8 control animals (level of significance was not stated). Treated and control animals had a high background incidence of pulmonary lesions including slight to mild bronchitis. No liver or kidney effects were detected in treated animals.

Nine purebred beagle dogs were treated orally (by capsule) with 70 mg "crude" (4 dogs) or "purified" (5 dogs) MDA in corn oil three days per week for a period ranging from approximately 3 to 7 years (Deichmann *et al.*, 1978). No concurrent controls were included since untreated animals were regularly maintained in the laboratory. After 2 years, cystoscopic examination was performed at 15-month intervals. After 4½ years, clinical chemistry tests were performed at 4 month intervals on 3 dogs from each group. Microscopic examination of urinary bladder, liver, heart, ovaries, uterus, and lymph nodes was performed on moribund animals or at the end of the experimental period (7 years, 2 months). Liver toxicity was noted in all the treated animals. Effects were described as fatty change, cell degeneration and necrosis, and lymphoid cell infiltration. One dog from each treatment group died from the toxic effect on the liver. The kidneys of four treated animals (two from each group) showed toxic effects including granuloma, glomerular nephritis, and congestion with cloudy swelling. Two dogs treated with "purified" and one dog treated with "crude" MDA showed toxicity to the spleen described as hemosiderosis and swelling with lymphocyte infiltration.

Wistar rats (5/sex/dose) were treated orally with 0, 0.0083, and 0.083 g MDA/kg body weight in propylene glycol daily for 12 weeks (Pludro *et al.*, 1969). Doses were 1% and 10% of the experimentally determined median lethal dose. No significant changes in body weight or hematological parameters were found, although serum albumin, β-globulin, and γ-globulin were elevated in animals in the 0.083 mg/kg dose group. The livers of all the animals in the high dose group showed signs of degeneration, including atrophy of the parenchyma and stromal hyperplasia in the portal areas. Also in this dose group, all animals showed hypertrophy of the lymphatic nodules of the spleen. In the low dose group, one animal showed a liver lesion and one a lesion in the spleen.

Schoental (1968) treated rats (8/sex) with MDA in 25% aqueous ethanol by stomach tube. Rats were given 20 mg doses a total of 2-5 times over several weeks up to 7½ months (frequency not specified). Animals showed necrosis of the liver and kidney and congestion and edema of the lungs.

Visual toxicity was reported in 15 cats treated perorally with 25-100 mg MDA/kg body weight in a 1% aqueous suspension (Schilling von Canstatt *et al.*, 1966). In four animals treated once with 100 mg/kg, no blindness was reported. In all the other treated animals (four with one dose of 100 mg/kg, two with one dose of 150 mg/kg, and two with three doses of 25 mg/kg and 3 doses of 50 mg/kg), blindness occurred within 8 days. Three of the eight recovered sight within 4 days. Two other treated animals were examined microscopically, one treated with 25 and then 50 mg/kg and one treated once with 200 mg/kg. The first was examined after 7 days and showed signs of granular degeneration of the rods and cones with some proliferation of the pigmented epithelium. The second was examined after 4¼ years and showed atrophy of the retinal neuroepithelium. The authors noted that no visual disturbances were found in other MDA treated experimental animals, including dog, rabbit, guinea pig, and rat.

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Leong *et al.*, 1987
Study population	Guinea pigs
Exposure method	Discontinuous inhalation exposure (nose only) of aerosols
Critical effects	Degeneration of retinal epithelium
LOAEL	440 mg/m^3 (54 ppm)
NOAEL	Not observed
Exposure continuity	4 hours/day, 5 days/week
Exposure duration	2 weeks
Average experimental exposure	52 mg/m^3 for LOAEL group (440 x 4/24 x 5/7) (6.4 ppm)
Human equivalent concentration	52 mg/m^3 using the default assumption of RGDR = 1 for a gas with systemic effects
LOAEL uncertainty factor	10 (incidence = 100%)
Subchronic uncertainty factor	10
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	3,000
Inhalation reference exposure level	0.02 mg/m^3 (20 µg/m^3; 0.002 ppm; 2 ppb)

Two specific types of toxicity have been associated with exposure to MDA: hepatotoxicity and ocular toxicity. Several studies have demonstrated hepatotoxicity in experimental animals. The best study of long term toxicity of MDA was the report by Lamb *et al.* (1986). In addition to addressing the carcinogenicity of MDA, Lamb described non-cancer health effects, which resulted from lifetime exposure of two species, rats and mice, to MDA at two concentrations in the drinking water. The 150 ppm dose level was a LOAEL for fatty change and focal cellular

change to the livers of male and female rats as well as for liver degeneration in male mice. The corresponding effects were also observed in high-dose male rats and male mice. Nephropathy was observed in mice of both sexes at the 150 and 300 ppm. There is abundant evidence from both human and animal studies that MDA is hepatotoxic. Bastian (1984), Williams *et al.* (1974), and McGill and Motto (1974) reported hepatitis in people exposed by inhalation and dermal absorption routes. Kopelman *et al.* (1966a,b) demonstrated human hepatotoxicity from exposure by the oral route. However, limited data detailing exposure levels associated with adverse health effects in humans preclude the development of a chronic REL from studies in humans.

The other toxic effect of potential concern from MDA exposure is ocular toxicity. Leong *et al.* (1987) reported damage to the retinas of guinea pigs exposed for 2 weeks to MDA aerosols (0.44 g/m^3 for 4 hr/day, 5 days/week; average experimental exposure = 52 mg/m^3) by inhalation. Schilling von Canstatt *et al.* (1966) also reported blindness in cats treated orally with MDA. A single case of retinopathy and visual toxicity in humans was reported in a man who accidentally ingested MDA with potassium carbonate and γ-butyrolactone. The Leong *et al.* (1986) study was selected for the development of the chronic REL because, although conducted for a relatively short period of time, the study appears to address the most sensitive endpoint of toxicity by the most appropriate route of exposure (inhalation). The studies, which established the hepatotoxicity of MDA, were conducted by the oral route of exposure.

As a comparison with the proposed REL, the study by Lamb *et al*. (1986) found a LOAEL of 9 mg/kg-day for liver changes in male rats. Use of a LOAEL UF of 3, an interspecies UF of 10, and an intraspecies UF of 10 results in an oral chronic REL of 0.03 mg/kg-day. Use of route-to-route extrapolation with the assumption that a 70 kg person breathes 20 m^3 of air per day leads to an inhalation chronic REL estimate of 100 $\mu g/m^3$. The proposed chronic REL based on Leong *et al*. (1987) is lower by a factor of 5 than that obtaimed by using Lamb *et al*. (1986) and should be protective of hepatotoxicity.

VII. Data Strengths and Limitations for Development of the REL

The strengths of the inhalation REL for 4,4′-methylene dianiline include the availability of a controlled exposure inhalation study. Major areas of uncertainty are the lack of adequate human exposure data, the lack of chronic inhalation exposure studies, the lack of reproductive and developmental toxicity studies, and the lack of observation of a NOAEL. In addition the test animals were under additional stress due to the restraint used to obtain nose-only exposure, while the control animals were not restrained. Liver toxicity has been included as a potential critical effect because of uncertainty regarding the relative potency of this compound in causing liver toxicity in different species by different routes of exposure.

When assessing the health effects of methylene dianiline, its carcinogenicity must also be assessed.

VIII. Potential for Differential Impacts on Children's Health

No evidence to support a differential effect of methylene dianiline on infants and children was found in the literature.

IX. References

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CHRONIC TOXICITY SUMMARY

SELENIUM AND SELENIUM COMPOUNDS

(other than Hydrogen Selenide**)**

Molecular Formula	*Synonyms*	*Molecular Weight* (g/mol)	*CAS Reg. No.*
Se	elemental selenium	78.96	7782-49-2
SeO_2	selenium dioxide; selenium oxide; selenious anhydride	110.96	7446-08-4
H_2SeO_3	selenious acid	128.97	7783-00-8
$SeOCl_2$	seleninyl chloride; selenium oxychloride; selenium oxichloric	165.86	7791-23-3
Na_2SeO_3	disodium selenite	263.01	10102-18-8
Na_2SeO_4	disodium selenate	188.94	13410-01-0
SeS	selenium sulfide; sulfur selenide	111.02	7446-34-6

I. Chronic Toxicity Summary

Inhalation reference exposure level **20 µg/m^3**
Oral reference exposure level **0.005 mg/kg/day** (USEPA RfD)
Critical effect(s) Clinical selenosis
Hazard index target(s) Alimentary system; cardiovascular system; nervous system

II. Chemical Property Summary (HSDB, 1995; Weast, 1980; Canady and Hodes, 1994; ACGIH, 1992)

Description	Se^0 crystal: metallic gray H_2SeO_4, Na_2SeO_3: white crystals H_2SeO_3, Na_2SeO_4: colorless crystals SeO_2: lustrous crystals; yellow vapor SeS: yellow to orange powder
Molecular formula	see above
Molecular weight	see above
Vapor pressure	0.001 torr @ 20°C
Melting point	SeO_2: 340°C SeS: decomposes at 118-119°C
Solubility	Se^0: insoluble in water, alcohol; slightly soluble in CS_2; soluble in ether H_2SeO_4: sol. in water; decomposes in alcohol H_2SeO_3: sol. in hot water, alcohol Na_2SeO_3: sol. in water Na_2SeO_4: 84 g/100 ml water at 35°C SeO_2: 38.4 g/100 ml water at 14°C SeS: insoluble in water
Conversion factor	Se^0: not applicable (particulate) SeO_2: 4.5 µg/m^3 per ppb at 20°C

III. Major Uses and Sources

Selenium occurs in four valence states: selenates (Se^{6+}), selenites (Se^{4+}), selenides (Se^{2-}), and elemental selenium (Se^0) (Goyer, 1991) which include compounds formed with oxygen, sulfur, metals, and/or halogens. Selenium compounds are used in the glass industry as decolorizing agents and in the rubber industry as vulcanizing agents. Selenium compounds are also found in toning baths used in photography and xerography, and in insecticides and photoelectric cells. Selenious acid is a component of gun cleaning chemicals (Quadrani *et al*., 2000). Selenium sulfide is used in shampoos as an anti-dandruff agent. The most widely used selenium compound in industry is selenium dioxide (SeO_2) which catalyzes reactions of organic compounds and is produced by the oxidation of selenium with nitric acid followed by evaporation or by burning selenium in oxygen (HSDB, 1995). The largest anthropogenic sources of atmospheric selenium are from the combustion of fossil fuels and the production/refining of copper; particulates are the primary expected form of the compound (National Academy of Sciences (NAS), 1976; U.S. EPA, 1984). The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 12,417 pounds of selenium and 4846 pounds of selenium sulfide (CARB, 1999).

Selenium is an essential trace element in humans and other species; selenium deficiency leads to cardiomyopathy in humans (Goyer, 1991). For dietary intake, the National Research Council has

set a U.S. Recommended Daily Allowance (RDA) of 0.87 μg/kg (55-70 μg/person/day) (Subcommittee on the Tenth Edition of the RDAs, 1989). The average daily oral intake of selenium is 125 μg/person (U.S. EPA, 1991). Organic selenium compounds (e.g., dimethyl selenide) are known to occur as metabolites and as microbial degradation products in the environment. These compounds appear to have relatively low toxicity.

IV. Effects of Human Exposures

Acute occupational exposure to SeO_2 resulted in bronchospasm, irritation of the upper respiratory passages, violent coughing, and gagging with nausea and vomiting (Wilson, 1962).

The relationship between inhalation exposure to selenium and the presence of selenium in the urine was investigated in a five year study of workers at a selenium rectifying plant (Glover, 1967). Workers were exposed to fumes and dusts of elemental red selenium, which, the author reported, is converted 80% to SeO_2 in the presence of air. Average air concentrations of selenium were reported to be 3.6 mg/m^3 in grinding processes, 0.04 mg/m^3 in annealing processes, and a range of averages of 0.23-0.87 mg Se/m^3 in various "special" processes, e.g., punching, scraping, sorting, refining, and testing. The same author previously reported symptoms among selenium exposed workers including garlic-like odor of the breath, skin rashes, indigestion, and poorly-defined "socio-psychological" effects including lassitude and irritability (Glover, 1954).

Clinical signs of toxicity were observed among a population exposed to high levels of selenium in soils and food supplies in China (Yang *et al.*, 1983). Approximately half of 248 people in this region showed symptoms including hair and nail loss, discoloration and decay of the teeth, and CNS disturbances including pain and anesthesia of the extremities. Animals in the region were also affected, with hoof damage and horn sloughing reported in water buffalo, cattle, and pigs. Populations in low-, medium-, and high-selenium areas of China were later studied to associate the symptoms with selenium intake. Estimated daily intake for adults in these areas were 70, 195, and 1438 μg Se for males and 62, 198, and 1238 μg for females, respectively (Yang *et al.*, 1989). Selenium intake was highly correlated with whole blood, breast milk, and 24-hour urine selenium levels. The authors also suggested the possibility of liver dysfunction as indicated by a delay in prothrombin time among persons with intake of 750-850 μg Se/day. More clearly recognized and characteristic clinical signs, however, were only observed in a group exposed to greater than 1261 μg Se/day and not among those exposed to less than 853 μg Se/day. Assuming a 55 kg body weight, these respective daily dose rates were 0.023 and 0.015 mg/kg-day.

A population of 142 subjects in seleniferous areas of western South Dakota and eastern Wyoming was examined for signs of selenosis over a two-year period with monitoring of selenium levels in diet, whole blood, serum, urine, and toenails (Longnecker *et al.*, 1991). Subjects completed health questionnaires, underwent physical examinations, provided blood samples for clinical assessment, and provided blood, urine, toenails, and duplicate-plate food collections for selenium analysis. About half of the 142 free-living subjects had selenium intakes greater than 2.54 mμmol/day (200 μg/day) (range 0.86-9.20 mμmol/day, or 68-724 μg/day). Average intake among the population was estimated at 239 μg Se/day. No clinical

signs and no changes in hematological function, clinical chemistry, or liver function were observed in the population, even in subjects whose intake was as high as 9.20 mμmol/day (724 μg/day).

V. Effects of Animal Exposures

Toxic effects from acute inhalation exposure to selenium dust were examined in rats, guinea pigs, and rabbits (Hall *et al.*, 1951). Twenty female rats were exposed once for 8 hours to 33 ± 10 mg Se/m^3. Many animals showed signs of pulmonary effects at both one week and 4 weeks after exposure; however, no control group was included in the experiment with which to compare incidence. Similarly, six female rabbits and 10 male guinea pigs were exposed to the same level of selenium dust for four 4-hour periods every 48 hours (8 days total duration). The animals showed signs of interstitial pneumonitis at one week (2 animals of each species) and lung congestion and alveolar infiltration of large macrophages.

Guinea pigs exposed one time to concentrations "less than 0.021 mg H_2Se/L" (22 mg Se/m^3 as hydrogen selenide) for 2, 4, or 8 hours exhibited difficulty breathing and a red-tinged discharge from the nose (Dudley and Miller, 1941). Mortality studies were conducted with guinea pigs (16/group) using the same exposure duration and selenium concentrations ranging from 1 to 43 mg Se/m^3. Fifty percent mortality was observed at 30 days among animals exposed once for 2 hours to 12 mg Se/m^3. Mortality after 30 days was 50% among animals exposed once to 1 mg Se/m^3 for 8 hours. Histopathological evaluation of guinea pigs exposed once for 4 hours to 8 mg Se/m^3 showed fatty change to the liver, pneumonia, lymphoid hyperplasia, and increased reticuloendothelial tissue in the spleen. These effects did not begin to resolve until more than 17 days after the exposure.

Several studies have addressed the toxicity of selenium compounds to animals when administered in either food or drinking water. Mice (50/group) treated with 0, 1, 4, or 8 ppm Na_2SeO_3 in drinking water over 50 weeks showed decreased growth rates at 8 ppm (Jacobs and Forst, 1981). The same group reported gross liver pathology in male mice treated by oral gavage for 3 days with 0.5 ml of 64 ppm Na_2SeO_3. Hamsters (8/sex/group) treated with 0.1 (unsupplemented), 1, 5, 10, or 20 ppm Na_2SeO_3 in the diet for 42 days showed histopathological changes to the liver (Beems and van Beek, 1985). Rats (6-8/group) treated in the diet with SeS_2, Na_2Se, Na_2SeO_3, or Na_2SeO_4 showed increased relative liver weights and/or decreased body weight gain at 10 ppm (for each compound) over a 5 week exposure (Dausch and Fullerton, 1993). A 13-week drinking water study of Na_2SeO_3, and Na_2SeO_4 in rats and mice showed increased mortality, decreased body weights, and histopathological changes to the kidneys in rats and decreased body weight and decreased water consumption in mice (Abdo, 1994). Decreased body weights were observed in rats treated for 6 weeks in drinking water with 2 ppm Na_2SeO_3 or Na_2SeO_4 (Palmer and Olson, 1974).

Decreased percentage of live spermatozoa, altered sperm morphology, and decreased body weight gain were observed in rats (6/group) treated for 5 weeks with 2 ppm Na_2SeO_3 in the diet (Kaur and Parshad, 1994). Rats (7-12/group) exposed to 0, 4, 8, or 16 ppm Na_2SeO_3 in drinking

water for 240 days showed alterations in testicular LDH and β-glucuronidase activity at 4 ppm (Nebbia *et al.*, 1987).

Developmental toxicity endpoints were examined in hamsters (5-10/group) exposed by oral gavage on gestational day 8 to Na_2SeO_3 and Na_2SeO_4 at concentrations ranging from 0 - 110 μmol/kg body weight (Ferm *et al.*, 1990). Effects observed at 100 μmol Na_2SeO_3/kg included decreased fetal crown-rump length and increased percentage of abnormal litters. At 90 μmol Na_2SeO_4/kg, an increased percentage of abnormal litters was observed. Mice (10 or 14/group) treated with 0, 3, or 6 ppm Na_2SeO_3 in drinking water from 30 days pre-gestation through gestation showed altered estrus cycle length, decreased fetal growth, and a decreased number of ossified vertebrae in offspring (Nobunaga *et al.*, 1979).

VI. Derivation of Chronic Reference Exposure Level (REL) (for selenium and selenium compounds other than hydrogen selenide)

Study	Yang *et al*., 1989
Study population	400 people in China
Exposure method	Low, medium, & high environmental levels of Se
Critical effects	Clinical selenosis (liver, blood, skin, CNS)
LOAEL	0.023 mg/kg-day* (1.261 mg/day / 55 kg)
NOAEL	0.015 mg/kg-day* (0.853 mg/day / 55 kg)
Exposure continuity	Continuous
Exposure duration	Lifetime
Average experimental exposure	70, 195, and 1438 μg/day for adult males; 62, 198, and 1238 μg/day for adult females
LOAEL uncertainty factor	1
Subchronic uncertainty factor	1
Interspecies factor	1
Intraspecies factor	3
Cumulative uncertainty factor	3
Oral reference exposure level	0.005 mg/kg/day (USEPA RfD)
Inhalation extrapolation factor	3,500 $\mu g/m^3$ per mg/kg-day
Inhalation reference exposure level	20 $\mu g/m^3$

*Factors: NOAEL (0.853 mg/day) and LOAEL (1.261 mg/day) calculated from regression analysis (log Y = 0.767 log X - 2.248, where Y = blood selenium and X = selenium intake) based upon the correlation (r = 0.962) between dietary selenium intake and blood selenium level for data showing incidence of clinical selenosis in adults based on an average adult body weight of 55 kg.

The inhalation chronic REL is based on the oral chronic REL, which is the same as the USEPA's oral reference dose (RfD) (U.S. EPA, 1996). In addition to being inhaled, airborne selenium can settle onto crops and soil and enter the body by ingestion. Thus an oral chronic reference exposure level for selenium is also required for Air Toxics Hot Spots health risk assessments. The chronic inhalation REL was derived by route-to-route extrapolation of the RfD. The

principal study used for the REL/RfD was that of Yang *et al*. (1989). Yang *et al*. (1989), in a follow-up to an earlier study (Yang *et al*., 1983), studied a population of approximately 400 individuals living in an area of China with unusually high environmental concentrations of selenium (Se). The subjects were evaluated for clinical and biochemical signs of Se intoxication. Three geographical areas with low, medium, and high selenium levels in the soil and food supply were chosen for comparison in the studies. The earlier study was conducted in response to endemic selenium intoxication in two separate areas with sample sizes of only 6 and 3. Comparisons were then made to a selenium-adequate area (n=8) and low-selenium area (n=13). The Yang *et al*. (1989) studies provide a much larger sample size and include additional analysis of tissue selenium levels. This allows a more accurate estimation of the dose-response relationship observed for selenium toxicity. Selenium levels in soil and approximately 30 typical food types commonly eaten by the exposed population showed a positive correlation with blood and tissue Se levels. The daily average Se intakes, based on lifetime exposure, were 70, 195, and 1438 μg for adult males and 62, 198, and 1238 μg for adult females in the low-, medium- and high-selenium areas, respectively. Significant correlations, demonstrated between Se concentrations of various tissues, were used to estimate the minimal daily Se intake values that elicited various alterations in biochemical parameters indicative of possible Se-induced liver dysfunction (i.e., prolongation of clotting time and serum glutathione titer) and clinical signs of selenosis (i.e., hair or nail loss, morphological changes of the nails, etc.). In this manner, a marginal safe level of daily Se intake was estimated. Analysis of the results indicated that persistent clinical signs of selenosis were observed only in 5/349 adults, a potentially sensitive subpopulation. The blood selenium concentration in this group ranged from 1.054 to 1.854 mg/L with a mean of 1.346 mg/L. Clinical signs observed included the characteristic "garlic odor" of excess selenium excretion in the breath and urine, thickened and brittle nails, hair and nail loss, lowered hemoglobin levels, mottled teeth, skin lesions, and CNS abnormalities (peripheral anesthesia, acroparesthesia, and pain in the extremities). Alterations in the measured biochemical parameters occurred at dietary intake levels of 750-850 μg/day. These alterations were described as a delay in prothrombin time, i.e., increase in blood coagulation time and reduction in blood glutathione concentration. However, these indicators were poorly characterized and are not typically used as an index for clinical selenosis resulting from chronic exposure to selenium (NAS, 1989). Based upon the blood selenium levels shown to reflect clinical signs of selenium intoxication, a whole blood selenium concentration of 1.35 mg/L corresponding to 1.261 mg of daily selenium intake is indicative of the lowest correlative selenium intake causing overt signs of selenosis. The next lowest whole blood selenium concentration of 1.0 mg/L, corresponding to 0.853 mg selenium/day, produces no clinical signs of selenosis. The NOAEL for this study is 0.85 mg Se/day and the LOAEL is 1.26 mg Se/day.

An intraspecies uncertainty factor of 3 was applied to the NOAEL to account for sensitive individuals. A full factor of 10 was not deemed necessary since similar NOAELs were identified in two moderately-sized human populations exposed to selenium levels in excess of the RDA throughout a lifetime without apparent clinical signs of selenosis. No modifying factor was applied by USEPA. OEHHA accepted the USEPA analysis.

Route-to-route extrapolation assumes by default that a chemical is equally absorbed by the inhalation and the oral routes and that the first pass effect due to metabolism by the liver is not important for the chemical. The latter assumption is applicable to most metals. There are

limited data to evaluate the assumption of equal absorption across the gastrointestinal tract and the lungs. Limited data indicate that 60% (range = 44-100%) of ingested Se is absorbed by the gastrointestinal tract, while in one study 30% (single estimate) of inhaled selenium was deposited in the respiratory tract (Owen, 1990). Deposition is dependent on particle size. The available data are not adequate to depart from the default assumption.

The USEPA stated its confidence in the RfD as: Study - Medium; Data Base - High; and RfD - High. Confidence in the chosen principal study is medium. Although this is a human epidemiological study in which a sizable population with sensitive subpopulations was studied, there are still several possible interactions that were not fully accounted for, e.g., fluoride intake and protein status. Also, except for clinical signs of selenosis there are no other reliable indicators, biochemical or clinical, of selenium toxicity. Confidence in the database is high because many animal studies and epidemiologic studies support the principal study. An additional human study with a freestanding NOAEL (Longnecker et al., 1991) provides support for the NOAEL identified in the principal study. Longnecker *et al*. (1991) found no effects at 238 µg Se per day, which would equate to 0.004 mg/kg-day for a 55 kg person. Therefore, high confidence in the RfD is selected based upon support of the critical study and the high level of confidence in the database.

There are insufficient data relating human inhalation exposure to selenium compounds to adverse health effects to use for the development of a chronic REL although toxicity has been reported from occupational exposure to gases of both H_2Se and SeO_2 (Buchan, 1947; Wilson, 1962). Experiments in animals have shown that H_2Se is toxic following inhalation exposure, with 8-hour exposures to concentrations as low as 1 mg H_2Se/m^3 causing "irritation sufficiently damaging to cause pneumonitis" and subsequently increasing 30-day mortality (Dudley, 1937; Dudley and Miller, 1941). Thus the selenium chronic REL is not meant to be applied to H_2Se, which may be considerably more toxic than other selenium compounds. At this time there are inadequate data to develop a REL for H_2Se. It is also not intended to be applied to organic metabolites of selenium.

VII. Data Strengths and Limitations for Development of the REL

The strengths of the REL for selenium include its basis on a study with a large number of human subjects in a non-occupational setting that determined both a NOAEL and a LOAEL. The weaknesses include its basis on a route of exposure other than inhalation and its lack of applicability to hydrogen selenide, the most toxic selenium compound.

VIII. Potential for Differential Impacts on Children's Health

The key study (Yang *et al*., 1989) included evaluation of children as young as one year old. Thus the chronic REL should be protective of infants and children. No adverse reproductive outcomes were reported, although only 400 people were studied. However, the inhalation REL is based on an oral REL of 0.005 mg/kg-day (0.06 µmol/kg-day). Ferm *et al*. (1990) did not find

adverse effects on hamster development with Se doses below 34 μmol/kg. Thus the chronic REL should also be protective of infants and children.

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CHRONIC TOXICITY SUMMARY

SULFURIC ACID

(dithionic acid; pyrosulphuric acid)

CAS Registry Number: 7664-93-9

I. Chronic Toxicity Summary

Inhalation reference exposure level	**1 µg/m^3**
Critical effect(s)	Bronchiolar epithelial hyperplasia, and thickening of the bronchial walls in monkeys
Hazard index target(s)	Respiratory system

II. Physical and Chemical Properties (HSDB, 1995; CRC, 1994; CARB, 1997)

Description	Colorless liquid
Molecular formula	H_2SO_4
Molecular weight	98.1 g/mol
Density	1.84 g/cm^3 @ 15° C
Boiling point	330±0.5°C (100%)
Melting point	10.36°C (100%)
Vapor pressure	<0.001 torr @ 25° C; 1 torr @ 145.8° C
Solubility	Soluble in water
Conversion factor	Not applicable

III. Major Uses or Sources

Sulfuric acid is a strong acid used as an intermediate in the synthesis of linear alkylbenzene sulfonation surfactants used in dyes, in petroleum refining, for the nitration of explosives, in the manufacture of nitrocellulose, in caprolactam manufacturing, as the electrolyte in lead-acid batteries, and as a drying agent for chlorine and nitric acid. Sulfuric acid is formed in the atmosphere from sulfur dioxide, from sulfur trioxide, and from oleum (a combination of sulfur trioxide and sulfuric acid used industrially). The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 4460 pounds of sulfuric acid (CARB, 1999).

IV. Effects of Human Exposures

Workers in the lead battery industry showed etching and erosion of the teeth after 4 months exposure to an average concentration of 0.23 mg/m^3 H_2SO_4 (Gamble *et al.*, 1984). Dental erosion increased in a dose-dependent manner with longer duration of exposure.

A study of 33 storage battery plant workers exposed to H_2SO_4 concentrations as high as 35 mg/m^3 showed a greater group mean decrease in FEV_1 across the time of their work shift compared to workers who were not exposed to sulfuric acid (El-Saddik *et al.*, 1972). The salivary pH of the sulfuric acid exposed workers, a qualitative measure of acid exposure, was lower than the controls during the course of the work shift.

OEHHA recently reviewed the California Ambient Air Quality Standard (CAAQS) for sulfates (25 $\mu g/m^3$ for 24 hours) to see if it adequately protects children (OEHHA, 2000). The report was peer-reviewed by the Air Quality Advisory Committee. The report indicates that H+ itself may play a role in the effects seen in epidemiological studies of sulfate air pollution. Controlled acute inhalation studies in humans and laboratory animals of pH neutral or nearly neutral sulfate salts (e.g., ammonium sulfate) (Utell et al., 1983; Lippman et al., 1987; Schlesinger et al., 1990), even at relatively high concentrations, do not produce the effects reported from epidemiologic studies of sulfates (asthma exacerbation, bronchoconstriction, decrements in lung function) that might be expected from short-term excursions. The controlled exposure studies show that sulfate aerosols containing strong acids, such as sulfuric acid and, to a lesser extent, ammonium bisulfate, produce functional and structural changes in healthy subjects consistent with those observed in epidemiological studies. A working hypothesis is that H^+ is a causal factor for adverse human health effects (e.g., see Lippmann and Thurston, 1996) and that, among the commonly measured particulate matter (PM) indices, $SO_4^=$ is the best surrogate metric for H^+.

A large number of epidemiologic studies have been conducted showing that elevated levels of several air pollutants, including acid aerosols, sulfur and nitrogen oxides, and particulate sulfates are correlated with an increased prevalence of pulmonary disease (U.S. EPA, 1989; OEHHA 2000). Elevated sulfate levels (1.6 ppb or 6.6 $\mu g/m^3$) have been associated with statistically significant decrements in FVC and FEV_1 in a cohort of Canadian children (Stern *et al.*, 1989). Further analysis of these data led Bates and Sitzo (1989) to conclude that H_2SO_4 was the most likely cause for the pulmonary changes observed. Similarly, Ostro *et al.* (1989) reported a statistical association between asthma-related symptoms reported by 209 asthmatics and sulfate and acidity levels in ambient air in Denver. Delfino et al. (1997) found that ambient H+ was associated with emergency room visits by children for respiratory symptoms in a study in Montreal. Additionally, Damokosh et al. (1993) in a follow-up analysis of the 6-City study suggested associations between average H+ concentration and chronic bronchitic symptoms. The relative odds of bronchitic symptoms with the highest acid concentration (58 $nmoles/m^3$ H+)_ versus the lowest concentration (16 $nmoles/m^3$) was 2.4 (95% CI:1.9 to 3.2). Furthermore in a study of children in 24 U.S. and Canadian communities (Dockery et al., 1996) in which the analysis was adjusted for the effects of gender, age, parental asthma, parental education, and parental allergies, bronchitic symptoms were confirmed to be significantly associated with strongly acidic PM (OR= 1.66; 95% CI 1.11-2.48). It was also found that FVC and FEV_1 were lower in locales with high particle acidity (Raizenne et al., 1996). Gwynn et al. (2000) reported an association between both H+ and sulfate particles and respiratory hospital admissions and mortality in Buffalo, NY. Acidic sulfates may act to increase the toxicity of particles by enhancing the availability of metals present in the particles to generate reactive oxygen species in the respiratory epithelium. This may account for some of the effects seen in these epidemiological studies and makes it difficult to use these studies as a basis for a Reference Exposure Level for sulfuric acid. The relationship between the effect levels observed in these

studies and the proposed REL is discussed in the section below on the potential for differential impacts on children's health.

The occupational standard for sulfuric acid is based on a study in human subjects by Amdur *et al*. (1952). In their study, 22 healthy male subjects were exposed to 0, 0.35, 0.4, 0.5, 1, 2, or 5 mg/m^3 for 5-15 minutes. The odor, taste, and irritation threshold was 1 mg/m^3. Since the basis for this standard is an acute exposure, it is not useful in determining a chronic non-cancer REL for sulfuric acid. A review of chronic human exposures to sulfuric acid and resulting carcinogenicity outcomes can be found in IARC (1992). However, none of the studies in that review examined non-cancer endpoints.

Sulfuric acid and oleum (supersaturated anhydrous sulfuric acid with varying concentrations of free sulfur trioxide) are absorbed as salts of sulfate anion (SO_4^{2-}), and are excreted as organic sulfates, neutral sulfur, or neutral sulfur compounds such as sulfur-containing amino acids. The low systemic toxicity of these metabolites is likely of secondary importance to the irritation caused by the inhaled acid.

V. Effects of Animal Exposures

An exposure of 9 cynomolgus monkeys per group to H_2SO_4 concentrations of 0, 0.38, 0.48, 2.43, and 4.79 mg/m^3 continuously for 78 weeks resulted in dose-dependent adverse histological changes in lung and bronchiolar epithelial and parenchymal tissue in addition to a dose-dependent decrease in blood oxygenation (Alarie *et al.*, 1973). In the animals exposed to 0.38 mg/m^3, significant bronchiolar epithelial hyperplasia was observed in 5 of 9 animals; thickening of the bronchiolar walls was observed in 3 of 9 animals. A slight focal bronchial epithelial hyperplasia was present in 4 of the 9 animals. One animal died after 4 weeks exposure to 0.38 mg/m^3. Although signs of pulmonary edema and cardiac hypertrophy were found, the cause of death was not determined.

Respiratory system effects of H_2SO_4 exposure in monkeys (Alarie *et al*., 1973)

H_2SO_4 (g/m^3)	*Particle size MMD*	*Bronchiolar epithelial hyperplasia Incidence – severity*	*Thickening of walls of respiratory bronchioles Incidence – severity*	*Increase in thickness of alveolar walls Incidence – severity*
0		0/9	0/9	0/9
0.38	2.15	5/8 – slight	3/8 - slight	0/8
0.48	0.54	0/8	0/8	0/8
2.43	3.60	8/8 – moderate	8/8 – moderate	8/8 – moderate
4.79	0.73	8/8 – moderate to severe	8/8 – moderate to severe	0/8

Alarie *et al.* (1973) also exposed groups of 50 guinea pigs of each sex to 0, 0.08, or 0.1 mg/m^3 H_2SO_4 continuously for 52 weeks. The group exposed to 0.1 mg/m^3 also received larger sized particulates than the 0.08 mg/m^3 group (2.78 μm vs. 0.84 μm, respectively). No exposure related effects were observed in the animals exposed to 0.08 mg/m^3, whereas exposure of 0.1 mg/m^3 resulted in decreased body weights in the female guinea pigs. No other histological changes in any organs were observed at the end of the 52-week study.

Rabbits (4 per group) were exposed to 250 μg/m^3 H_2SO_4 1 hour/day, 5 days/week for 4, 8, or 12 months. They showed significantly increased bronchoconstriction upon acetylcholine challenge after 8 and 12 months exposure, compared with a control group of 4 animals that received no H_2SO_4 (Gearhart and Schlesinger, 1986, 1988). Mucociliary clearance was also impaired by H_2SO_4 exposure and did not improve 3 months after cessation of exposure. A decline in dynamic lung compliance was observed after 12 months exposure. There was no evidence of inflammatory cell infiltration in the lungs of the exposed animals.

In guinea pigs, significantly slower and irregular breathing patterns were noted when the animals had inhaled albumin followed by 30 minute exposures to H_2SO_4 at 1.91 mg/m^3 twice per week for 5 weeks (Kitabatake *et al.*, 1979). Similarly, when guinea pigs were exposed to 2.49 mg H_2SO_4/m^3 for 4 hours/day, 6 days/week for 4 weeks, *in vitro* lung histamine release was significantly enhanced following heterogeneous albumin inhalation, compared to control animals unexposed to albumin (Fujisawa *et al.*, 1986; Iguchi *et al.*, 1986). In guinea pigs, sulfuric acid caused significantly greater lung function changes when adsorbed on the surface of zinc oxide particles as compared with pure sulfuric acid (Amdur and Chen, 1989). An exposure to 24 μg/m^3 sulfuric acid, layered on zinc oxide, produced significant reductions in lung function when followed by a brief exposure to 0.15 ppm ozone (Chen *et al.*, 1991).

A chronic exposure of beagle dogs to an average concentration of 889 μg/m^3 H_2SO_4 for 21 hours/day over a 620 day period resulted in increased expiratory resistance, reduced carbon monoxide diffusing capacity, reduced total and residual lung volume, and decreased lung and heart weights (Lewis *et al.*, 1973).

In apparent contrast to the above studies, rats and guinea pigs exposed to H_2SO_4 at 10 mg/m^3 for 6 hours/day, 5 days/week for 6 months exhibited no adverse histologic changes in lung tissue. Lung function measurements were not reported in this study (Cavender *et al.*, 1978).

Mice inhaled sulfuric acid mist at a concentration of 1.4 mg/m^3 in combination with a carbon particle mixture (1.5 mg/m^3) for 3 hours/day, 5 days/week for up to 20 weeks. The exposure resulted in significant alterations in specific antibody titer (decreased IgG, Ig_{2a}, IgM; increased IgG_{2b}), depression of primary splenic antibody response, and decreased resistance to respiratory infection as measured by mortality and survival time compared to controls (Fenters *et al.*, 1979).

There are no reliable studies indicating that sulfuric acid is a developmental or reproductive toxicant. In the absence of massive overexposure leading to maternal acidemia, H_2SO_4 will be neutralized in the maternal circulation and is unlikely to reach the fetus.

VI. Derivation of Chronic Reference Exposure Level

Study	Alarie *et al.*, 1973
Study population	Cynomolgus monkeys (5 males and 4 females per group or vice versa)
Exposure method	Continuous inhalation exposures (0, 380, 480, 2400, or 4800 $\mu g/m^3$) for 78 weeks
Critical effects	Significantly increased bronchial epithelial hyperplasia and bronchial thickening
LOAEL	380 $\mu g/m^3$
NOAEL	Not observed
Exposure continuity	The exposure was continuous during the experiment.
Exposure duration	78 weeks
Average experimental exposure	380 $\mu g/m^3$ for the LOAEL group
Human equivalent concentration	380 $\mu g/m^3$
LOAEL uncertainty factor	3 (slight effects)
Subchronic uncertainty factor	3
Interspecies uncertainty factor	3 (non-human primate)
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	300
Reference exposure level	1 $\mu g/m^3$

The study by Alarie *et al.* (1973) identified a LOAEL for chronic exposure to sulfuric acid of 380 $\mu g/m^3$. The principal uncertainties of this study are the small sample size of the test groups and the absence of an observed NOAEL. A lower chronic LOAEL for bronchial reactivity is presented by Gearhart and Schlesinger (1986, 1988) for rabbits (250 $\mu g/m^3$). This study was not selected as the basis of the REL because Gearhart and Schlesinger used only a single concentration of sulfuric acid, exposed the animals only for 1 hour per day for 5 days/week, used only 4 animals per group, and measured effects over the course of up to 12 months. The predominant weakness in the rabbit study, however, was the extreme discontinuity of the exposures (1 hour/day, 5 days/week), which would have necessitated use of a very large continuity adjustment. For these reasons, in addition to obvious physiological and genetic similarity arguments, the study in monkeys by Alarie *et al.* (1973) was felt to be more appropriate as the basis for the chronic REL for sulfuric acid. Alarie *et al.* (1975) determined a NOAEL for sulfuric acid in monkeys of 0.1 mg/m^3. However, other particulate matter (fly ash) was also present during the exposure. The Alarie *et al.* (1973) report provides data from exposure to sulfuric acid alone.

A free-standing NOAEL for histological changes in 100 guinea pigs exposed continuously for 1 year to 0.08 mg/m^3 was reported by Alarie *et al.* (1973). Guinea pigs respond to high concentrations of sulfuric acid by occasional laryngeal spasms that appear similar to a human asthmatic attack (Silbaugh *et al.*, 1981; Amdur and Chen, 1989). As a result, guinea pigs are thought to be sensitive models for the acute effects of sulfuric acid. For chronic effects of sulfuric acid on the lung, monkeys are likely a suitable model due to their physiological and structural similarites to humans.

For comparison, a chronic REL based on the guinea pig free-standing NOAEL of 0.08 mg/m^3 in animals exposed continuously for one year (Alarie *et al*., 1973) would be 0.8 μg/m^3.

VII. Data Strengths and Limitations for Development of the REL

The major strength of the study on sulfuric acid is the use of health effects observations from continuous long-term exposures to a primate. The major weaknesses are the lack of adequate human health effects data and the lack of a NOAEL observation.

VIII. Potential for Differential Impacts on Children's Health

There are no reliable studies indicating that sulfuric acid is a developmental or reproductive toxicant. Children are likely to be at greater risk from long-term exposures because their bodies are growing, and their developmental processes, especially in the lung, may well be impacted by air pollution exposures. Elevated sulfate levels (1.6 ppb or 6.6 μg/m^3) have been associated with statistically significant decrements in FVC and FEV_1 in a cohort of Canadian children (Stern *et al.*, 1989). The chronic REL for sulfuric acid of 1 μg/m^3 is below the level associated with those decrements in pulmonary function. However, in a study of moderately to severe asthmatic children (ages 7-13) (Thurston *et al*., 1997), a sensitive subpopulation for sulfate effects, approximately 1 μg/m^3 was the lowest level of ambient sulfate measured. The mean daily morning to afternoon peak airflow change, the use of beta-agonist medication, and the number of chest symptoms versus sulfate concentration in these children extrapolated linearly down to 1 μg/m^3. Thurston *et al*. (1997) also examined earlier data from Ontario (Burnett et al., 1994) on respiratory admissions to hospitals, and concluded that the sulfate threshold of effects, if it exists, lies below 5 μg/m^3, perhaps at about 2 μg/m^3. It should be noted that the sulfate and hydrogen ion effects are difficult to disentangle from each other and from the effcts of other PM constituents. The chronic REL of 1 μg/m^3 appears to have a relatively low margin of safety with respect to the epidemiological studies, but these observations are consistent with the proposed REL of 1 μg/m^3 since asthmatic children appear to be the critically sensitive human population for exposure to sulfuric acid (or sulfate).

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CHRONIC TOXICITY SUMMARY

VINYL ACETATE

(1-acetoxyethylene; acetic acid, vinyl ester; acetic acid, ethenyl ester; VAC; vinyl A monomer; ethenyl ethanoate)

CAS Registry Number: 108-05-4

I. Chronic Toxicity Summary

Inhalation reference exposure level	**200 µg/m^3** (50 ppb)
Critical effect(s)	Nasal epithelial lesions in rats and mice
Hazard index target(s)	Respiratory system

II. Physical and Chemical Properties (HSDB, 1994)

Description	Colorless liquid
Molecular formula	$C_4H_6O_2$
Molecular weight	86.09 g/mol
Density	0.932 g/cm^3 @ 20°C
Boiling point	72.7° C
Melting point	–93.2°C
Vapor pressure	115 torr @ 25°C
Solubility	Slightly soluble in water, soluble in ethane, acetone, chloroform; >10% soluble in ethanol and benzene
Conversion factor	1 ppm = 3.52 mg/m^3 @ 25°C

III. Major Uses and Sources

The major use of vinyl acetate monomer is in the manufacture of polyvinyl and vinyl acetate copolymers, which are used in water-based paints, adhesives, paper coatings, and applications not requiring service at extreme temperatures (HSDB, 1994). It is also used in safety glass interlayers and in hair sprays (HSDB, 1994). In the atmosphere vinyl acetate breakdown can result in formation of acetaldehyde. The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 3855 pounds of vinyl acetate (CARB, 2000).

IV. Effects of Human Exposures

Deese and Joyner (1969) conducted an occupational study of 21 chemical workers with a mean length of employment of 15.2 years and exposed to a time-weighted average of 8.6 ppm (30.3 mg/m^3) VA. No adverse effects were noted following chest x-ray, electrocardiogram, blood chemistry, and urinalysis. The control group (sample size unspecified) consisted of workers in

units not exposed to VA. Deese and Joyner (1969) also showed intolerable eye irritation in 3 out of 3 subjects exposed for an unspecified extended period of time to 21.6 ppm (76 mg/m^3) VA. Upper respiratory irritation was also experienced by a majority of 5 subjects. Odor was detected at 0.4 ppm (1.4 mg/m^3) in 3 out of 3 subjects.

V. Effects of Animal Exposures

A 104-week inhalation study in rats and mice (90/sex/group) was conducted using concentrations of 0, 50, 200, or 600 ppm (0, 176, 704, or 2113 mg/m^3) vinyl acetate (VA) (Owen, 1988). The study was later published by Bogdanffy *et al.* (1994). Exposures were for 6 hours/day, 5 days/week. Histology was performed on all major organs. There was no mortality resulting from these exposures. A close examination of the effects of VA on the lung and nasal passages showed significant lesions in the nasal cavity, bronchi, and lungs of rats exposed to 600 ppm VA. Lesions included olfactory epithelial metaplasia/atrophy (see table below) and nest-like epithelial folds in the nasal cavity, exfoliation of bronchial epithelium, fibrous intraluminal projections in the bronchi, and pigmented histiocyte accumulation in the lungs. Body weight gain of rats was significantly decreased in the 600 ppm VA group. Rats treated with 200 ppm VA showed some evidence of epithelial atrophy and metaplasia in the nasal cavity. No effects were observed in the rats exposed to 50 ppm VA.

Number of male rats with olfactory epithelial atrophy (Bogdanffy *et al*. 1994)

VA (ppm)	N in group	Very slight	Slight	Moderate	Severe
0	58	0	0	0	0
50	59	1	2	0	0
200	60	4	47***	2	0
600	60	0	7*	33***	10***

* $p<0.05$; ***$p<0.001$ by Fisher's pair-wise test compared to control group

Mice also exhibited significant histological lesions in the respiratory tract following exposure to 200 ppm VA or greater. The lesions included atrophy of the olfactory epithelium and submucosal gland. At 600 ppm, hyperplasia of the trachea was observed, in addition to exfoliation/flattening of the bronchial epithelium and decreased body weight gain. Relative brain and kidney weights were increased in the 600 ppm group at the end of the study, and absolute liver, heart and kidney weights were also significantly elevated. No adverse effects were observed in the 50 ppm group.

A 13-week study on the effects of VA in mice was conducted by Owen (1980a). Mice (10/sex/concentration) were exposed to 0, 50, 200, or 1000 ppm (0, 176, 704, or 3520 mg/m^3) VA for 6 hours/day, 5 days/week for 13 weeks. A concentration-dependent increase in the incidence of diffuse rhinitis, beginning at the 200 ppm concentration, was detected using histopathological examination. Focal pneumonitis was observed in the 1000 ppm treatment group. No adverse effects were seen in the 50 ppm treatment group. An identical study in rats was also conducted by Owen (1980b). In this study, body weight gain was significantly reduced in male and female rats exposed to 1000 ppm VA. An increase in the incidence of mild histiocytic alveolitis was observed in the 1000 ppm group.

Irvine (1980) conducted a study on the developmental toxicity of VA in rats. Groups of 24 pregnant female rats were exposed to 0, 52, 198, or 1004 ppm (0, 182, 696, or 3533 mg/m^3) VA for 6 hours/day on days 6-15 of gestation. Significant maternal toxicity, as measured by reduced weight gain from day 10 through day 15, was observed in animals exposed to 1004 ppm. Fetotoxicity, as measured by reduced crown-rump length, reduced body weight, and increased incidence of ossification defects in the sternebrae and occipital regions, was observed in the 1004 ppm group. No maternal or fetal effects were seen at the lower two VA treatments.

In another developmental toxicity study, groups of 23-24 Crl:CD(SD)BR rats were given 0, 200, 1000, or 5000 ppm VA in drinking water or exposed 6 hr/day to 0, 50, 200, or 1000 ppm VA on gestation days 6-15 of gestation. The authors (Hurtt *et al*., 1995) estimated that the doses by both routes were approximately 0, 25, 100, or 500 mg/kg/day. VA in the drinking water produced no evidence of maternal or developmental toxicity at any dose. In the inhalation study, maternal toxicity was indicated by a reduction in weight gain of dams exposed to 1000 ppm. Fetal toxicity was evident by a significant decrease in mean fetal weight and mean crown-rump length in fetuses from the 1000-ppm group and by a significant increase in the incidence of minor skeletal alterations (especially delayed ossification) in fetuses from dams exposed to 1000 ppm VA. These results indicated to the authors that VA is not uniquely toxic to the conceptus. The NOAEL was greater than 5000 ppm via the drinking water and 200 ppm by the inhalation route.

VI. Derivation of Chronic Reference Exposure Level

Study	Bogdanffy *et al*., 1994
Study population	Male and female Sprague-Dawley rats and CD-1 mice (90/sex/group)
Exposure method	Discontinuous inhalation exposures (0, 50, 200, or 600 ppm) over 104 weeks
Critical effects	Histological lesions of the nasal epithelium
LOAEL	200 ppm
NOAEL	50 ppm
Exposure continuity	6 hours/day, 5 days/week
Exposure duration	104 weeks
Average experimental exposure	8.9 ppm for NOAEL group (50 x 6/24 x 5/7)
Human Equivalent Concentration (HEC)	1.4 ppm for NOAEL group (RGDR = 0.15 based on a gas with respiratory effects in both rats and mice)
LOAEL uncertainty factor	1
Subchronic uncertainty factor	1
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	30
Inhalation reference exposure level	0.05 ppm (50 ppb, 0.2 mg/m^3, 200 μg/m^3)

The chronic REL is the U.S. EPA RfC (U.S. EPA, 1995) for vinyl acetate. Acetaldehyde, a hydrolysis product of vinyl acetate, was present in the Owen (1988) study at a concentration of 49 ppm (89 mg/m^3). The duration-adjusted concentration for acetaldehyde was 16 mg/m^3, whereas the NOAEL for histological lesions in rats by Appleman *et al.* (1982) was 48.75 mg/m^3 acetaldehyde. Therefore, the concentration of acetaldehyde was not considered to account for significant irritation in the Owen (1988) study. OEHHA accepted the U.S. EPA analysis.

For comparison, Irvine (1980) obtained a NOAEL of 198 ppm for fetotoxicity in rats exposed 6 hours/day on days 6-15 of gestation. This is equivalent to 50 ppm continuous exposure during development. Multiplying by an RGDR of 1 and dividing by a total UF of 30 (3 for interspecies and 10 for intraspecies) results in a REL estimate based on fetotoxicity of 1.7 ppm. The results of Hurtt *et al*. (1995) also yield an estimate of 1.7 ppm.

VII. Data Strengths and Limitations for Development of the REL

The strengths of the inhalation REL for vinyl acetate include the availability of controlled exposure lifetime inhalation studies in multiple species at multiple exposure concentrations and with adequate histopathological analysis, and the observation of a NOAEL. The major area of uncertainty is the lack of adequate human exposure data.

VIII. Potential for Differential Impacts on Children's Health

Since the chronic REL (0.05 ppm) is lower than the comparison estimate based on developmental effects (1.7 ppm), the REL is likely to be protective of children. However, there is no direct evidence in the literature to quantify a differential effect of vinyl acetate in infants and children relative to adults.

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