DRINKING WATER TOXICITY PROFILES

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1. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Water, provides information on the health effects and other useful data that can aid in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. The EPA has an ongoing cooperative agreement with the Department of the Army to prepare drinking water Health Advisories (HA) for munitions and other environmental contaminants. Drinking water Toxicological Profiles are short summaries of the pertinent mammalian health effects literature, and are used by the Office of Water to determine if a data base is sufficient to allow the development of HAs. The following databases were searched for information on *p*-bromofluorobenzene: CANCERLINE, CHEMFATE, DART, DTIC, EMICBACK, ENVIROLINE, RTECS, TOXLINE, TOXLINE65, TOXLIT, and TOXLIT65. Secondary sources were also used.

This Drinking Water Toxicological Profile summarizes information on *p*-bromofluorobenzene, an aryl halide, used as a chemical intermediate, particularly in the production of *p*-fluorophenol (a fungicide and an intermediate for pharmaceuticals) (Hawley, 1987). Military uses of *p*-bromofluorobenzene were not found in the available literature. The structure of *p*-bromofluorobenzene is shown below.

para-Bromofluorobenzene

2. SELECTED GENERAL INFORMATION

Physicochemical data for *p*-bromofluorobenzene are presented in Table 1.

TABLE 1. PHYSICOCHEMICAL DATA

Common name	*para*-bromofluorobenzene	Hawley, 1987
Synonyms	4-bromofluorobenzene	TOXLINE, 1992
CAS Registry No.	460-00-4	
RTECS No.	ND[a]	
Chemical formula	C_6H_4BrF	Hawley, 1987
Molecular weight	175	Derived
Physical state	colorless liquid	Hawley, 1987
Vapor pressure	ND	
Specific gravity	1.593 at 15°C	Hawley, 1987
Freezing/Boiling/Flash Point	-17.4°C/151-152°C/ND	Hawley, 1987
Solubility in water	insoluble	Hawley, 1987
Log KOW	ND	
Bioconcentration factor (BCF)	ND	
Conversion factors in air	1 mg/m^3 = 0.14 ppm 1 ppm = 7.14 mg/m^3	Calculated[b]
Odor threshold	ND	
Henry's Law constant	ND	

[a]ND: no data

[b]Formula: $\text{ppm by volume} = mg/m^3 \times \frac{24.45}{\text{mol. wt. in grams}}$

3. SOURCES OF EXPOSURE

3.1. Occurrence in Water

No information was found in the available literature.

3.2. Human Exposure

No information was found in the available literature.

4. ENVIRONMENTAL FATE

No information was found in the available literature.

5. TOXICOKINETICS

No information was found in the available literature.

6. HEALTH EFFECTS

6.1. Noncancer Effects

6.1.1. Oral Exposure

6.1.1.1. Human. No information was found in the available literature.

6.1.1.2. Animal. No information was found in the available literature.

6.1.2. Other Exposure Routes

6.1.2.1. Human. No information was found in the available literature.

6.1.2.2. Animal. No information was found in the available literature.

6.2. Carcinogenicity

6.2.1. Oral Exposure

6.2.2.1. Human. No information was found in the available literature.

6.2.2.2. Animal. No information was found in the available literature.

6.2.2 Other Exposure Routes

6.2.2.1. Human. No information was found in the available literature.
6.2.2.2. Animal. No information was found in the available literature.

6.3. Genotoxicity

No information was found in the available literature.

7. EXISTING STANDARDS, CRITERIA, GUIDANCE

7.1. EPA RfDs, RfCs, CRAVE Classifications

RfD:	None established
RfC:	None established
Oral Slope Factor:	None established
Drinking Water Unit Risk:	None established
Inhalation Slope Factor:	None established
Inhalation Unit Risk:	None established
U.S. EPA CRAVE Cancer Classification:	Not established

7.2. IARC Carcinogenicity Classification

Not established

7.3. OSHA, ACGIH, and NIOSH Standards and Criteria

OSHA (8-hr TWA):	None established
OSHA STEL:	None established
OSHA Ceiling Limit:	None established
ACGIH (8-hr TWA):	None established
ACGIH STEL:	None established
NIOSH RELs:	None established

8. REFERENCES

Hawley GG. 1987. The Condensed Chemical Dictionary, 9th ed. New York: Van Nostrand Reinhold Company, pp. 126, 532.

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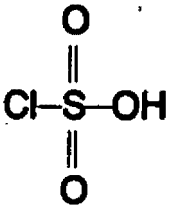
1. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Water, provides information on the health effects and other useful data that can aid in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. The EPA has an ongoing cooperative agreement with the Department of the Army to prepare drinking water Health Advisories (HA) for munitions and other environmental contaminants. Drinking water Toxicological Profiles are short summaries of the pertinent mammalian health effects literature, and are used by the Office of Water to determine if a data base is sufficient to allow the development of HAs. The following databases were searched for information on chlorosulfonic acid: CANCERLINE, CHEMFATE, DART, DTIC, EMICBACK, ENVIROLINE, RTECS, TOXLINE, TOXLINE65, TOXLIT, and TOXLIT65. Secondary sources were also used.

This Drinking Water Toxicological Profile summarizes information on chlorosulfonic acid, considered to be the monoacid chloride of sulfuric acid (Burrus, 1978). Its principal use is in organic synthesis to form sulfates, sulfonates, sulfonyl chlorides, and some organics such as hydrocarbons, alcohols, phenols, and amines (Burris, 1978). It is a chemical intermediate for dyes, pesticides, ion-exchange resins, pharmaceuticals, alkyl sulfate surfactants, and alkylphenol ethoxylate sulfate surfactants (HSDB, 1991). The military uses chlorosulfonic acid as a screening smoke/obscurant and in corrosion testing of various materials (DTIC, 1992). The structure of chlorosulfonic acid is shown below.



Chlorosulfonic acid

2. SELECTED GENERAL INFORMATION

Chlorosulfonic acid is a very corrosive liquid (Budavari et al., 1989). It reacts with water with explosive violence to form hydrochloric acid and sulfuric acid (HSDB, 1991). The physicochemical properties of chlorosulfonic acid are presented in Table 2.

TABLE 2. PHYSICOCHEMICAL DATA

Common name	chlorosulfonic acid	RTECS, 1992
Synonyms	chlorosulfuric acid; monochlorosulfuric acid; sulfuric chlorohydrin	RTECS, 1992
CAS Registry No.	7790-94-5	RTECS, 1992
RTECS No.	FX5730000	RTECS, 1987
Chemical formula	$ClHO_3S$	RTECS, 1992
Molecular weight	116.52	RTECS, 1992
Physical state	colorless or slightly yellow liquid	Budavari et al., 1989
Vapor pressure	0.75 mm Hg at 20°C	CHEMFATE, 1992
Specific gravity	1.753 at 20°C/4°C[a]	Budavari et al., 1989
Melting/Boiling/Flash point	-80°C/158°C/ND[b]	CHEMFATE, 1992
Solubility in water	hydrolyzes violently in water	CHEMFATE, 1992
Log K_{OW}	ND	
Bioconcentration factor (BCF)	ND	
Conversion factors in air	1 mg/m^3 = 0.2098 ppm 1 ppm = 4.766 mg/m^3	calculated[c]
Odor threshold	ND; pungent odor	Budavari et al., 1989
Henry's Law constant	ND	

[a]Density of liquid at 20°C relative to the density of water at 4°C
[b]ND = no data

[c]Formula: $\text{ppm by volume} = mg/m^3 \times \frac{24.45}{\text{mol. wt. in grams}}$

3. SOURCES OF EXPOSURE

3.1. Occurrence in Water

Chlorosulfonic acid is released to the aquatic environment from facilities using the chemical as an intermediate for such products as detergents, pharmaceuticals, and pesticides (HSDB, 1991). However, because the chemical rapidly hydrolyzes in water, its aquatic half-life would not be significant.

3.2. Human Exposure

Exposure to chlorosulfonic acid will be mainly occupational via inhalation and perhaps dermal contact (HSDB, 1991). Based on the 1981-1983 National Occupational Exposure (NOES) Survey, NIOSH estimated that 3,260 U.S. workers are potentially exposed to chlorosulfonic acid (NIOSH, 1983).

4. ENVIRONMENTAL FATE

If released to water, chlorosulfonic acid will hydrolyze violently to produce hydrochloric acid and sulfuric acid (Burrus, 1979). This reaction would preclude significant bioconcentration, biodegradation, volatilization, and adsorption to sediment and suspended solids (HSDB, 1991).

No data were found for chlorosulfonic acid released to soil. However, based on the rapid hydrolysis of the chemical in water, chlorosulfonic acid released to moist soil would be expected to hydrolyze; thus, biodegradation, adsorption, and volatilization processes in moist soil should not be significant (HSDB, 1991). In dry soil, volatilization of the chemical could be significant, based on the vapor pressure of 0.75 mm Hg at 20°C (HSDB, 1991).

In the atmosphere, chlorosulfonic acid would probably undergo hydrolysis in moist air and would be susceptible to photooxidation (HSDB, 1991). Chlorosulfonic acid would react with 5 x 10^5 photochemically produced hydroxyl radicals per cm^3 of air with an estimated half-life of 1.2 years (HSDB, 1991).

5. TOXICOKINETICS

5.1. Absorption

No information was found in the available literature.

5.2. Distribution

No information was found in the available literature.

5.3. Metabolism

No information was found in the available literature.

5.4. Excretion

No information was found in the available literature.

6. HEALTH EFFECTS

6.1. Noncancer Effects

6.1.1. Oral Exposure

6.1.1.1. Human. No information was found in the available literature.

6.1.1.2. Animal. No information was found in the available literature.

6.1.2. Other Exposure Routes

6.1.2.1. Human. Chlorosulfonic acid is extremely caustic, giving off fumes that are irritating to the eyes, skin, and respiratory tract (Grant, 1974; Budavari, 1989). A laboratory worker was splashed in the face when a flask containing chlorosulfonic acid and chlorobenzene fell into water and exploded (Grant, 1974). The victim sustained burns of the cornea and conjunctiva, but because he washed his eyes and skin immediately, the injuries were restricted to the palpebral fissure. The lids, more severely burned, exhibited increasing swelling and loss of patches of skin. The immediate rinsing of the affected areas saved his eyes and within two weeks all injuries were healing.

6.1.2.2. Animal. A brief abstract of a Russian document reported LC_{50} values of 38.5 mg/m^3/4 hours and 52.5 mg/m^3/2 hours for chlorosulfonic acid in the rat and mouse, respectively (Mamleeva and Bakhtizina, 1976). The animals had respiratory tract irritation, eye irritation, and histopathological changes in the internal organs. Experimental details were not available. Based on these data, the investigators recommended a maximum permissible concentration of 0.1 mg/m^3 for chlorosulfonic acid.

6.2. Carcinogenicity

6.2.1. Oral Exposure

6.2.1.1. Human. No information was found in the available literature.

6.2.1.2. Animal. No information was found in the available literature.

6.2.2. Other Exposure Routes

6.2.2.1. Human. No information was found in the available literature.

6.2.2.2. Animal. No information was found in the available literature.

6.4. Genotoxicity

No information was found in the available literature.

7. EXISTING STANDARDS, CRITERIA, GUIDANCE

7.1. EPA RfDs, RfCs, CRAVE Classifications

RfD:	None established
RfC:	None established
Oral slope factor:	None established
Drinking Water Unit Risk:	None established
Inhalation Slope Factor:	None established
Inhalation Unit Risk:	None established
EPA CRAVE Cancer Classification:	Not established

7.2. IARC Carcinogenicity Classification

Not established

7.3. OSHA, ACGIH, and NIOSH Standards and Criteria

OSHA (8-hr TWA):	None established
OSHA STEL:	None established
OSHA Ceiling Limit:	None established
ACGIH (8-hr TWA):	None established
ACGIH Ceiling Limit:	None established
NIOSH RELs:	None established

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Mamleeva NK, Bakhtizina GZ. 1976. Evaluation of the acute toxicity of the easily hydrolyzed compound - chlorosulfonic acid (sulfuric acid chloride). Gig. Tr. Okhr. Zdorov'ya Rab. Neft. Neftekhim. Prom-sti. 9:110-113. (Cited in TOXLIT65)

NIOSH. 1983. National Institute of Occupational Safety and Health. The National Occupational Exposure Survey (NOES), 1983. (Cited in RTECS, 1992)

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1. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Water, provides information on the health effects and other useful data that can aid in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. The EPA has an ongoing cooperative agreement with the Department of the Army to prepare drinking water Health Advisories (HA) for munitions and other environmental contaminants. Drinking Water Toxicological Profiles are short summaries of the pertinent mammalian health effects literature, and are used by the Office of Water to determine if a data base is sufficient to allow the development of HAs. The following data bases were searched for information on copper naphthenate: TOXLINE, TOXLINE65, TOXLIT, TOXLIT65, CANCERLINE, DART, EMICBACK, CHEMFATE, ENVIROLINE, DTIC and RTECS. Secondary sources were also used.

This Drinking Water Toxicological Profile summarizes information on copper naphthenate. Copper naphthenate is a cycloparaffin that contains between 6% and 11.5% copper (Sax and Lewis, 1987). It is a combination of copper salts and naphthenic acid, a monobasic carboxylic acid mixed with low-molecular weight fatty acids and cyclopentanoic acid (Bluhm et al., 1992). Copper naphthenate is used as an insecticide, fungicide, antifouling agent in paints, and as a preservative of wood, rope, and canvas (Sax and Lewis, 1987). The chemical has also been used in veterinary medicine for the treatment of wounds, foot rot, and ringworm (Jones et al., 1979). The structure for copper naphthenate, a naphthenic acid salt, was not available. The structure of naphthenic acid is shown below.

Naphthenic acid

2. SELECTED GENERAL INFORMATION

Physicochemical data and registry numbers for copper naphthenate are presented in Table 3.

TABLE 3. PHYSICOCHEMICAL DATA

Common name	copper naphthenate	
Synonyms	naphthenic acid copper salt; cuprinol; troysan; copper uversol; Wittox C	RTECS, 1986
CAS Registry No.	1338-02-9	
RTECS No.	QK9100000	RTECS, 1986
Chemical formula	$(C_6H_5COO)_2Cu$	Sax, 1984
Molecular weight	221.9	Sax, 1984
Physical state	liquid at 15°C	Weiss, 1980
Vapor pressure	<0.001 mm Hg at 100°C	Spencer, 1982
Specific gravity	1.055	Weiss, 1980
Melting/boiling/flash point	ND/310 to 395°F/212°F	Sax and Lewis, 1987; Weiss, 1980
Solubility in water	practically insoluble	Spencer, 1982
Log K_{ow}	ND[a]	
Bioconcentration factor (BCF)	little potential for bioaccumulation	Weiss, 1980
Conversion factors in air	1 ppm = 9.08 mg/m^3 1 mg/m^3 = 0.11 ppm	calculated[b]
Odor threshold	ND, gasoline-like odor	Weiss, 1980
Henrys' Law constant	ND	

[a]ND: no data

[b]Formula: ppm by volume = $mg/m^3 \times \frac{24.45}{\text{mol. wt. in grams}}$

3. SOURCES OF EXPOSURE

3.1. Occurrence in Water

No information was located in the available literature.

3.2. Human Exposure

The only exposure data that is available is for exposure to copper naphthenate that was applied as a fungicide to a private residence. The precise route of exposure or the component of the compound responsible for the adverse health effects were not known (Bluhm et al., 1992).

4. ENVIRONMENTAL FATE

No specific data were available regarding the environmental fate of copper naphthenate and because it is nearly insoluble in water, appreciable dissociation of the copper moiety is not likely. No additional data were available regarding degradation products of copper naphthenate or the persistence of the compound in soil or groundwater.

5. TOXICOKINETICS

5.1. Absorption

Although quantitative data were not available, it may be assumed that because of its high lipid solubility (Bluhm et al., 1992), copper naphthenate may be absorbed through the skin and mucous membranes. Some degree of absorption may also be implied based upon the urinary excretion of copper by individuals exposed (see Section 6.1.2.1) to copper naphthenate.

5.2. Distribution

Because of its lipid solubility, it is possible that copper naphthenate may have a wide volume of distribution in the body once it is absorbed. However, no quantitative or confirming data are available.

5.3. Metabolism

No information was located in the available literature.

5.4. Excretion

Urinary copper increased following acute exposure to copper naphthenate vapors (Bluhm et al., 1992). A reported serum half-life of 40 months for copper was based upon data from one individual exposed to copper naphthenate vapors (Bluhm et al., 1992).

6. HEALTH EFFECTS

6.1. Noncancer Effects

Data are limited regarding the noncancer effects of copper naphthenate. It may be assumed that some degree of toxicity can be attributed to both the metal and organic component of the chemical. Worthington and Walker (1987) reported that both the metal and acid components contribute to the antifungal activity of this chemical.

6.1.1. Oral Exposure

6.1.1.1. Human. No information was located in the available literature.

6.1.1.2. Animal. An LD_{50} of 2 g/kg has been reported for rats, and an LD_{Lo} of 110 mg/kg was reported for mice (RTECS, 1986). A rat oral LD_{50} of 450 mg/kg has also been reported by Spencer (1981). A rat oral LD_{50} of >6 g/kg for copper naphthenate (8% copper) was reported by Rockhold (1955). The rat oral LD_{50} values for naphthenic acid fractions from crude kerosine acids and mixed crude acids were 3.0 and 5.2 g/kg, respectively. Angerhofer and Taylor (1988a) reported that orally administered Cunapsol 5 (a wood preservative containing about 48% copper naphthenate) was of low toxicity to laboratory animals (LD_{50} values of 3154 and 2258 mg/kg for male and female rats, respectively).

6.1.2. Other Exposure Routes

6.1.2.1. Human. A case report by Bluhm et al. (1992) noted adverse health effects consisting of nausea, headaches, eye irritation, and dizziness within 1 hour after entering a private residence to which 25 gallons of 6% copper naphthenate had been applied to the foundation. The route of exposure was not specified but assumed to be inhalation. Serum and urinary copper levels were initially elevated but slowly returned to normal. The authors indicated that it was unclear whether or not the adverse health effects were due to the copper naphthenate exposure or to the mold content for which the building was treated. It was also not possible to attribute the adverse effects to a particular component (copper versus organic solvent) of copper naphthenate.

Skin irritation in humans has been associated with copper naphthenate exposure (Vickland, 1947).

6.1.2.2. Animal. A copper naphthenate-containing wood preservative (Cunapsol 5) was shown to cause severe dermal and ocular irritation in laboratory animals exposed via these routes (Angerhofer and Taylor, 1988a). This report also noted that dermal application of Cunapsol 5 (2000 mg/kg) was fatal to rabbits. Inhalation exposure of rabbits to "high atmospheric concentrations" of copper naphthenate-containing wood preservative (M-Gard W-510) caused death (Angerhofer and Taylor, 1988b). Rats exposed for eight hours to copper naphthenate at concentrations as high as 0.50 mg/L or to Cunapsol 5 at concentrations as high as 16.60 mg/L did not result in observable signs of toxicity (Angerhofer and Taylor, 1988a).

6.2. Carcinogenicity

6.2.1. Oral Exposure

6.2.2.1. Human. No information was located in the available literature.

6.2.2.2. Animal. No information was located in the available literature.

6.2.2. Other Exposure Routes

6.2.2.1. Human. No information was located in the available literature.

6.2.2.2. Animal. No information was located in the available literature.

6.3. Genotoxicity

Chromosomal aberration tests (Chinese hamster ovary test), mouse lymphoma mutation assays, and dominant lethal assays using copper naphthenate were negative (Angerhofer and Taylor, 1988b).

7. EXISTING STANDARDS, CRITERIA, GUIDANCE

7.1. EPA RfDs, RfCs, CRAVE Classifications

RfD:	None established
RfC:	None established
Oral Slope Factor:	None established
Drinking Water Unit Risk:	None established
Inhalation Slope Factor:	None established
Inhalation Unit Risk:	None established
U.S. EPA CRAVE Cancer Classification:	EPA has not evaluated copper naphthenate as to carcinogenicity

7.2. IARC Carcinogenicity Classification

IARC has not evaluated copper naphthenate as to its carcinogenic potential in humans.

7.3. OSHA, ACGIH, and NIOSH Standards and Criteria

OSHA TWA (8-hr):	None established
ACGIH TLV (8-hr TWA):	None established
STEL:	None established
NIOSH RELs:	None established

8. REFERENCES

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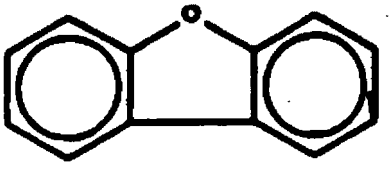
This Drinking Water Toxicological Profile summarizes information on dibenzofuran. Dibenzofuran is a non-substituted polynuclear aromatic hydrocarbon. The addition of chlorine atoms will result in the formation of various congeners with greatly varying degrees of toxicity; the 2,3,7,8-substituted congeners are generally considered to be the most toxic. This document, however, addresses only dibenzofuran. Considerable information exists for the chlorinated congeners (U.S. EPA, 1987a; Barnes et al., 1989; USAF, 1989).

Although considerable amounts of data are available for the chlorinated dibenzofurans, very little information is available regarding the non-substituted form. Most environmental contamination and toxicity data are for mixtures of polychlorinated biphenyls (PCBs), polychlorinated dibenzofurans (PCDFs), and polychlorinated quinones (PCQs) which might contain dibenzofuran. Because of the importance of the position and number of chlorine atom substitutions in affecting the biological activity of dibenzofurans, extrapolation from data for the chlorinated congeners to the non-substituted form would be precarious. The structure of dibenzofuran is shown below.



Dibenzofuran

2. SELECTED GENERAL INFORMATION

Physicochemical data and registry numbers for dibenzofuran are presented in Table 4.

TABLE 4. PHYSICOCHEMICAL DATA

Common name	dibenzofuran	
Synonyms	diphenylene oxide; (1,1'-biphenyl)-2,2'-diyl oxide; 2,2'-biphenylene oxide	IRIS, 1990
CAS Registry No.	132-64-9	
RTECS No.	ND[a]	
Chemical formula	$C_{12}H_8O$	U.S. EPA, 1987b
Molecular weight	168.20	U.S. EPA, 1987b
Physical state	crystalline	U.S. EPA, 1987b
Vapor pressure	1.8×10^{-2} mm Hg	U.S. EPA, 1987b
Specific gravity	ND	
Melting/boiling/flash point	82.8-83°C/276-287°C/ND	U.S. EPA, 1987b
Solubility in water	3.1 mg/L	Lu et al., 1978
Log K_{ow}	4.12	Hansch and Leo, 1981
Bioconcentration factor (BCF)	3.13, fathead minnow; 83 alga; 947, *Gambusia* (fish); 2860, *Physa* (snail)	SRC, 1988; Carlson et al., 1979 Lu et al., 1978
Conversion factors in air	1 ppm = 6.88 mg/m^3 1 mg/m^3 = 0.14 ppm	Calculated[b]
Odor threshold	120 µg/L	U.S. EPA, 1975
Henrys' Law constant	1.26×10^{-5} atm·m^3/mole	SRC, 1988

[a]ND: no data

[b]Formula: ppm by volume = $mg/m^3 \times \frac{24.45}{\text{mol. wt. in grams}}$

3. SOURCES OF EXPOSURE

3.1. Occurrence in Water

Dibenzofuran may enter water systems via discharge from coal conversion plants (Lu et al., 78). Because it is an atmospheric pollutant and occurs in particulate form, it may also enter surface water via settling. The chemical has been detected in a shallow aquifer beneath a creosote facility (Bedient et al., 1984).

3.2. Human Exposure

No data specific for dibenzofuran were available. It may be assumed that exposure to dibenzofuran would coincide with exposures to PCDFs and PCDDs; i.e. from combustion products such as fly ash or as the result of exposure to other chemicals in which the dibenzofurans are contaminants.

4. ENVIRONMENTAL FATE

No definitive data were available regarding the persistence or degradation of dibenzofuran in water. However, dibenzofuran may absorb to sediments resulting in an extremely long half-life (U.S. EPA, 1987b). Microbial degradation of dibenzofuran by *Pseudomonas* strains to 4-(2'-(3'-hydroxy)-benzofuranyl)-2-keto-3-butenic acid was reported by Selifonov et al. (1991). Biodegradation of dibenzofuran has been reported for a *Salmonella* strain (Selifonov et al., 1991) and for a strain of *Sphingomonas* (Wittich et al., 1992).

5. TOXICOKINETICS

5.1. Absorption

No information was located in the available literature.

5.2. Distribution

No information was located in the available literature.

5.3. Metabolism

No information was located in the available literature.

5.4. Excretion

No information was located in the available literature.

6. HEALTH EFFECTS

6.1. Noncancer Effects

6.1.1. Oral Exposure

6.1.1.1. Human. No information was located in the available literature.

6.1.1.2. Animal. No information was available regarding the toxicity of dibenzofuran. However, studies have shown that chlorinated dibenzofurans may induce a wide range of toxic effects (U.S. EPA, 1987a,b). Toxicity data for dibenzofuran was not available. However, based upon the Toxicity Equivalent Factor (TEF) methodologies (U.S. EPA, 1987a, Barnes et al., 1989), the lack of chlorine atom substitutions on the dibenzofuran molecule would set the TEF equal to 0, suggesting minimal toxicity relative to 2,3,7,8,-tetrachlorodibenzofuran. This rationale is presented in IRIS (1990).

6.1.2. Other Exposure Routes

6.1.2.1. Human. No information was located in the available literature.

6.1.2.2. Animal. No information was located in the available literature.

6.2. Carcinogenicity

6.2.1. Oral Exposure

6.2.1.1. Human. No information was located in the available literature.

6.2.1.2. Animal. No information was located in the available literature.

6.2.2. Other Exposure Routes

6.2.2.1. Human. No information was located in the available literature.

6.2.2.2. Animal. No information was located in the available literature.

6.3. Genotoxicity

Dibenzofuran was not mutagenic in standard *Salmonella* strains (U.S. EPA, 1987b).

7. EXISTING STANDARDS, CRITERIA, GUIDANCE

7.1. EPA RfDs, RfCs, CRAVE Classifications

RfD:	None established
RfC:	None established
Oral Slope Factor:	None established
Drinking Water Unit Risk:	None established
Inhalation Slope Factor:	None established
Inhalation Unit Risk:	None established
U.S. EPA CRAVE Cancer Classification:	Group D; not classifiable as to human carcinogenicity

An ambient water quality criteria of 120 μg/L for dibenzofuran was recommended by the U.S. EPA using organoleptic properties as the criterion (U.S. EPA, 1987b).

7.2. IARC Carcinogenicity Classification

IARC (1987) has not evaluated dibenzofuran as to its carcinogenicity to humans.

7.3. OSHA, ACGIH, and NIOSH Standards and Criteria

OSHA TWA (8-hr):	None established
ACGIH TLV (8-hr TWA):	10 ppm (45 mg/m^3); skin notation (ACGIH, 1992)
STEL:	20 ppm (90 mg/m^3)
NIOSH RELs:	None established

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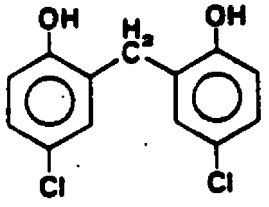
1. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Water, provides information on the health effects and other useful data that can aid in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. The EPA has an ongoing cooperative agreement with the Department of the Army to prepare drinking water Health Advisories (HA) for munitions and other environmental contaminants. Drinking Water Toxicological Profiles are short summaries of the pertinent mammalian health effects literature, and are used by the Office of Water to determine if a data base is sufficient to allow the development of HAs. The following data bases were searched for information on dichlorophene: TOXLINE, TOXLINE65, TOXLIT, TOXLIT65, CANCERLINE, DART, EMICBACK, CHEMFATE, ENVIROLINE, DTIC and RTECS. Secondary sources were also used.

This Drinking Water Toxicological Profile summarizes information on dichlorophene. Dichlorophene is used as an antimicrobial, germicide, and agricultural fungicide. It has also been used therapeutically as an anthelmintic and antiprotozoan. The structure of dichlorophene is shown below.



Dichlorophene

2. SELECTED GENERAL INFORMATION

Physicochemical data and registry numbers for dichlorophene are presented in Table 5.

TABLE 5. PHYSICOCHEMICAL DATA

Common name	dichlorophene	
Synonyms	dichlorophen; 2,2'-dihydroxy-5,5'-dichlorophenylmethane; Anthiphen; *bis*(5-chloro-2-hydroxyphenyl)methane, G-4	RTECS, 1986 Budavari, 1989
CAS Registry No.	97-23-4	RTECS, 1986
RTECS No.	SM0175000	RTECS, 1986
Chemical formula	$C_{13}H_{10}Cl_2O_2$	Budavari, 1989
Molecular weight	269.12	Budavari, 1989
Physical state	crystalline	Budavari, 1989
Vapor pressure	ND[a]	
Specific gravity	ND	
Melting/boiling/flash point	ND/ND/ND	
Solubility in water	practically insoluble	Budavari, 1989
Log K_{ow}	ND	
Bioconcentration factor (BCF)	ND	
Conversion factors in air	1 mg/m^3 = 0.09 ppm 1 ppm = 11.0 mg/m^3	Calculated[b]
Odor threshold	ND	
Henrys' Law constant	ND	

[a]ND: no data

[b]Formula: $\text{ppm by volume} = \text{mg/m}^3 \times \frac{24.45}{\text{mol. wt. in grams}}$

3. SOURCES OF EXPOSURE

3.1. Occurrence in Water

No information was located in the available literature.

3.2. Human Exposure

No information was located in the available literature.

4. ENVIRONMENTAL FATE

No information was located in the available literature.

5. TOXICOKINETICS

5.1. Absorption

Dixon (1982) reported gastrointestinal absorption of orally administered dichlorophene (50 mg/kg) by rats.

5.2. Distribution

Following oral administration to rats, dichlorophene or its metabolites enter the systemic circulation and may reach other organs (Dixon, 1982). Radioactivity was detected in the blood, bile, and urine of rats orally administered ^{14}C-dichlorophene (Dixon, 1982).

5.3. Metabolism

Dixon (1982) detected sulfate, monoglucuronide, and diglucuronide metabolites in rats given an oral dose of dichlorophene. It was hypothesized that the sulfate and monoglucuronide metabolites were formed during passage of the chemical through the gut wall. The diglucuronide was formed in the liver and possibly other organs perfused by the systemic circulation.

5.4. Excretion

The sulfate and diglucuronide metabolites were excreted in the urine but most of the monoglucuronide metabolite underwent biliary excretion (Dixon, 1982).

6. HEALTH EFFECTS

6.1. Noncancer Effects

6.1.1. Oral Exposure

6.1.1.1. Human. Side-effects of nausea, vomiting, gastro-intestinal colic and diarrhea have been reported following therapeutic doses (total of 6 g in divided doses over two successive days; equivalent to 85.7 mg/kg for a 70 kg human) of dichlorophene (Bowman and Rand, 1980).

6.1.1.2. Animal. Based upon LD_{50} values, dichlorophene appears to have a low order of acute oral toxicity. Oral LD_{50} values for rats, mice, dogs, and guinea pigs are 1506, 1000, 2000, and 1250 mg/kg (RTECS, 1986).

6.1.2. Other Exposure Routes

6.1.2.1. Human. An anecdotal report indicates that inhalation of dichlorophene may cause irritation of the respiratory tract and dyspnea (Watt, 1991). Contact dermatitis (itching, burning, swelling, and vesiculation) was reported for three patients using a topical medication containing dichlorophene (Schorr, 1970).

6.1.2.2. Animal. No information was located in the available literature.

6.2. Carcinogenicity

6.2.1. Oral Exposure

6.2.2.1. Human. No information was located in the available literature.

6.2.2.2. Animal. No information was located in the available literature.

6.2.2. Other Exposure Routes

6.2.2.1. Human. No information was located in the available literature.

6.2.2.2. Animal. No information was located in the available literature.

6.3. Genotoxicity

Dichlorophene (50 nmol/plate) was mutagenic in *Salmonella typhimurium* without S9 (RTECS, 1986).

7. EXISTING STANDARDS, CRITERIA, GUIDANCE

7.1. EPA RfDs, RfCs, CRAVE Classifications

RfD:	None established
RfC:	None established
Oral Slope Factor:	None established
Drinking Water Unit Risk:	None established
Inhalation Slope Factor:	None established
Inhalation Unit Risk:	None established
U.S. EPA CRAVE Cancer Classification:	The EPA has not evaluated the carcinogenicity of dichlorophene

7.2. IARC Carcinogenicity Classification

IARC has not evaluated dichlorophene.

7.3. OSHA, ACGIH, and NIOSH Standards and Criteria

OSHA TWA (8-hr):	None established
ACGIH TLV (8-hr TWA):	None established
STEL:	None established
NIOSH RELs:	None established

8. REFERENCES

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1. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Water, provides information on the health effects and other useful data that can aid in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. The EPA has an ongoing cooperative agreement with the Department of the Army to prepare drinking water Health Advisories (HA) for munitions and other environmental contaminants. Drinking Water Toxicological Profiles are short summaries of the pertinent mammalian health effects literature, and are used by the Office of Water to determine if a data base is sufficient to allow the development of HAs. The following data bases were searched for information on diethylenetriamine: TOXLINE, TOXLINE65, TOXLIT, TOXLIT65, CANCERLINE, DART, EMICBACK, CHEMFATE, ENVIROLINE, DTIC and RTECS. Secondary sources were also used.

This Drinking Water Toxicological Profile summarizes information on diethylenetriamine. Diethylenetriamine is used in various industrial applications such as hardeners and stabilizers for epoxy resins, as a solvent, for vulcanization of rubber, and in the synthesis of detergents, softeners, dyes, and plastics (DePass et al., 1987). The structure of diethylenetriamine is shown below.

$$NH_2\text{-}CH_2CH_2\text{-}NH\text{-}CH_2CH_2\text{-}NH_2$$

Diethylenetriamine

2. SELECTED GENERAL INFORMATION

Physicochemical data and registry numbers for diethylenetriamine are presented in Table 6.

TABLE 6. PHYSICOCHEMICAL DATA

Common name	diethylenetriamine	
Synonyms	*N*-(2-aminoethyl)-1,2-ethanediamine; amino-ethylethanediamine; 3-azapentane-1,5-diamine; DETA; *bis*(2-aminoethyl)amine	RTECS, 1986 Weiss, 1980
CAS Registry No.	111-40-0	
RTECS No.	IE1225000	RTECS, 1986
Chemical formula	$NH_2(CH_2)_2NH(CH_2)_2NH_2$	Weiss, 1980
Molecular weight	103.2	Weiss, 1980
Physical state	liquid	RTECS, 1986
Vapor pressure	0.2175 mm Hg at 20°C	Parrish, 1983
Specific gravity	0.954 at 20°C	Weiss, 1980
Melting/boiling/flash point	-39°C/206.9°C/ND[a]	Riddick et al., 1986
Solubility in water	very soluble	Hann and Jensen, 1977
Log K_{ow}	ND	
Bioconcentration factor (BCF)	little potential for bioaccumulation	Weiss, 1980
Conversion factors in air	1 ppm = 4.2 mg/m^3 1 mg/m^3 = 0.24 ppm	ACGIH, 1991-1992
Odor threshold	10 ppm	Weiss, 1980
Henrys' Law constant	1.09×10^{-14} atm·m^3/mole	SRC, 1988

[a]ND: no data

3. SOURCES OF EXPOSURE

3.1. Occurrence in Water

No information was located in the available literature.

3.2. Human Exposure

No information was located in the available literature.

4. ENVIRONMENTAL FATE

Popp (1977) reported that diethylenetriamine in wastewater underwent moderate (50%) biodegradation which was less than that of other polyamines examined.

5. TOXICOKINETICS

5.1. Absorption

No information was located in the available literature.

5.2. Distribution

No information was located in the available literature.

5.3. Metabolism

No information was located in the available literature.

5.4. Excretion

No information was located in the available literature.

6. HEALTH EFFECTS

6.1. Noncancer Effects

6.1.1. Oral Exposure

6.1.1.1. Human. No information was located in the available literature.

6.1.1.2. Animal. Although an oral LD_{50} of 1080 mg/kg resulting in convulsions and death of rats is listed by RTECS (1986), other studies have shown exposure to much higher doses to be without lethal effects.

Fourteen-week exposure of male and female F344 rats (10/sex/group) to diethylenetriamine at dietary concentrations of 5,000, 10,000, 25,000, or 50,000 ppm (corresponding to approximate doses of 580, 1150, 2000, and 4550 mg/kg/day) did not affect mortality rate but mean body weights were significantly reduced in males of the two highest dose groups and of females of the three highest dose groups (EPA/OTS, 1986). However, significant reductions in food consumption were also observed for both sexes at the two highest dose groups and may have caused or contributed to the reduced body weight. A reduction in mean and relative spleen weights was noted for both sexes at the two highest dose groups. No other significant toxic effects were reported.

Reduction in body weights (3-7%) were also observed for male and female F344 rats receiving dietary diethylenetriamine at dietary concentrations of 7500 and 15,000 ppm for 90 days (EPA/OTS, 1991). No other treatment-related effects were reported.

6.1.2. Other Exposure Routes

6.1.2.1. Human. Based on patch-testing results, Ormerod et al. (1989) found allergic sensitivity to diethylenetriamine in five offshore drilling workers previously exposed to oil-based mud.

6.1.2.2. Animal. Acute inhalation exposure of female rats to diethylenetriamine (1.8 mg/L for 4 hours; whole body exposure) resulted in the death of nine of 10 rats during days 1 and 5 of the postexposure observation period (EPA/OTS, 1964). Necropsy revealed pulmonary hyperemia. Rats exposed to vapors at a concentration of 300 ppm (duration not specified) showed no adverse effects (Clayton and Clayton, 1978).

A 15% solution of diethylenetriamine applied to eyes of rats caused severe corneal injury but application of a 5% solution did not cause injury (Clayton and Clayton, 1978).

6.2. Carcinogenicity

6.2.1. Oral Exposure

6.2.2.1. Human. No information was located in the available literature.

6.2.2.2. Animal. No information was located in the available literature.

6.2.2. Other Exposure Routes

6.2.2.1. Human. No information was located in the available literature.

6.2.2.2. Animal. Lifetime treatment of male C3H/HeJ mice with high purity or commercial grade diethylenetriamine (25 μL of a 5% solution of each; equivalent to 1.25 mg applied to shaved dorsal skin three times per week; 50 mice per treatment group) produced no oncogenic effects and had no effect on mortality rate (DePass et al., 1987).

6.3. Genotoxicity

No information was located in the available literature.

7. EXISTING STANDARDS, CRITERIA, GUIDANCE

7.1. EPA RfDs, RfCs, CRAVE Classifications

RfD:	None established
RfC:	None established
Oral Slope Factor:	None established
Drinking Water Unit Risk:	None established
Inhalation Slope Factor:	None established
Inhalation Unit Risk:	None established
U.S. EPA CRAVE Cancer Classification:	EPA has not evaluated diethylenetriamine as to carcinogenicity.

7.2. IARC Carcinogenicity Classification

IARC has not evaluated diethylenetriamine as to its carcinogenic potential in humans.

7.3. OSHA, ACGIH, and NIOSH Standards and Criteria

OSHA TWA (8-hr):	1 ppm (4 mg/m^3) (OSHA, 1989)
ACGIH TLV (8-hr TWA):	1 ppm (4.2 mg/m^3) (with skin notation) (ACGIH, 1992)
STEL:	None established
NIOSH RELs:	None established

Germany has established a maximum allowable concentration (MAK) of 0.2 mg diethylenetriamine/L drinking water (Sittig, 1985).

8. REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 1992. Threshold Limit Values for Chemicals and Physical Substances. ACGIH, Cincinnati, OH.

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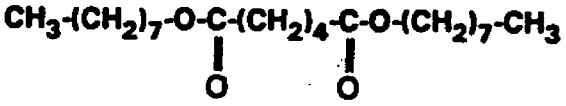
1. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Water, provides information on the health effects and other useful data that can aid in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. The EPA has an ongoing cooperative agreement with the Department of the Army to prepare drinking water Health Advisories (HA) for munitions and other environmental contaminants. Drinking Water Toxicological Profiles are short summaries of the pertinent mammalian health effects literature, and are used by the Office of Water to determine if a data base is sufficient to allow the development of HAs. The following data bases were searched for information on dioctyl adipate: CANCERLINE, CHEMFATE, DART, DTIC, EMICBACK, ENVIROLINE, RTECS, TOXLINE, TOXLINE 65, TOXLIT, AND TOXLIT65. Secondary sources were also used.

This Drinking Water Toxicological Profile summarizes information on dioctyl adipate, an adipic acid ester used in conjunction with other plasticizers as a binder for cellulose-nylon blend materials with improved handling and folding properties (Danly and Campbell, 1978). No information was found concerning the health effects of this compound. The structural formula for dioctyl adipate is shown below.



Dioctyl adipate

2. SELECTED GENERAL INFORMATION

Physicochemical data for dioctyl adipate are presented in Table 7.

TABLE 7. PHYSICOCHEMICAL DATA

Common Name	dioctyl adipate	
Synonyms	ND[a]	
CAS Registry No.	123-79-5	
RTECS No.	ND	
Chemical formula	$C_{22}H_{42}O_4$	Danly and Campbell, 1978
Molecular weight	371	Danly and Campbell, 1978
Physical state	ND	
Vapor pressure	ND	
Specific gravity	0.9135 at 20°C/4°C[b]	Danly and Campbell, 1978
Melting/Boiling/Flash Point	9.7°C/175°C/ND	Danly and Campbell, 1978
Solubility in water	ND	
Log K_{ow}	ND	
Bioconcentration factor (BCF)	ND	
Conversion factors in air	1 ppm = 15.17 mg/m^3 1 mg/m^3 = 0.066 ppm	Calculated[c]
Odor threshold	ND	
Henrys' Law constant	ND	

[a]ND: no data
[b]Density of liquid at 20°C relative to the density of water at 4°C

[c]Formula: $\text{ppm by volume} = \text{mg/m}^3 \times \frac{24.45}{\text{mol. wt. in grams}}$

3. SOURCES OF EXPOSURE

3.1. Occurrence in Water

Dioctyl adipate has been detected in the Delaware, Hudson, and Ohio river basins at concentrations ranging from 2 to 86 ppb (Ewing et al., 1977).

3.2. Human Exposure. No information was found in the available literature.

4. ENVIRONMENTAL FATE

No information was found in the available literature.

5. TOXICOKINETICS

5.1. Absorption

No information was found in the available literature.

5.2. Distribution

No information was found in the available literature.

5.3. Metabolism

No information was found in the available literature.

5.4. Excretion

No information was found in the available literature.

6. HEALTH EFFECTS

6.1. Noncancer Effects

6.1.1. Oral Exposure

6.1.1.1. Human. No information was found in the available literature.

6.1.1.2. Animal. No information was found in the available literature.

6.1.2. Other exposure routes

6.1.2.1. Human. No information was found in the available literature.

6.1.2.2. Animal. No information was found in the available literature.

6.2. Carcinogenicity

6.2.1. Oral Exposure

6.2.1.1. Human. No information was found in the available literature.

6.2.1.2. Animal. No information was found in the available literature.

6.2.2. Other Exposure Routes

6.2.2.1. Human. No information was found in the available literature.

6.2.2.1. Animal. No information was found in the available literature.

6.3. Genotoxicity

No information was found in the available literature.

7. EXISTING STANDARDS, CRITERIA, GUIDANCE

7.1. EPA RfDs, RfCs, CRAVE Classifications

RfD:	None established
RfC:	None established
Oral slope factor:	None established
Drinking Water Unit Risk:	None established
Inhalation Slope Factor:	None established
Inhalation Unit Risk:	None established
EPA CRAVE Cancer Classification:	Not evaluated

7.2. IARC Carcinogenicity Classification

Not evaluated

7.3. OSHA, ACGIH, and NIOSH Standards and Criteria

OSHA (8-hr TWA):	None established
OSHA STEL:	None established
OSHA Ceiling Limit:	None established
ACGIH (8-hr TWA):	None established
NIOSH RELs:	None established

8. REFERENCES

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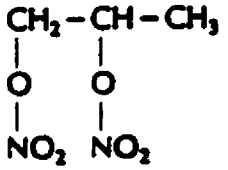
1. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Water, provides information on the health effects and other useful data that can aid in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. The EPA has an ongoing cooperative agreement with the Department of the Army to prepare drinking water Health Advisories (HA) for munitions and other environmental contaminants. Drinking Water Toxicological Profiles are short summaries of the pertinent mammalian health effects literature, and are used by the Office of Water to determine if a data base is sufficient to allow the development of HAs. The following data bases were searched for information on dipropylene glycol 1,2-dinitrate: CANCERLINE, CHEMFATE, DART, DTIC, EMICBACK, ENVIROLINE, RTECS, TOXLINE, TOXLINE65, TOXLIT, AND TOXLIT65. Secondary sources were also used.

This Drinking Water Toxicological Profile summarizes information on dipropylene glycol 1,2-dinitrate, a colorless liquid with a disagreeable odor. It is a major component of a volatile torpedo propellant, Otto Fuel II, used by the U.S. Navy (ACGIH, 1986). Otto Fuel II contains approximately 75% dipropylene glycol 1,2-dinitrate, 20% di-*n*-butyisebacate, a sensitizer, and 5% 2-nitrophenylamine, a stabilizer. Dipropylene glycol 1,2-dinitrate is similar to ethylene glycol dinitrate in explosive characteristics (Forman, 1988; ACGIH, 1986). The structural formula for dipropylene glycol 1,2-dinitrate is shown below.



Dipropylene glycol 1,2-dinitrate

SELECTED GENERAL INFORMATION

The physicochemical properties for dipropylene glycol 1,2-dinitrate are listed in Table 8.

TABLE 8. PHYSICOCHEMICAL DATA

Common name	propylene glycol dinitrate (PGDN)	
Synonyms	1,2-propylene glycol dinitrate; 1,2-propanediol, dinitrate; propylene glycol dinitrate	RTECS, 1992
CAS Registry No.	6423-43-4	
RTECS No.	67115	RTECS, 1992
Chemical formula	$C_3H_6N_2O_6$	ACGIH, 1986
Molecular weight	166.09	ACGIH, 1986
Physical state	liquid	ACGIH, 1986
Vapor pressure	0.094 mm Hg at 25°C	Wyman et al., 1984
Density	1.232 g/ml at 25°C	ACGIH, 1986
Melting/Boiling/Flash Point	-27.7°C/92°C at 10 torr (decomposes above 121°C)/ND	ACGIH, 1986
Solubility in water	1300 mg/L	ACGIH, 1986
Log K_{ow}	ND[a]	
Bioconcentration factor (BCF)	ND	
Conversion factors in air	1 ppm = 6.79 mg/m^3 1 mg/m^3 = 0.147 ppm	calculated[b]
Odor threshold	ND	
Henrys' Law constant	3.3 x 10^2 mm Hg	Wyman et al., 1984

[a]ND: no data

[b]Formula: $\text{ppm by volume} = \text{mg/m}^3 \times \frac{24.45}{\text{mol. wt. in grams}}$

3. SOURCES OF EXPOSURE

3.1. Occurrence in Water

Low concentrations of dipropylene glycol 1,2-dinitrate were detected in wastewater from torpedo refueling facilities (Kessick et al., 1978).

3.2. Human Exposure

Human exposure would most likely occur in occupational settings, i.e., manufacture, use, and maintenance of torpedo propellant. In the workplace, inhalation is the main route of exposure, although considerable potential exists for dermal exposure (Bogo et al., 1987).

4. ENVIRONMENTAL FATE

Dipropylene glycol 1,2-dinitrate rapidly evaporates from aqueous solutions, with a volatility considerably greater than that expected from its vapor pressure. The unexpected volatility of dipropylene glycol 1,2-dinitrate from water is attributed to the formation of a dipropylene glycol 1,2-dinitrate-water azeotrope (Wyman et al., 1984). Using an activated sludge system under aerobic conditions, Cornell et al. (1981) demonstrated biodegradation of dipropylene glycol 1,2-dinitrate via sequential hydrolytic cleavage of nitrate groups. Wyman et al. (1984), by contrast, found the compound resistant to biodegradation by microorganisms present in sewage sludge, by a pure culture of *Pseudomonas*, and by a commercially available culture.

Dipropylene glycol 1,2-dinitrate is photolabile in ultraviolet light, decomposing to pyruvic and lactic acids. Ultraviolet light degraded 94% of dipropylene glycol 1,2-dinitrate in 42 hours (Wyman et al., 1984). Other degradation products identified in previous studies include nitrogen oxide, nitrogen dioxide, and nitrous acid (Csizmadia and Haywood, 1965; Rebbert, 1963). Dipropylene glycol 1,2-dinitrate combustion products include carbon monoxide and cyanide gas (Forman, 1988).

5. TOXICOKINETICS

5.1. Absorption

Oral and pulmonary absorption may be inferred from dipropylene glycol 1,2-dinitrate-induced systemic toxicity. The compound is lipid soluble, permitting ready dermal absorption (Forman, 1988). At least 10% of topically administered dipropylene glycol 1,2-dinitrate penetrated the skin of rats within 30 minutes (Clark and Litchfield, 1969).

5.2. Distribution

One minute after subcutaneous injection, 15% of injected dipropylene glycol 1,2-dinitrate was found in arterial blood and 3-5% in venous blood of rabbits (Kylin et al., 1964). Additional information regarding the distribution of dipropylene glycol 1,2-dinitrate in the body were not

available. However, distribution to organs and tissues may be inferred from documented systemic toxic effects.

5.3. Metabolism

Following absorption into systemic circulation, dipropylene glycol 1,2-dinitrate is rapidly metabolized to a mononitrate, an inorganic nitrate, and nitrite. The mononitrate, in turn, is metabolized and excreted as inorganic nitrate (Forman, 1988). *In vivo* and *in vitro* studies with rats showed that 50% of administered dipropylene glycol 1,2-dinitrate was metabolized in blood within 1 hour and 50% of the remainder in the following hour (Clark and Litchfield, 1969).

5.4. Excretion

Dipropylene glycol 1,2-dinitrate was detected in the breath of humans immediately following exposure, but not 15 minutes post-exposure (Stewart et al., 1974). Excretion was complete 24 hours following subcutaneous injection of rats with dipropylene glycol 1,2-dinitrate. The major metabolite in urine was inorganic nitrate, accounting for 56% of the dose (Clark and Litchfield, 1969).

6. HEALTH EFFECTS

6.1. Noncancer Effects

6.1.1. Oral Exposure

6.1.1.1. Human. No information was found in the available literature.

6.1.1.2. Animal. Oral LD_{50} values for rats range from 250 to 1190 mg/kg (RTECS, 1992; Forman, 1988). Acute exposure to dipropylene glycol 1,2-dinitrate resulted in almost complete conversion of hemoglobin to methemoglobin in rats. Associated clinical symptoms included ataxia, lethargy, and respiratory depression. Death was attributed to anoxia (Andersen and Mehl, 1973; Clark and Litchfield, 1969). Additional information regarding the oral toxicity of dipropylene glycol 1,2-dinitrate in animals was not available.

6.1.2. Other exposure routes

6.1.2.1. Human. Exposure to dipropylene glycol 1,2-dinitrate most frequently occurs by the dermal or inhalation routes (Forman, 1988). Accidental overexposure to dipropylene glycol 1,2-dinitrate, a potential methemoglobin former, has resulted in a spectrum of symptoms, ranging from headache, nasal congestion, dizziness, and eye irritation to vasomotor collapse, and unconsciousness (Stewart et al., 1974).

Most healthy male volunteers exposed to dipropylene glycol 1,2-dinitrate vapor for 1 or 2 hours experienced disruption in the organization of visual response (VER) and headache at $\geq$ 2 ppm. Subjects exposed to 0.2 ppm for 8 hours on a daily basis developed a tolerance to headache, but changes in VER appeared cumulative. Exposure to 0.5 ppm caused impaired balance after 6.5 hours and a consistent increase of diastolic pressure after 8 hours, while 40 min of exposure to 1.5 ppm added eye irritation to the list of symptoms (Stewart et al., 1974).

Horvath et al. (1981) reported headaches, nasal congestion, and decreased oculomotor function, but no evidence of chronic cardiovascular or neurotoxic disorders in 87 U.S. Navy

torpedo workers exposed to dipropylene glycol 1,2-dinitrate at peak airborne concentrations ranging from 0 to 22 ppm (most samples contained ≤0.1 ppm). A cohort of 1352 potentially exposed U.S. Navy torpedo workers showed a significantly higher risk of being hospitalized for myocardial infarction or angina pectoris during a 10-year period compared with a non-exposed control group (Forman, 1987). However, there were no deaths due to cardiovascular disease in the exposed group during this time period. Although dosimetry data were not available, measured 8-hour TWA values were below 0.05 ppm, the TLV-TWA recommended by OSHA (1989) and ACGIH (1991-1992).

Exposure to dipropylene glycol 1,2-dinitrate did not affect pregnancy outcomes in women naval munitions workers engaged in torpedo repair work (Forman, 1988).

6.1.2.2. Animal LD_{50} values for the subcutaneous route of exposure are 463 and 524 mg/kg for male and female rats, respectively; 1208 mg/kg for mice; and 200-300 mg/kg for cats (Clark and Litchfield, 1969). In common with other nitrate esters, dipropylene glycol 1,2-dinitrate causes vasodilation and methemoglobinemia. Subcutaneous injection with 65 mg/kg or topical administration of 50 mg/kg of dipropylene glycol 1,2-dinitrate resulted in decreased blood pressure in rats. Subcutaneous injections of LD_{50} concentrations produced methemoglobinemia in rats, mice, and cats (Clark and Litchfield, 1969).

Jones et al. (1972) conducted a series of inhalation studies with four animals species of both sexes. Rats exposed to 10 ppm dipropylene glycol 1,2-dinitrate for 30 days exhibited no toxic effects. Dogs continuously exposed to 10 ppm for 90 days had hemosiderin deposits in the liver and kidneys. Continuous exposure to 35 ppm for 90 days produced decreased hemoglobin and hematocrit levels and increased methemoglobin levels in rats, guinea pigs, dogs, and monkeys; heavy hemosiderin in the liver, spleen, and kidney of dogs and monkeys; focal and tubular necrosis of the liver in female rats; and vacuolar changes of the liver and increased serum urea nitrogen and decreased alkaline phosphatase, suggestive of renal effects, in monkeys.

No discernible effects on the central nervous system were observed in rhesus monkeys exposed by inhalation to dipropylene glycol 1,2-dinitrate at concentrations of 2-33 ppm for 4 hours or to 0.4-4.2 ppm for 125 days (Mattson et al., 1981). However, direct injection into neural tissue by intracysternal administration severely affected motor performance in the rat 12 min after a 10-μL dose of dipropylene glycol 1,2-dinitrate (Bogo et al., 1987).

A 20-day dermal toxicity study with rabbits showed minor skin irritation at 1 g/kg; weakness and slight cyanosis at 2 g/kg; and methemoglobinemia and high mortality at 4 g/kg (Jones et al., 1972). Primary skin irritation tests were negative, and ocular instillation produced slight eye irritation in rabbits (Jones et al., 1972).

6.2. Carcinogenicity

6.2.1. Oral Exposure

6.2.1.1. Human. No information was found in the available literature.

6.2.1.2. Animal. No information was found in the available literature.

6.2.2. Other Exposure Routes

6.2.2.1. Human. No information was found in the available literature.

6.2.2.2. Animal. In a 1-year inhalation study, exposure of male and female F344 rats, C57BL/6 mice, and beagle dogs (6 hours/day, 5 days/week) to Otto Fuel II failed to produce a significant tumorigenic response. Rats and mice were exposed 1.4 and 240 mg/m^3, and dogs to 1.4 mg/m^3 dipropylene glycol 1,2-dinitrate (Gaworski et al., 1985).

6.3. Genotoxicity

Negative responses were reported in several genotoxicity assays using Otto Fuel II. The fuel did not induce mutations in *Salmonella typhimurium*, sister chromatid exchanges in L5178Y mouse lymphoma cells, cytogenetic changes in mouse bone marrow cells, or dominant lethal mutations in mice. A positive response was reported in the mouse lymphoma forward mutation assay, but only under conditions toxic to the cells (Forman, 1988). Dipropylene glycol 1,2-dinitrate was mutagenic in the extracellular bacteriophage T4B of *Escherichia coli* (Kononova et al., 1972).

7. EXISTING STANDARDS, CRITERIA, GUIDANCE

7.1. EPA RfDs, RfCs, CRAVE Classifications

RfD:	None established
RfC:	None established
Oral slope factor:	None established
Drinking Water Unit Risk:	None established
Inhalation Slope Factor:	None established
Inhalation Unit Risk:	None established
EPA CRAVE Cancer Classification:	Not evaluated

7.2. IARC Carcinogenicity Classification

Not evaluated

7.3. OSHA, ACGIH, and NIOSH Standards and Criteria

OSHA (8-hr TWA):	0.05 ppm (0.3 mg/m^3) (OSHA, 1989)
OSHA STEL:	None established
OSHA Ceiling Limit:	None established
ACGIH TLV (8-hr TWA):	0.05 ppm (0.34 mg/m^3) (with skin notation) (ACGIH, 1991-1992)
NIOSH RELs:	None established

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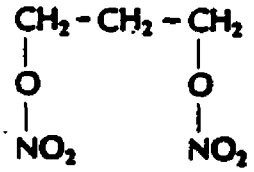
1. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Water, provides information on the health effects and other useful data that can aid in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. The EPA has an ongoing cooperative agreement with the Department of the Army to prepare drinking water Health Advisories (HA) for munitions and other environmental contaminants. Drinking Water Toxicological Profiles are short summaries of the pertinent mammalian health effects literature, and are used by the Office of Water to determine if a data base is sufficient to allow the development of HAs. The following data bases were searched for information on dipropylene glycol 1,3-dinitrate: CANCERLINE, CHEMFATE, DART, DTIC, EMICBACK, ENVIROLINE, RTECS, TOXLINE, TOXLINE65, TOXLIT, AND TOXLIT65. Secondary sources were also used.

This Drinking Water Toxicological Profile summarizes information on dipropylene glycol 1,3-dinitrate. Dipropylene glycol 1,3-dinitrate is a nitric acid ester, used as an explosive plasticizer for nitrocellulose (Lindner, 1980). Virtually no information was found concerning the health effects of this compound. The structural formula for dipropylene glycol 1,3-dinitrate is shown below:



Dipropylene glycol 1,3-dinitrate

2. SELECTED GENERAL INFORMATION

Physicochemical data for dipropylene glycol 1,3-dinitrate are presented in Table 9.

TABLE 9. PHYSICOCHEMICAL DATA

Common Name	1,3-propanediol dinitrate	
Synonyms	PDN	Lindner, 1980
CAS Registry No.	3457-90-7	
RTECS No.	not assigned	
Chemical formula	$C_3H_6N_2O_6$	
Molecular weight	166.11	
Physical state	liquid	Lindner, 1980
Vapor pressure	0.0116 mm Hg at 15°C; 0.0327 mm Hg at 25°C	Lindner, 1980
Specific gravity	ND[a]	
Melting/Boiling/Flash Point	ND	
Solubility in water	less than 1 g in 100 ml	Kononova et al., 1972
Log K_{ow}	ND	
Bioconcentration factor (BCF)	ND	
Conversion factors in air	1 ppm = 6.8 mg/m^3 1 mg/m^3 = 0.147 ppm	calculated[b]
Odor threshold	ND	
Henrys' Law constant	ND	

[a]ND: no data

[b]Formula: $\text{ppm by volume} = \text{mg/m}^3 \times \frac{24.45}{\text{mol. wt. in grams}}$

3. SOURCES OF EXPOSURE

3.1. Occurrence in Water.

No information was found in the available literature.

3.2. Human Exposure.

No information was found in the available literature.

4. ENVIRONMENTAL FATE

No information was found in the available literature.

5. TOXICOKINETICS

5.1. Absorption

No information was found in the available literature.

5.2. Distribution

No information was found in the available literature.

5.3. Metabolism

No information was found in the available literature. By analogy to other nitrate esters, dipropylene glycol 1,3-dinitrate is likely metabolized to a mononitrate, inorganic nitrite, and inorganic nitrate.

5.4. Excretion

No information was found in the available literature.

6. HEALTH EFFECTS

6.1. Noncancer Effects

6.1.1. Oral Exposure

6.1.1.1. Human. No information was found in the available literature.

6.1.1.2. Animal. No information was found in the available literature.

6.1.2. Other exposure routes

6.1.2.1. Human. No information was found in the available literature. By analogy to other nitrate esters, inhalation or dermal exposure to dipropylene glycol 1,3-dinitrate may cause vasodilation resulting in decreases in blood pressure and headaches.

6.1.2.2. Animal. No information was found in the available literature.

6.2. Carcinogenicity

6.2.1. Oral Exposure

6.2.1.1. Human. No information was found in the available literature.

6.2.1.2. Animal. No information was found in the available literature.

6.2.2. Other Exposure Routes

6.2.2.1. Human. No information was found in the available literature.

6.2.2.1. Animal. No information was found in the available literature.

6.3. Genotoxicity

Dipropylene glycol 1,3-dinitrate was mutagenic in extracellular bacteriophage T4B of *Escherichia coli* (Kononova et al., 1972).

7. EXISTING STANDARDS, CRITERIA, GUIDANCE

7.1. EPA RfDs, RfCs, CRAVE Classifications

RfD:	None established
RfC:	None established
Oral slope factor:	None established
Drinking Water Unit Risk:	None established
Inhalation Slope Factor:	None established
Inhalation Unit Risk:	None established
EPA CRAVE Cancer Classification:	Not evaluated

7.2. IARC Carcinogenicity Classification

Not evaluated

7.3. OSHA, ACGIH, and NIOSH Standards and Criteria

OSHA (8-hr TWA):	None established
OSHA STEL:	None established
OSHA Ceiling Limit:	None established
ACGIH (8-hr TWA):	None established
NIOSH RELs:	None established

8. REFERENCES

Kononova SD, Korolev AM, Eremenko LT, Gumanov LL. 1972. The mutagenic effect of some esters of nitric acid on bacteriophage T4B. Sov. Genet. 8:635-640.

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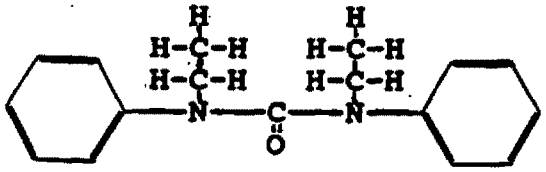
1. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Water, provides information on the health effects and other useful data that can aid in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. The EPA has an ongoing cooperative agreement with the Department of the Army to prepare drinking water Health Advisories (HA) for munitions and other environmental contaminants. Drinking water Toxicological Profiles are short summaries of the pertinent mammalian health effects literature, and are used by the Office of Water to determine if a data base is sufficient to allow the development of HAs. The following data bases were searched for information on ethyl centralite: TOXLINE, TOXLINE65, TOXLIT, TOXLIT65, CANCERLINE, DART, EMICBACK, CHEMFATE, ENVIROLINE, DTIC and RTECS. Secondary sources were also used.

This Drinking Water Toxicological Profile summarizes information on ethyl centralite which is used as a component of military and commercial explosive mixtures (smokeless powder) and proposed for use as an age retardant in vulcanized rubber products (Sax and Lewis, 1989; Budavari et al., 1989). It is an explosive hazard and burns releasing toxic fumes of NO_x (Sax and Lewis, 1989). The structure of ethyl centralite is shown below.



Ethyl centralite

2. SELECTED GENERAL INFORMATION

General information, physical and chemical data are presented in Table 10.

TABLE 10. PHYSICOCHEMICAL DATA

Common name	ethyl centralite	
Synonyms	*bis*(*N*-ethyl-*N*-phenyl)urea; *N,N*-diethylcarbanilide; *N,N'*-diethyl-*N,N'*diphenylurea; sym-diethyldiphenylurea; USAF EK-1047	Sax and Lewis, 1989 Budavari et al., 1989
CAS registry no.	85-98-3	
RTECS no.	FE0350000	RTECS, 1987
Chemical formula	$C_{17}H_{20}N_2O$	Sax and Lewis, 1989
Molecular weight	268.39	Sax and Lewis, 1989
Physical state	colorless crystals	Budavari et al., 1989
Vapor pressure	ND[a]	
Specific gravity	1.12 at 20°C	Hawley, 1977
Melting/Boiling/ Flash point (°C)	73/326/302	Sax and Lewis, 1989
Solubility in water	insoluble	Budavari et al., 1989
Log K_{ow}	ND	
Bioconcentration factor (BCF)	ND	
Conversion factors in air	1 ppm = 10.95 mg/m^3 1 mg/m^3 = 0.09 ppm	Calculated[b]
Odor/taste threshold	ND/0.5 mg/L water	Korolev et al., 1976
Henrys' law constant	ND	

[a]ND: no data

[b]Formula: $\text{ppm by volume} = \text{mg/m}^3 \times \frac{24.45}{\text{mol. wt. in grams}}$

3. SOURCES OF EXPOSURE

3.1. Occurrence in Water

The occurrence of ethyl centralite in water is limited by its lack of solubility (Sax and Lewis 1989; Weeks and McCreesh, 1977; Budavari et al., 1989).

3.2. Human Exposure

Human exposure is primarily to workers in the munitions industry who handle this material. The most likely routes of exposure are dermal and possibly inhalation. The low volatility of ethyl centralite appears to preclude inhalation exposure at room temperature, however the volatility increases with increased temperature. Weeks and McCreesh (1977) reported ethyl centralite air concentrations of 0 mg/L, 0.4 mg/L, and 198 mg/L at temperatures of 23°C, 50°C, and 100°C, respectively in a controlled inhalation chamber with an air flow of 1 L/min. The air flow was directed through a container with crystalline ethyl centralite at the given temperatures then into the inhalation chamber.

4. ENVIRONMENTAL FATE

Korolev et al. (1976) reported a color change in an aqueous solution of ethyl centralite after 3 to 5 days, which may indicate an oxidation process. No other more specific information was available.

5. TOXICOKINETICS

5.1. Absorption

No quantitative absorption data was located, however, it can be inferred from effects on the nervous system, liver and blood (see section 6) that ethyl centralite is absorbed from the gastrointestinal system and by inhalation (Weeks and McCreesh, 1977;Korolev et al., 1976).

5.2. Distribution

No quantitative distribution data was located, however, it can be inferred from effects on the nervous system, liver and blood that ethyl centralite is generally distributed by the blood throughout the body (Weeks and McCreesh, 1977;Korolev et al., 1976).

5.3. Metabolism

No information was located in the available literature.

5.4. Excretion

No information was located in the available literature.

6. HEALTH EFFECTS

6.1. Noncancer Effects

6.1.1. Oral Exposure

6.1.1.1. Human. No information was located in the available literature.

6.1.1.2. Animal. Acute exposure of male rats to 1810 to 3160 mg/kg ethyl centralite in corn oil resulted in tremors, lethargy, tonic convulsions and death within 12 hours (LD_{50} = 2560 mg/kg). Survivors were killed and autopsied after 14 days. No gross compound related tissue changes were observed in any animals, although the treated animals had decreased weight gain during the 14 day experiment (Weeks and McCreesh, 1977). Schafer and Bowles (1985) fed grain contaminated with ethyl centralite to deer mice in an experiment designed to test the ability of the chemical to repel the mice from the grain. The average amount of chemical ingested by each animal over the test period of 3 days without killing more than 50% of the test animals was calculated to be 1125 mg/kg/day. Chronic exposure (duration was not specified) to 5 mg/kg/day resulted in altered conditioned reflexes, excretory liver function, peroxidase activity, and levels of blood sulfhydryl groups and ceruloplasmin (Korolev et al., 1976). The specific liver function tested was not described.

6.1.2. Other Exposure Routes

6.1.2.1. Human. No information was located in the available literature.

6.1.2.2. Animal. Ethyl centralite is reported to be an eye irritant, and acetone solutions of the chemical are mildly irritating to the skin of rabbits. Repeated intradermal injections of ethyl centralite did not result in compound sensitization. Acute (80 min.) inhalation exposure to air concentrations up to 198 mg/L resulted in no toxic signs during exposure and for up to 14 days after exposure (Weeks and McCreesh, 1977).

6.2. Carcinogenicity

6.2.1. Oral Exposure

6.2.2.1. Human. No information on human carcinogenicity of ethyl centralite was available.

6.2.2.2. Animal. No information on animal carcinogenicity of ethyl centralite was available.

6.2.2. Other Exposure Routes

6.2.2.1. Human. No information was located in the available literature.

6.2.2.2. Animal. No information was located in the available literature.

6.3. Genotoxicity

Ethyl centralite was negative in mutagenicity tests with *Saccharomyces cerevisiae* and five strains of *Salmonella typhimurium* with or without a rat liver activation system (Weeks and McCreesh, 1977; Zeiger et al., 1988).

7. EXISTING STANDARDS, CRITERIA, GUIDANCE

7.1. EPA RfDs, RfCs, CRAVE Classifications

RfD:	None established
RfC:	None established
Oral slope factor:	None established
Oral unit risk:	None established
Inhalation slope factor:	None established
Inhalation unit risk:	None established
EPA CRAVE Cancer Classification:	Not classified

7.2. IARC Carcinogenicity Classification

Not evaluated

7.3 ACGIH, OSHA, and NIOSH Standards and Criteria

OSHA (8-hr TWA):	None established
OSHA STEL:	None established
OSHA Ceiling Limit:	None established
ACGIH (8-hr TWA):	None established
NIOSH RELs:	None established

A maximal permissible water level of ethyl centralite in Russia was set at 0.5 mg/L, which was also the taste threshold in a report by Korolev et al. (1976).

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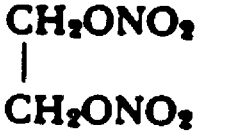
1. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Water, provides information on the health effects and other useful data that can aid in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. The EPA has an ongoing cooperative agreement with the Department of the Army to prepare drinking water Health Advisories (HA) for munitions and other environmental contaminants. Drinking Water Toxicological Profiles are short summaries of the pertinent mammalian health effects literature, and are used by the Office of Water to determine if a data base is sufficient to allow the development of HAs. The following data bases were searched for information on ethylene glycol dinitrate: CANCERLINE, CHEMFATE, DART, DTIC, EMICBACK, ENVIROLINE, RTECS, TOXLINE, TOXLINE65, TOXLIT, AND TOXLIT65. Secondary sources were also used.

This Drinking Water Toxicological Profile summarizes information on ethylene glycol dinitrate, an explosive and a freezing point depressant for nitroglycerin. It is produced by nitrating a mixture of glycerin and ethylene glycol in the presence of sulfuric acid. In combination with nitroglycerin it is used to make low-freezing dynamites and other explosives. The usual mixtures in dynamite are 60 or 80% ethylene glycol dinitrate and 40 or 20% nitroglycerin. Ethylene glycol dinitrate is comparable to nitroglycerin in explosive energy, but its relatively high volatility precludes its use in military propellants (ACGIH, 1986; Parmeggiani, 1983; Lindner, 1980). It is a contaminant of the naval torpedo propellants Otto Fuel II and NOSET-A (Kuriansik and Andersen, 1976). The structural formula for ethylene glycol dinitrate is shown below.



Ethylene glycol dinitrate

2. SELECTED GENERAL INFORMATION

Physicochemical data for ethylene glycol dinitrate are presented in Table 11.

TABLE 11. PHYSICOCHEMICAL DATA

Common Name	ethylene glycol dinitrate	
Synonyms	EGDN; dinitroglycol; ethylene nitrate; ethylene dinitrate; ethanediol dinitrate; 1,2-ethanediol dinitrate; nitroglycol	RTECS, 1992; Rowe and Wolf, 1982
CAS Registry No.	628-96-6	
RTECS No.	KW5600000	RTECS, 1992
Chemical formula	$C_2H_4N_2O_6$	Rowe and Wolf, 1982
Molecular weight	152.06	Lide, 1991-1992
Physical state	liquid	Parmeggiani, 1983
Vapor pressure	0.038 mm Hg at 20°C	Parmeggiani, 1983
Specific gravity	1.418 at 20°C/4°C[a]	Lide, 1991-1992
Melting/Boiling/Flash point	-22.3°C/197±3°C/215°C	Parmeggiani, 1983
Solubility in water	insoluble	Parmeggiani, 1989
Log K_{ow}	1.16	Hansch, 1987
Bioconcentration factor (BCF)	ND[b]	
Conversion factors in air	1 ppm = 6.22 mg/m^3 1 mg/m^3 = 0.161 ppm	Calculated[c]
Odor threshold	ND	
Henrys' Law constant	ND	

[a]Density of liquid at 20°C relative to the density of water at 4°C
[b]ND: no data

[c]Formula: $\text{ppm by volume} = \text{mg/m}^3 \times \frac{24.45}{\text{mol. wt. in grams}}$

3. SOURCES OF EXPOSURE

3.1. Occurrence in Water

Pollutants from glycol nitrate explosives are primarily produced during manufacture of explosives and the acids used in nitration. They are also produced during incorporation into munitions and in clean-up and disposal operations (Lindner, 1980). Ethylene glycol dinitrate has been detected in wastewater effluents from a nitration plant (Michelson and Ostern, 1979).

3.2. Human Exposure

Human exposures would most likely occur in occupational settings, i.e., in the production of ethylene glycol dinitrate, dynamite, or related explosives and their uses. Inhalation of vapor and dermal contact are the most likely routes of exposure, usually involving mixtures of ethylene glycol dinitrate with nitroglycerin.

4. ENVIRONMENTAL FATE

No information was found in the available literature.

5. TOXICOKINETICS

5.1. Absorption

Ethylene glycol dinitrate is readily absorbed through intact skin in toxic amounts. It is also absorbed through the lungs and gastrointestinal tract (Stokinger, 1982). Percutaneous absorption is of particular concern in dynamite workers handling ethylene glycol dinitrate and nitroglycerin. According to a review by Rowe and Wolf (1982), dermal contact with ethylene glycol dinitrate resulted in practically complete absorption in 8 days, with up to one-third being absorbed within the first 4-12 hours. The risk of toxic effects from dermal absorption was considered low if less than 0.25 mg was absorbed in 8 hr, moderate if 0.25-0.75 mg was absorbed, and high if more than 0.75 mg was absorbed.

5.2. Distribution

When humans or animals are exposed to ethylene glycol dinitrate, the chemical appears in the blood immediately, with concentrations peaking in about 30 min and falling to zero 8 hours later (Rowe and Wolf, 1982). Measured blood levels ranged from 0 to 145 ng/mL in dynamite workers at the end of a work day, with the higher levels noted in those workers who had frequent skin contact (Fukuchi, 1981). There were no data concerning the presence of ethylene glycol in other organs or tissues.

5.3. Metabolism

Ethylene glycol dinitrate is rapidly metabolized in blood, yielding mainly inorganic nitrate, inorganic nitrite, and ethylene glycol mononitrate. The mononitrate, in turn, is metabolized to inorganic nitrate and inorganic nitrite. Ethylene glycol dinitrate disappears within 4 hours from the blood; inorganic nitrite and nitrate levels in the blood peaked in 1-2 and 3-5 hours, respectively, returning to normal levels within 12 hours. The nitrite is oxidized to the nitrate and excreted in the urine (Rowe and Wolf, 1982).

5.4. Excretion

The compound was detected in urine of dynamite workers, but not in exhaled air of workers with high blood levels of ethylene glycol dinitrate (Hagstredt, 1984). Urine of rats collected 24 hours after a series of subcutaneous injections at a dose of 65 mg/kg/day contained <0.1% ethylene glycol dinitrate, 0.6% ethylene glycol mononitrate, 58% inorganic nitrate, and <0.1% inorganic nitrite (Clark and Litchfield, 1969). Only trace amounts of ethylene glycol dinitrate were detected in feces following oral administration (Rowe and Wolf, 1982).

6. HEALTH EFFECTS

6.1. Noncancer Effects

6.1.1. Oral Exposure

6.1.1.1. Human. No information was found in the available literature.

6.1.1.2. Animal. The LD_{50} for rats is 616 mg/kg, with vasodilation as the primary acute effect (Rowe and Wolf, 1982). No other information regarding the oral toxicity of ethylene glycol dinitrate was available.

6.1.2. Other Exposure Routes

6.1.2.1. Human. Most of the toxicity data of ethylene glycol dinitrate are for mixtures with nitroglycerin resulting from inhalation of vapor and/or dermal contact. Since ethylene glycol dinitrate is considerably more volatile than nitroglycerin, inhalation effects in operations where both are handled are due mainly to ethylene glycol dinitrate (ACGIH, 1986).

Major clinical effects resulting from acute exposure are lowered blood pressure due to vasodilation, increased pulse rate, severe headache, dizziness, nausea and vomiting, hypotension, tachycardia, peripheral paresthesia, and chest pain (Rowe and Wolf, 1982). Following long-term exposure (6-10 years), anginal-type attacks, and in some cases deaths, occurred in workers, usually 30 to 64 hours after cessation of exposure. Exposed workers became tolerant during the work week, but lost this tolerance over the weekend or when away from exposure (Parmeggiani, 1983; Rowe and Wolff, 1982). Epidemiologic studies indicate that exposure to ethylene glycol dinitrate and nitroglycerin increases the risk of death from ischemic heart disease (Craig et al., 1985; Fine, 1983). Headaches and changes in blood pressure may occur at concentrations below 0.2 ppm and EEG changes, chest pain, palpitation, and nausea at concentrations ranging from 0.25 to 2.3 ppm (ACGIH, 1986). In addition to systemic effects, ethylene glycol dinitrate can cause contact dermatitis (Kanerva et al., 1991). Although methemoglobin formation was demonstrated in laboratory animals exposed to ethylene glycol dinitrate, there are no indications that the chemical produces methemoglobinemia in humans (Rowe and Wolf, 1982).

6.1.2.2. Animal. Subcutaneous administration of 400 and 100 mg/kg of ethylene glycol dinitrate was fatal to rabbits and cats, respectively. A subcutaneous dose of 60 mg/kg produced methemoglobinemia and Heinz bodies in blood of cats. In rabbits, a dose of 12.5 mg/kg resulted in hypotension, but no methemoglobin formation (Stokinger, 1982). Intramuscular injection of 5 mg/kg, 11 times/week for 15 weeks produced an increase of catecholamines in myocardial tissue of rats (Rowe and Wolf, 1982).

Rats and guinea pigs exposed to 80 ppm ethylene glycol dinitrate for 6 months produced drowsiness, Heinz body formation in red blood cells, and fatty changes in the liver, heart, muscle, and kidney, with pigment deposits similar to those seen in anemia (Rowe and Wolf, 1982).

6.2. Carcinogenicity

6.2.1. Oral Exposure

6.2.1.1. Human. No information was found in the available literature.

6.2.1.2. Animal. No information was found in the available literature.

6.2.2. Other Exposure Routes

6.2.2.1. Human. No information was found in the available literature.

6.2.2.2. Animal: No information was found in the available literature.

6.3. Genotoxicity

Ethylene glycol dinitrate was mutagenic in the extracellular bacteriophage T4B of *Escherichia coli* (Kononova et al., 1972).

7. EXISTING STANDARDS, CRITERIA, GUIDANCE

7.1. EPA RfDs, RfCs, CRAVE Classifications

RfD:	None established
RfC:	None established
Oral slope factor:	None established
Drinking Water Unit Risk:	None established
Inhalation Slope Factor:	None established
Inhalation Unit Risk:	None established
EPA CRAVE Cancer Classification:	Not evaluated

7.2. IARC Carcinogenicity Classification

Not evaluated

7.3. OSHA, ACGIH, and NIOSH Standards and Criteria

OSHA (8-hr TWA):	None established
OSHA STEL:	0.1 mg/m^3, with skin notation (OSHA, 1989)
OSHA Ceiling Limit:	None established
ACGIH (8-hr TWA):	0.05 ppm (0.31 mg/m^3), with skin notation (ACGIH, 1991-1992)
NIOSH RELs:	
NIOSH (10-hr TWA):	0.1 mg/m^3, with skin notation (NIOSH, 1990)
NIOSH IDLH:	500 mg/m^3 (NIOSH, 1990)

According to an agreement between OSHA and the Institute of Makers of Explosives (IME), the STEL of 0.1 mg/m^3 applies only when ethylene glycol dinitrate is used in the manufacture of civilian explosives. A temporary stay of this exposure limit was granted to manufacturers of products for the military (Industrial and Health Hazards Update, 1992).

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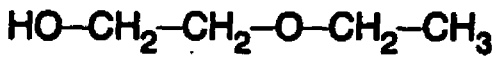
1. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Water, provides information on the health effects and other useful data that can aid in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. The EPA has an ongoing cooperative agreement with the Department of the Army to prepare drinking water Health Advisories (HA) for munitions and other environmental contaminants. Drinking water Toxicological Profiles are short summaries of the pertinent mammalian health effects literature, and are used by the Office of Water to determine if a data base is sufficient to allow the development of HAs. The following databases were searched for information on ethylene glycol monoethyl ether (EGMEE): CANCERLINE, CHEMFATE, DART, DTIC, EMICBACK, ENVIROLINE, RTECS, TOXLINE, TOXLINE65, TOXLIT, and TOXLIT65. Secondary sources were also used.

This Drinking Water Toxicological Profile summarizes information on (EGMEE), a glycol ether of ethyl alcohol. The chemical is a solvent for nitrocellulose, natural and synthetic resins, and lacquers (Sax and Lewis, 1987). It is used in varnish removers, cleaning solutions, and dye baths; for finishing leather with water pigments and dye solutions; and to increase the stability of emulsions (Budavari et al., 1989). It is also used as an anti-icing additive for aviation fuels (Sax and Lewis, 1987). Specific military uses of the chemical were not identified in the available literature. The structure of EGMEE is shown below:



Ethylene glycol monoethyl ether

2. SELECTED GENERAL INFORMATION

The physicochemical properties of EGMEE are listed in Table 12.

TABLE 12. PHYSICOCHEMICAL DATA

Common name	ethyleneglycol monoethyl ether	Parrish, 1978
Synonyms	2-ethoxyethanol; cellosolve; ethyl cellosolve; Dowanol; Ektasolve	RTECS, 1992; Lide, 1991-1992
CAS Registry No.	110-80-5	RTECS, 1992
RTECS No.	KK8050000	RTECS, 1987
Chemical formula	$C_4H_{10}O_2$	Parrish, 1978
Molecular weight	90.12	Lide, 1991-1992
Physical state	Colorless liquid	Budavari et al., 1989
Vapor pressure	5.12 mm Hg @ 25°C	Daubert and Danner, 1989
Specific gravity	0.9297 at 20°C/4°C[a]	Lide, 1991-1992
Melting/boiling/flash point	-70°C/135°C/44°C (closed cup), 49°C (open cup)	Budavari et al., 1989
Solubility in water	Miscible	Dow Chemical Co., 1981
Log K_{OW}	-0.10	Hansch and Leo, 1985
Bioconcentration factor (BCF)	2.1 (calculated)	SRC, 1988
Conversion Factors in Air	1 ppm = 3.686 mg/m^3 1 mg/m^3 = 0.2713 ppm	Calculated[c]
Odor threshold	ND[b]; practically odorless	Budavari et al., 1989
Henry's Law constant	1.23 × 10^{-7} atm•m^3/mole	SRC, 1988

[a]Density of liquid at 20°C relative to the density of water at 4°C
[b]ND: no data

[c]Formula: $\text{ppm by volume} = \text{mg/m}^3 \times \frac{24.45}{\text{mol. wt. in grams}}$

3. SOURCES OF EXPOSURE

3.1. Occurrence in Water

The main sources of EGMEE released to the aquatic environment are the effluents from chemical facilities producing and using the chemical (U.S. EPA, 1985). Shackelford and Keith (1976) reported the detection of unspecified concentrations of EGMEE in the effluents from a chemical plant in Brandenburg, KY, in 1974 and from an unidentified chemical facility in 1975. The STORET data base reports that on 2/8/74 EGMEE was present, at the concentration of 0.1 µg/L, in an effluent from the Olin Corporation facility in Brandenburg, KY (U.S. EPA, 1985). EGMEE (1200 ppb) was detected on 4/20/80 in the air of a Japanese city, the site of a leather industry (Yasuhara et al., 1981).

3.2. Human Exposure

The general population may be exposed to EGMEE in the atmosphere in emissions released from production and use plants (U.S. EPA, 1981) and from consumer products, such as paints and varnishes (U.S. EPA, 1985). Occupational exposure may occur in facilities producing and using EGMEE. An exposure assessment of industries using ethylene glycol ethers concluded that most breathing zone samples contained ether concentrations well below the relevant OSHA or ACGIH standards; whereas a high potential for dermal exposure exists at some facilities (Piacitelli et al., 1990). (The industries surveyed included an aerospace equipment manufacturer, a glycol ethers formulator, an automotive assembly factory, an air craft maintenance hanger, a jet fuel terminal, a coatings formulator, a paperboard manufacturer and an electronics parts manufacturer). In 1983, NIOSH's National Occupational Exposure Survey (NOES) reported that 264,436 employees in 153 industries were exposed to EGMEE in the workplace (RTECS, 1992).

4. ENVIRONMENTAL FATE

In water, biodegradation appears to be the main fate process for EGMEE. The Dow Chemical Company (1981) reported a 20-day BODT (theoretical biochemical oxygen demand) of 81% for the chemical; a 20-day BODT of >50% indicates that the material will largely be removed in a biological wastewater treatment plant (U.S. EPA, 1985). Experiments of other investigators have demonstrated that, in natural waters, biodegradation rates for the chemical may vary according to the microorganism tested (e.g., rapid degradation for *Pseudomonas 324,* but no degradation for *Flavobacterium brevis* [Ellis et al., 1956]) and that the process is more rapid in acclimated sludge and in freshwater than in unacclimated sludge and saltwater (Bridie et al., 1979; Price et al., 1974). In addition, EGMEE has a vapor pressure of 5.12 mm Hg at 25°C, suggesting that EGMEE may undergo volatilization in the aquatic environment. Hydrolysis, oxidation, bioaccumulation, bioconcentration, and adsorption are not expected to be important processes for EGMEE in water (U.S. EPA, 1985).

In the soil, moderate leaching of EGMEE is suggested by a soil sorption coefficient (K_{OC}) of 113 predicted by Sabljic (1984); however, a lower K_{OC} value of 21 was derived by SRC (1988). Standard evaporation tests and the vapor pressure of 5.31 mm Hg suggest that EGMEE will evaporate from both dry and moist soils (U.S. EPA, 1985; CHEMFATE, 1992). One study demonstrated rapid biodegradation of EGMEE using microorganisms isolated from the soil (Fincher and Payne, 1962).

EGMEE released to the atmosphere would be susceptible to photolysis and significant degradation by hydroxyl radicals. The estimated photolytic half-life for EGMEE is 9.8 hours (Joshi et al., 1982); the estimated half-life for its reaction with hydroxyl radicals is one day (Atkinson, 1989).

5. TOXICOKINETICS

5.1. Absorption

The absorption of EGMEE administered orally, via inhalation, and to the skin is implied by the systemic toxicity of the chemical in experimental animals and the recovery of metabolites of EGMEE in the urine 24 hours after oral and inhalation exposure (see Sections 5.4 and 6.1). In addition, Dugard et al. (1984) reported that, *in vitro*, EGMEE was absorbed by isolated human abdominal epidermis at the rate of 0.796 mg/cm^2/hour.

5.2. Distribution

Levels of ^{14}C-labeled EGMEE fed to Sprague-Dawley rats peaked (0.31% of the dose) in the testes at 2 hours, then rapidly declined to 0.06% of the dose within 6 hours (Cheever et al., 1984). Ethoxyacetic acid was identified as the radioactive metabolite in the testes. Data for the distribution of EGMEE to other organs were not found in the available literature.

5.3. Metabolism

The proposed pathway of EGMEE oxidation is via an acetaldehyde moiety to the corresponding acid and subsequent partial conjugation with glycine; the acid may be the ultimate toxic species (U.S. EPA, 1985; Cheever et al., 1984). Urinary metabolites of EGMEE (excreted by male rats dosed orally with labeled EGMEE) include ethoxyacetic acid and N-ethoxyacetyl glycine which together accounted for ~75% of the administered dose and for ~95% of the total radioactivity recovered in the urine (Cheever at al., 1984. ECETOC (1985) proposed that ten minor unidentified urinary metabolites account for 3-5% of the dose and CO_2 accounts for up to 12% of the dose. In a recent study, male F344 rats were allowed access to EGMEE (2-ethoxy[U-14C]ethanol, 189-2590 ppm) in their drinking water for 24 hours (Medinsky et al., 1990). Over 72 hours, <5% of the dose (measured as radioactivity) was exhaled as unchanged EGMEE; an unspecified amount was exhaled as CO_2; 25-40% of the dose was eliminated in the urine as ethoxyacetic acid and 20% as CO_2; and 18% of the dose was excreted in the urine as ethylene glycol, a previously unreported metabolite of EGMEE. The formation of ethylene glycol suggests that dealkylation of the ether occurs prior to oxidation to the alkoxyacetic acid and that an alternate metabolic pathway exists that does not involve the formation of the toxic acid metabolite.

5.4. Excretion

In Sprague-Dawley rats orally dosed with ^{14}C-labeled EGMEE (labeled either at the ethoxy-1 or the ethanol-1,2 position), ~75% of the radioactivity was excreted in the urine within 24 hours and ~80% was excreted within 96 hours (Cheever et al., 1984). Depending on the position of the label, respiratory $^{14}CO_2$ accounted for 4.6% (ethanol label) or 11.7% (ethoxy label) of the label. The recovery of label in volatile organics, feces and carcass was minimal compared with urinary excretion. The biological half-life of the chemical, dependant upon the position of the label, was 12.5 hours (ethanol derivative) or 9.9 hours (ethoxy derivative).

6. HEALTH EFFECTS

6.1. Noncancer Effects

6.1.1. Oral Exposure

6.1.1.1. Human. One abstract mentions that there have been reports of poisoning to humans following ingestion of EGMEE (IPCS, 1990). Details were not given.

6.1.1.2. Animal. Table 13 summarizes the acute toxicity of EGMEE. Oral LD_{50} values range from 1.5 g/kg for the rabbit (Stenger et al., 1971) to 5.5 g/kg for the rat (Carpenter et al., 1956), indicating low oral acute toxicity for EGMEE (O'Bryan and Ross, 1988).

Table 14 summarizes the subchronic, chronic, reproductive, and developmental effects of orally administered EGMEE. Generally, the subchronic or chronic toxicity of the chemical is low by the oral route. The adverse effects of EGMEE on the testes and developing spermatozoa are well documented; oral studies in animals also demonstrate embryo- and fetotoxicity, hematotoxicity, and effects on the liver, kidney, and spleen, mostly at doses in excess of 1 g/kg/day (Table 14).

6.1.2. Other Exposure Routes

6.1.2.1. Human. On quantitative data were found in the available literature for EGMEE. However, an abstract mentions that repeated exposure of workers to EGMEE and 2-methoxyethanol and/or their acetates has resulted in anemia, leukopenia, general weakness, ataxia and immunological effects; and that epidemiological studies have shown an increased incidence of altered sperm counts (IPCS, 1990).

6.1.2.2.Animal. Table 13 summarizes the acute toxicity of EGMEE to animals. Inhalation LC_{50} values range from 1357 ppm (5.02 g/m^3) for mice, rabbits, and cats to >6000 ppm (>22.2 g/m^3) for guinea pigs; a dermal LD_{50} of 3.56 mL/kg was reported for rabbits (Browning, 1965). These values indicate low acute toxicity for EGMEE by inhalation and skin contact.

EGMEE administered via inhalation and skin application can cause significant embryolethality and teratogenicity in rats and rabbits at doses that are marginally toxic to the dams (see Table 15). Two inhalation studies identified NOEL values for the developmental effects of EGMEE - 50 ppm in the rabbit and 10 ppm in the rat (Tinston et al., 1983a,b).

Chronic inhalation studies were not found in the available literature. Subchronic exposure of rabbits to 400 ppm of EGMEE for 13 weeks resulted in testicular and hematological effects; no adverse effects were noted at 100 ppm (Barbee et al., 1984). Rats exposed to the same concentrations had no biologically significant effects (Barbee et al., 1984).

6.2. Carcinogenicity

6.2.1. Oral Exposure

6.2.1.1. Human. No information was found in the available literature.

6.2.1.2. Animal. Melnick (1984) conducted a 2-year study in Fischer 344/N rats and B6C3F$_1$ mice. Treatment of both species was by gavage; doses were 0.5, 1.0, or 5.0 g/kg EGMEE/day, 5 days/week. The 2.0 g/kg dose caused excessive mortality and those groups were discontinued by the 18th week. There was no increase in tumor incidence in any of the other groups. Morris et al. (1942) observed no tumors in rats administered 1.45% EGMEE (725 mg/kg/day) in the diet for 2 years.

TABLE 13. ACUTE TOXICITY OF EGMEE

Route	Species	Dose (g/kg)	Response	Reference
Oral	rats	3.22	LD_{50}	Laug et al., 1939
Oral	rats (male)	5.0	LD_{50}	Carpenter et al., 1956
Oral	rats (female)	5.4	LD_{50}	Carpenter et al., 1956
Oral	rats (female)	5.5	LD_{50}	Carpenter et al., 1956
Oral	rats (male)	3.0	LD_{50}	Smyth et al., 1941
Oral	rats	2.3	LD_{50}	Cheever et al., 1984
Oral	rats	4.5	LD_{50}	Stenger et al., 1971
Oral	rats	1.89	LD_{50}	Patty, 1963
Oral	mice	4.8	LD_{50}	Stenger et al., 1971
Oral	mice	4.0	LD_{50}	Laug et al., 1939
Oral	mice	4.84	LD_{50}	Laug et al., 1939
Oral	mice	3.5	LD_{50}	Saparmamedov, 1974
Oral	mice	4.8	LD_{50}	Stenger et al., 1971
Oral	guinea pigs	2.6	LD_{50}	Laug et al., 1939
Oral	guinea pigs	1.4 (10% solution)	LD_{50}	Carpenter et al., 1956
Inhalation	rabbits	1357 ppm, 8 hours/day for 12 days	LC_{50}	Browning, 1965
Inhalation	guinea pigs	0.3% for 24 hours	5/6 dead 24 hours after exposure	Waite et al., 1930
Inhalation	guinea pigs	>6000 ppm for 1 hour	LC_{50}	Browning, 1965
Inhalation	cats	1357 ppm, 8 hours/day for 4-5 days	LC_{50}	Browning, 1965
Dermal	rabbits	3.56 mL/kg (undiluted, contact with clipped skin for 24 hours, 14 day observation)	LD_{50}	Carpenter et al., 1956
Ocular	rabbits	90 mg	moderate injury	Carpenter et al., 1956
Ocular	rabbits	1 drop (undiluted)	hyperemia and edema of conjunctiva	von Oettingen and Jirouch, 1931

TABLE 14. PHYSIOLOGICAL EFFECTS OF ORALLY ADMINISTERED EGGMEE

Species/strain/sex	Exposure	Response	Reference
CD-1 mice, females	0, 1000, 1800, 2600, 3400, or 4200 mg/kg body wt/day by gavage on gestation days 8 through 14	signs of maternal toxicity ≥1,800 mg/kg; dose-related increased incidences of embryo resorption ($p \leq 0.05$ at ≥1800 mg/kg/day; 100% at 4200 mg/kg/day); reduced fetal body weights ($p \leq 0.05$ at ≥1000 mg/kg/day); increased incidences of fetal malformations ($p \leq 0.05$ at ≥1800 mg/kg/day)	Wier et al., 1987
JCL-ICR mice, males	2.5% in drinking water for 18 days (~4250 mg/kg/day)	depressed testicular weight; leukopenia	Nagano et al., 1979
JCL-ICR mice, males	500, 1000, 2000, or 4000 mg/kg by gavage, 5 days/week for 5 weeks	dose-related decrease in testes weights; degeneration of the seminiferous tubules, reduction in number of spermatocytes, spermatids, spermatozoa at ≥1000 mg/kg; almost complete absence of spermatids and spermatozoa at 2000 mg/kg; dose-related leukopenia	Nagano et al., 1979
B6C3F$_1$ mice, males and females	0, 2500, 5000, 10,000, 20,000, or 40,000 ppm[a] in drinking water for 13 weeks	decreased body weights and changes in relative and absolute organ weights at 2 highest doses; aspermia and atrophy of seminiferous tubules at high dose; ovarian interstitial atrophy at two highest doses; and, in females only, fatty degeneration of the adrenal zona reticularis, splenic lymphoid hyperplasia, and hematopoietic cell proliferation at 3 highest doses	NTP, draft
CD-1 mice, males and females	0.5% (~850 mg/kg/day), 1.0% (~1500 mg/kg/day), 2.0% (~2600 mg/kg/day) in drinking water for 7 days pre-mating and 14 weeks thereafter for continuous breeding	no litters at 2%; reduced fertility in crossover matings at 1 and 2%; reduction in numbers of litters/pair, live pups/litter, pups born alive and live pup weight at 1%; decreased testes weight and sperm motility at 2%; dose-related increase in number of abnormal sperm at 1% and 2%	Lamb et al., 1984
B6C3F$_1$ mice, males and females	500, 1000, or 2000 mg/kg/day, 5 days/week for 103 weeks, gavage	excessive mortality and stomach ulcers at 2.0 g/kg (this group discontinued at 17-18 weeks); testicular degeneration (1.0 and 2.0 g/kg)	Melnick, 1984
Sprague-Dawley rats, males	250, 500 or 1000 mg/kg/day for 11 days	reductions in relative testicular weights and significant degeneration of primary spermatocytes at two highest doses	Creasy and Foster, 1984
Long-Evans rats, male	0, 936, 1972, or 2808 mg/kg/day for 5 days (week 1), oral intubation	depressed sperm counts in mid- and high-dose groups (week 4) and in low- dose group (week 7); azoospermia in mid- and high-dose groups (week 7); recovery by week 16	Zenick et al., 1984

TABLE 14. (Continued)

Species/strain/sex	Exposure	Response	Reference
Rats, males	0 or 936 mg/kg, 5 days/week for 6 weeks, oral intubation	decreased body weight gain, decreased weights of testes, epididymis and cauda epididymus; decreased sperm counts, increased numbers of abnormal sperm; increased brain and spleen weights; depressed hematocrit and hemoglobin levels	Zenick et al., 1984
Rat (sex not given)	210 or 740 mg/kg/day in drinking water for 90 days	microscopic lesions and altered weights of liver and kidney, reduced body weight gain and food consumption at 740 mg/kg/day	Smyth et al., 1951
Rat/F344, males and females	0, 1250, 2500, 5000, 10,000, or 20,000 ppm[b] in drinking water for 13 weeks	mortality at 20,000 ppm (group not evaluated further); decreased body weights ($p < 0.01$) and organ weights at 10,000 ppm); macrocytic hemolytic anemia at 10,000 ppm; decreased sperm values and alterations in estrous cycle at 10,000 ppm	NTP, draft
F344 rats, males and females	0.5, 1.0, or 2.0 g/kg, 5 days/week for 103 weeks, gavage	excessive mortality at 1.0 g/kg (males) and 2.0 g/kg (this group discontinued at 17-18 weeks); testicular degeneration (2.0 g/kg); enlarged adrenals in males (0.5 and 1.0 g/kg)	Melnick, 1984
Albino rats, males	1.45% in diet ad libitum for 2 years (725 mg/kg/day calculated by U.S. EPA, 1985)	testicular enlargement, edema and tubular atrophy in two-thirds of the animals	Morris et al. 1942
Beagle dogs (sex not given)	0, 50, 100, or 200 µL/kg/day in gelatin capsules for 13 weeks[c]	22% reduction in hemoglobin, 24% decrease in hematocrit value	Stenger et al., 1971

[a]Based on EPA's reference values for the mouse (body weight, 0.03 kg; water consumption, 0.0057 L/day) (U.S. EPA, 1985), these concentrations would be equal to doses of 475, 950, 1900, 3800, and 7600 mg/kg/day (calculated by ORNL).
[b]Based on EPA's reference values for the rat (body weight, 0.35 kg; water consumption, 0.049 L/day) (U.S. EPA, 1985), these concentrations would be equal to doses of 175, 350, 700, 1400 and 2800 mg/kg/day (calculated by ORNL).
[c]Based on the specific gravity of EGMEE (0.9297), the doses would equal 46.485, 92.97, and 185.94 mg/kg/day (calculated by ORNL).

TABLE 15. PHYSIOLOGICAL EFFECTS OF EGMEE ADMINISTERED VIA INHALATION AND SKIN APPLICATION

Strain/species	Exposure	Response	Reference
New Zealand rabbits	0, 25, 100, OR 400 ppm in vapor 6 hours/day, 5 days/week for 13 weeks	decreased body weight gain, testicular effects, and hematological effects at 400 ppm; NOAEL, 100 ppm	Barbee et al., 1984
New Zealand rabbits	0, 160 or 617 ppm in vapor on gestation days 1 to 18	maternal and fetal toxicity at both doses. 100% resorptions at 617 ppm; fetal malformations ($p \leq 0.05$) at 160 ppm	Andrew et al., 1981
Dutch rabbits	0, 10, 50, or 175 ppm of vapor, 6 hours/day on gestation days 6 through 18	no observable maternal effects; indications of fetal toxicity at 175 ppm; clear-cut NOAEL for embryo/fetotoxicity and teratogenicity 50 ppm	Tinston et al., 1983a
Sprague-Dawley rats	25, 100, 400 ppm in vapor 6 hours/day, 5 days/week for 13 weeks	no observed adverse effects at 25 and 100 ppm; decreased pituitary to body weight ratio for males and decreased absolute spleen weight for females at 400 ppm. "These effects are not considered to be biologically significant". NOAEL 400 ppm	Barbee et al., 1984
Sprague-Dawley rats	0 100, or 200 ppm in vapor 7 hours/day on gestation days 7-13	no maternal toxicity; extended pregnancy duration at 200 ppm; neurobehavioral and neurochemical effects in fetuses	Nelson et al., 1982a,b
Rats	0, 202, or 767 ppm from mating through gestation day 19	slight maternal toxicity at and 100% resorptions at 767 ppm; retardation of intrauterine growth at 202 ppm; increased cardiovascular defects and skeletal variants	Andrew et al., 1981
Alderley Park (Wistar derived) rats	0, 10, 50, or 250 ppm, 6 hours/day on days 6-15 of gestation	slight maternal toxicity (hematological changes) at 250 ppm; fetotoxicity but no teratogenicity at 250 ppm; some evidence for reduced fetal ossification at 50 ppm. NOAEL 10 ppm.	Tinston et al., 1983b
Sprague-Dawley rats	undiluted, applied to shaved skin 4 x/day (1 or 2 mL/day) on gestation days 7-16 (931-1862 mg/day)	slight maternal toxicity; 100% resorptions at 2 mL/day; 52% resorptions at 1 mL/day; increased incidence of fetal anomalies and skeletal alterations in survivors at 1 mL/day	Hardin et al., 1982
Dogs	840 ppm in vapor 7 hours/day 5 days/week for 13 weeks	anemia; calcium oxalate crystals in urine	Werner et al., 1943b

6.2.2. Other Exposure Routes

6.2.1. Human

No data were found in the available literature.

6.2.2. Animal

No data were found in the available literature.

6.3. Genotoxicity

EGMEE is not considered to pose a significant genetic hazard (U.S. EPA, 1985). Although the chemical induced sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells *in vitro* with and without metabolic activation, it did not induce sex-linked recessive lethal mutations in *Drosophila melanogaster* (ECETOC, 1985). EGMEE was also nonmutagenic, with and without metabolic activation, for reverse mutation in *Salmonella typhymurium* strains TA1538, TA1537, TA1535, TA100, and TA98 and in *Escherichia coli* Sd-4-73 (Kawalek and Andrews, 1980; Ong, 1980; Zeiger et al., 1982; Szybalski, 1958).

7. EXISTING STANDARDS, CRITERIA, GUIDANCE

7.1. EPA RfDs, RfCs, CRAVE Classifications

RfD:	Chronic, 4×10^{-1} mg/kg/day (U.S. EPA, 1992)
	Subchronic, 5×10^{-1} mg/kg/day (U.S. EPA, 1992)
RfC:	Chronic, 2×10^{-1} mg/m^3 (U.S. EPA, 1991)
	Subchronic, 2×10^{0} mg/m^3 (U.S. EPA, 1992)
Oral slope factor:	None established
Drinking Water Unit Risk:	None established
Inhalation Slope Factor:	None established
Inhalation Unit Risk:	None established
EPA CRAVE Cancer Classification:	Not established

7.2. IARC Carcinogenicity Classification

Not established

7.3. OSHA, ACGIH, and NIOSH Standards and Criteria

OSHA (8-hr TWA):	In process of 6B rulemaking (OSHA, 1989)
OSHA STEL:	In process of 6B rulemaking (OSHA, 1989)
OSHA Ceiling Limit:	In process of 6B rulemaking (OSHA, 1989)
OSHA PEL:	8-hour TWA, 200 ppm (740 mg/m^3) (skin notation) (OSHA, 1989)
ACGIH (8-hr TWA):	5 ppm (skin notation) (ACGIH, 1986)
ACGIH Ceiling Limit:	None established
NIOSH RELs:	None established

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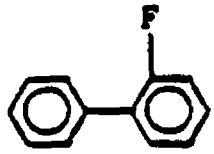
1. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Water, provides information on the health effects and other useful data that can aid in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. The EPA has an ongoing cooperative agreement with the Department of the Army to prepare drinking water Health Advisories (HA) for munitions and other environmental contaminants. Drinking Water Toxicological Profiles are short summaries of the pertinent mammalian health effects literature, and are used by the Office of Water to determine if a data base is sufficient to allow the development of HAs. The following data bases were searched for information on 2-fluorobiphenyl: CANCERLINE, CHEMFATE, DART, DTIC, EMICBACK, ENVIROLINE, RTECS, TOXLINE, TOXLINE65, TOXLIT, AND TOXLIT65. Secondary sources were also used.

This Drinking Water Toxicological Profile summarizes information on 2-fluorobiphenyl, a ring-fluorinated aromatic compound. There was no information regarding the uses of 2-fluorobiphenyl; however, related fluorobiphenyls are used as analgesics and anti-inflammatory agents (Baudakian, 1980). The structural formula for 2-fluorobiphenyl is shown below.



2-Fluorobiphenyl

2. SELECTED GENERAL INFORMATION

Physicochemical data for 2-fluorobiphenyl are presented in Table 16.

TABLE 16. PHYSICOCHEMICAL DATA

Common name	2-fluorobiphenyl	
Synonyms	ND[a]	
CAS Registry No.	321-60-8	
RTECS No.	not assigned	
Chemical formula	$C_{12}H_9F$	Lide, 1991-1992
Molecular weight	172.20	Lide, 1991-1992
Physical state	ND	
Vapor pressure	ND	
Specific gravity	1.2452 at 25°C/4°C[b]	Lide, 1991-1992
Melting/Boiling/Flash Point	73.5°C/248°C/ND	Lide, 1991-1992
Solubility in water	ND	
Log K_{ow}	ND	
Bioconcentration factor (BCF)	ND	
Conversion factors in air	1 ppm = 7.04 mg/m^3 1 mg/m^3 = 0.14 ppm	calculated[c]
Odor threshold	ND	
Henrys' Law constant	ND	

[a]ND: no data
[a]Density of liquid at 25°C relative to the density of water at 4°C

[c]Formula: $\text{ppm by volume} = \text{mg/m}^3 \times \frac{24.45}{\text{mol. wt. in grams}}$

3. SOURCES OF EXPOSURE

3.1. Occurrence in Water

No information was found in the available literature.

3.2 Human Exposure

No information was found in the available literature.

4. ENVIRONMENTAL FATE

No information was found in the available literature.

5. TOXICOKINETICS

5.1. Absorption

No information was found in the available literature.

5.2. Distribution

No information was found in the available literature.

5.3. Metabolism

No information was found in the available literature.

5.4. Excretion

No information was found in the available literature.

6. HEALTH EFFECTS

6.1. Noncancer Effects

6.1.1. Oral Exposure

6.1.1.1. Human. No information was found in the available literature.

6.1.1.2. Animal. No information was found in the available literature.

6.1.2. Other exposure routes

6.1.2.1. Human. No information was found in the available literature.

6.1.2.2. Animal. No information was found in the available literature.

6.2. Carcinogenicity

6.2.1. Oral Exposure

6.2.1.1. Human. No information was found in the available literature.

6.2.1.2. Animal. No information was found in the available literature.

6.2.2. Other Exposure Routes

6.2.2.1. Human. No information was found in the available literature.

6.2.2.2. Animal. No information was found in the available literature.

6.3. Genotoxicity

No information was found in the available literature.

7. EXISTING STANDARDS, CRITERIA, GUIDANCE

7.1. EPA RfDs, RfCs, CRAVE Classifications

RfD:	None established
RfC:	None established
Oral slope factor:	None established
Drinking Water Unit Risk:	None established
Inhalation Slope Factor:	None established
Inhalation Unit Risk:	None established
EPA CRAVE Cancer Classification:	Not evaluated

7.2. IARC Carcinogenicity Classification

Not evaluated

7.3. OSHA, ACGIH, and NIOSH Standards and Criteria

OSHA (8-hr TWA):	None established
OSHA STEL:	None established
OSHA Ceiling Limit:	None established
ACGIH (8-hr TWA):	None established
NIOSH RELs:	None established

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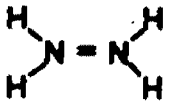
1. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Water, provides information on the health effects and other useful data that can aid in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. The EPA has an ongoing cooperative agreement with the Department of the Army to prepare drinking water Health Advisories (HA) for munitions and other environmental contaminants. Drinking Water Toxicological Profiles are short summaries of the pertinent mammalian health effects literature, and are used by the Office of Water to determine if a data base is sufficient to allow the development of HAs. The following data bases were searched for information on hydrazine: TOXLINE, TOXLINE65, TOXLIT, TOXLIT65, CANCERLINE, DART, EMICBACK, CHEMFATE, ENVIROLINE, DTIC and RTECS. Secondary sources were also used.

This Drinking Water Toxicological Profile summarizes information on hydrazine, a simple diamine and is a powerful reducing agent that is extremely reactive with many other chemicals (Mark et al., 1978). Hydrazine is used as a chemical intermediate in the manufacture of pharmaceuticals, plastic blowing agents, dyes, agricultural chemicals, as a ploymer additive, and as an oxygen scavenger (Mark et al., 1978). Military applications include its use as a missile and rocket propellant, and in chemical power sources (USAF, 1989). The structure of hydrazine is shown below.



Hydrazine

2. SELECTED GENERAL INFORMATION

The health and environmental effects of hydrazine and hydrazine sulfate have been reviewed more extensively by the U.S. EPA (U.S. EPA, 1988) and the U. S. Air Force (USAF, 1989). Physicochemical data are presented in Table 17.

TABLE 17. PHYSICOCHEMICAL DATA

Common name	hydrazine	
Synonyms	diamide; diamine; hydrazine base; hydrazine anhydrous; levoxine	Budavari et al., 1989 USAF, 1989
CAS Registry No.	302-01-2	
RTECS No.	MU7175000	RTECS, 1987
Chemical formula	H_2NNH_2	Budavari et al., 1989
Molecular weight	32.05	Budavari et al., 1989
Physical state	liquid	Budavari et al., 1989
Vapor pressure	14.4 mm Hg at 25°C	U.S. EPA, 1989
Specific gravity	1.011 at 15°C/4°C[a]	Budavari et al., 1989
Melting/boiling/flash point	2.0°C/113.5°C/37.8°C	Mack et al., 1980 Weiss, 1980
Solubility in water	miscible	Budavari et al., 1989
Log K_{ow}	-2.07	Hansch and Leo, 1985
Bioconcentration factor (BCF)	very low potential for bioaccumulation	USAF, 1989
Conversion factors in air	1 mg/m^3 = 0.76 ppm 1 ppm = 1.3 mg/m^3	USAF, 1989
Odor threshold	3.0 to 4.0 ppm; ammonia-like odor	USAF, 1989
Henrys' Law constant	2.0×10^{-7} atm·m^3/mol at 20°C	USAF, 1989

[a]Density of liquid at 15°C relative to the density of water at 4°C

3. SOURCES OF EXPOSURE

3.1. Occurrence in Water

There is potential for drinking water contamination due to the mobility of hydrazine in the soil/ground-water system. However, the volatility of hydrazine and biodegradation in the soil may limit the significance of this exposure source (USAF, 1989).

3.2. Human Exposure

Human exposure would most likely occur in occupational settings (hydrazine production and use) and would likely involve dermal exposure and possibly inhalation of vapors (USAF, 1989). Hydrazine is a component of cigarette smoke and the primary source of hydrazine exposure appears to be mainstream cigarette smoke (USAF, 1989).

4. ENVIRONMENTAL FATE

In the absence of metal catalysts (certain metal ions), hydrazine is remarkably stable in water. Aqueous oxidation of 0.1 mmol of hydrazine after 5 days was <2% in distilled water, 20% in filtered pond water, and 40% in sea water (MacNaughton et al., 1978). Addition of metal catalysts such as copper will greatly increase the oxidation of hydrazine.

The half-life of hydrazine is approximately 5 days in oxygenated water and about 8.3 days in filtered pond water (USAF, 1989). Its degradation is enhanced by organic matter and bacteria.

5. TOXICOKINETICS

5.1. Absorption

Only limited data on the absorption of hydrazine was available. Preece et al. (1992) reported that plasma concentration of hydrazine was not directly proportional to dose in male Sprague-Dawley rats given single oral doses of hydrazine (4.7, 14.1, 42.2, or 126 mg hydrazine hydrate/kg, equivalent to 3, 9, 27, or 81 mg hydrazine/kg), and that this finding may be indicative of a saturable uptake mechanism. Pulmonary, gastrointestinal, and dermal absorption may be inferred from information indicating hydrazine-induced systemic toxicity, and also from metabolism/excretion data resulting from nonparenteral routes of exposure.

5.2. Distribution

Preece et al. (1992) measured hydrazine levels in the livers of rats given oral doses (4.7, 14.1, 42.2, or 126 mg/kg) of hydrazine hydrate (equivalent to 3, 9, 27, or 81 mg hydrazine/kg). Additional quantitative data regarding the distribution of hydrazine in the body was not available. Because of documented systemic toxic effects and its urinary and pulmonary excretion, it may be assumed that the chemical is distributed in the blood compartment and, therefore, has potential for a wide volume of distribution.

5.3. Metabolism

Based upon limited data, hydrazine metabolism appears to vary somewhat among species (rats, mice, and rabbits). Acetylation of hydrazine and splitting of symmetrically distributed hydrazines into amines are possible metabolic pathways (IARC, 1982). Preece et al. (1992) reported the appearance of hydrazine and acetylhydrazine in the urine of rats 24 hours after being given a single intraperitoneal injection of hydrazine.

5.4. Excretion

Hydrazine is excreted primarily in the urine (approximately 50% in rats, mice, and dogs over a 48-hour period). Pulmonary excretion may also occur in these species, and may account for 25 to 40% of the hydrazine dose (Clayton and Clayton, 1978). Both hydrazine and acetylhydrazine were detected in the urine of rats 24 hours after a single intraperitoneal injection (81.25 mg/kg) of hydrazine (Preece et al., 1992).

6. HEALTH EFFECTS

6.1. Noncancer Effects

6.1.1. Oral Exposure

6.1.1.1. Human. Immediate vomiting and loss of consciousness followed by a two-week recovery period involving sensory and motor coordination deficiencies was reported for a man who accidentally ingested "between a mouthful and a cupful" of hydrazine (Reid, 1965). No other data regarding the oral toxicity of hydrazine to humans were available.

6.1.1.2. Animal. Oral LD_{50}s of 60 and 59 mg/kg have been reported for rats and mice, respectively (Verschueren, 1985). Histological alterations in hepatic mitochondria were observed in rats receiving dietary hydrazine (1%) for up to 7 days (Wakabayashi et al., 1987). Preece et al. (1992) reported reduced body weight and liver weight for rats given a single oral dose (81 mg/kg) of hydrazine.

6.1.2. Other Exposure Routes

6.1.2.1. Human. Dermal and inhalation exposure represent the most frequently encountered routes of exposure to hydrazine. Dermal exposure may result in chemical burns and dermatitis (U.S. EPA, 1989). Short-term inhalation of hydrazine vapors has resulted in central nervous system effects, eye irritation (including temporary blindness), nausea, dizziness, and respiratory tract irritation (USAF, 1989). Occupational exposure (inhalation and/or dermal) to hydrazine has been associated with central nervous system disorders and respiratory tract toxicity that may be fatal for severe exposure, as well as hepatotoxicity, cardiovascular disorders, and varying degrees of dermatitis (USAF, 1989).

6.1.2.2. Animal. Inhalation LC_{50}s (4-hr) of 570 and 252 ppm have been reported for rats and mice, respectively (Verschueren, 1983). One-year inhalation exposure (6 hrs/day, 5 days/week) of rats, mice, dogs, and hamsters to hydrazine concentrations up to 5 ppm (1 ppm for mice and dogs) resulted in a variety of species-dependent effects on the respiratory tract, reproductive system, liver, kidney, thyroid, and adrenal glands (Vernot et al., 1985).

6.2. Carcinogenicity

6.2.1. Oral Exposure

6.2.1.1. Human. Epidemiologic data are inadequate to determine the carcinogenicity of hydrazine in humans (IARC, 1982; IRIS, 1991).

6.2.1.2. Animal. Gavage and drinking water exposure of rodents to hydrazine or hydrazine sulfate have resulted in increased incidences of lung and liver tumors in rodents (IRIS, 1991; USAF, 1989). For mice of both sexes, a dose of 1.13 mg hydrazine sulfate/kg/day, 6 days/week for 25 weeks resulted in an increased incidence of hepatic tumors and lung metastasis (Biancifiori, 1970). There is some evidence of hormonal-mediated mechanisms in the increased incidence of hydrazine sulfate-induced pulmonary tumors in mice (Biancifiori, 1970).

Lifetime exposure of male and female Wistar rats (50 of each sex/group) to hydrazine in the drinking water (2, 10, or 50 mg/L) failed to produce a significant tumorigenic response (Steinhoff et al., 1990). Although the highest exposure group exhibited clear signs of overt toxicity, mortality was not increased and only an 11.5% incidence of benign liver tumors was detected. Similar studies using mice have also provided negative results although histological evaluations are not currently complete.

Hepatic carcinomas and spindle cell sarcomas were found in male rats, and adenomas and adenocarcinomas of the lung were observed in female rats receiving 68-week gavage treatment with 12-18 mg hydrazine sulfate (Severi and Biancifiori, 1968).

6.2.2. Other Exposure Routes

6.2.2.1. Human. No definitive information was available regarding the carcinogenic effects of hydrazine in humans.

6.2.2.2. Animal. Neoplasms of the nasal epithelium were observed in rats and hamsters following 1-year inhalation exposure to 5 ppm free base hydrazine (Vernot et al., 1985).

6.3. Genotoxicity

Hydrazine is mutagenic in various *Salmonella* and *Escherichia coli* assays. *In vivo* alkylation of hepatic DNA and RNA, and strand breaks in liver and lung DNA of mice have also been demonstrated (IRIS, 1991).

7. EXISTING STANDARDS, CRITERIA, GUIDANCE

7.1. EPA RfDs, RfCs, CRAVE Classifications

RfD:	None established
RfC:	None established
Oral Slope Factor:	3.0 $(mg/kg/day)^{-1}$ (IRIS, 1991)
Drinking Water Unit Risk:	8.5E-5 $(\mu g/L)^{-1}$ (IRIS, 1991)
Inhalation Slope Factor:	1.7E+1 $(mg/kg/day)^{-1}$ (U.S. EPA, 1992)
Inhalation Unit Risk:	4.9E-3 $(\mu g/m^3)^{-1}$ (IRIS, 1991)
EPA CRAVE Cancer Classification:	B2 (probable human carcinogen) (IRIS, 1991)

Currently, there are no water criteria values or an MCL for hydrazine.

7.2. IARC Carcinogenicity Classification

Group 2B (probably carcinogenic to humans) (IARC, 1982)

7.3. OSHA, ACGIH, and NIOSH Standards and Criteria

OSHA (8-hr TWA):	0.1 ppm; with skin notation	(OSHA, 1989)
OSHA STEL:	None established	(OSHA, 1989)
OSHA Ceiling Limit:	None established	(OSHA, 1989)
ACGIH TLV (8-hr TWA):	0.1 ppm (with skin notation); A2 (suspected human carcinogen)	(ACGIH, 1992)
NIOSH RELs:		
IDLH	carcinogen (no IDLH value assigned)	(NIOSH, 1990)
120-min. Ceiling Limit:	0.04 mg/m^3	(NIOSH, 1990)

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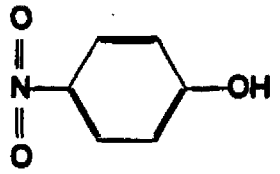
1. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Water, provides information on the health effects and other useful data that can aid in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. The EPA has an ongoing cooperative agreement with the Department of the Army to prepare drinking water Health Advisories (HA) for munitions and other environmental contaminants. Drinking water Toxicological Profiles are short summaries of the pertinent mammalian health effects literature, and are used by the Office of Water to determine if a data base is sufficient to allow the development of HAs. The following databases were searched for information on *p*-nitrophenol: CANCERLINE, CHEMFATE, DART, DTIC, EMICBACK, ENVIROLINE, RTECS, TOXLINE, TOXLINE65, TOXLIT, and TOXLIT65. Secondary sources were also used.

This Drinking Water Toxicological Profile summarizes information on *p*-nitrophenol. Nitrophenols, classified as nitroaromatic hydrocarbons, exist as the *ortho*-, *meta*-, and *para*-isomers. The uses of *p*-nitrophenol include the manufacture of acetaminophen (APAP) (55%), exports (35%), and leather tanning, dyestuffs, oxydianiline and miscellaneous uses (10%) (Chem. Mkt. Rep., 1987). The acetaminophen market has been a slowly growing outlet for the chemical (Chem. Mkt. Rep., 1987). The domestic production of parathion pesticides, formerly the largest U.S. use of *p*-nitrophenol ceased in 1986, whereas overseas parathion production is growing, accounting for increasing exportation of the chemical (Chem. Mkt. Rep., 1987). *p*-Nitrophenol-based fungicides are used to prevent fungal infections of the foot and have been used extensively in the manufacture of footwear issued to U.S. Army personnel (NTP, draft). According to the Chemical Marketing Reporter (1987) the only two manufacturers of *p*-nitrophenol, Du Pont and Monsanto, had a total production capacity of 46 million pounds per year in 1987. The projected demand for the chemical in 1991 was 25 million pounds. The structure of *p*-nitrophenol is shown below:



p-Nitrophenol

2. SELECTED GENERAL INFORMATION

Physicochemical data for *p*-nitrophenol are listed in Table 18.

TABLE 18. PHYSICOCHEMICAL DATA

Common name	*p*-nitrophenol	Budavari et al., 1989
Synonyms	4-nitrophenol; hydroxynitrobenzene	RTECS, 1992
CAS No.	100-02-7	RTECS, 1992
RTECS No.	58136	RTECS, 1992
Molecular weight	139.12	RTECS, 1992
Molecular formula	$C_6H_5NO_3$	RTECS, 1992
Physical state	colorless to slightly yellow, odorless crystals	Budavari et al., 1989
Vapor pressure	4.1×10^{-5} mm Hg at 25°C (extrapolated)	Howard et al., 1976 (cited in CHEMFATE, 1992)
Specific gravity	1.270 at 120°C/4°C[a]	Budavari et al., 1989
Melting point/boiling point/flash point	113-114°C/279°C (decomposes; sublimes)/ND[b]	Lide, 1991-1992
Solubility in water	11,570 mg/L at 20°C	Schwarzenbach et al., 1988
Log K_{OW}	1.91	Hansch and Leo, 1985 (cited in CHEMFATE, 1992)
Log bioconcentration factor (BCF)	1.9 and 2.5 (test concentrations, 4.1 and 44.1 µg/L, respectively; 22°C; fathead minnow)	Call et al., 1980
Conversion factors in air	1 mg/m^3 = 0.176 ppm 1 ppm = 5.68 mg/m^3	Calculated[c]
Odor threshold	58.3 mg/L	Makhinya, 1964 (cited in U.S. EPA, 1980)
Henry's Law constant	4.15×10^{-10} atm-m^3/mol at 25°C	CHEMFATE, 1992

[a]Density of liquid at 120°C relative to the density of water at 4°C
[b]ND: no data

[c] Formula: $\text{ppm by volume} = \text{mg/m}^3 \times \frac{24.45}{\text{mol. wt. in grams}}$

3. SOURCES OF EXPOSURE

3.1. Occurrence in Water

Industries engaged in manufacturing mononitrophenols or using them as intermediates in chemical synthesis are potential sources for the contamination of water with *p*-nitrophenol (U.S. EPA, 1980). Various investigators have detected *p*-nitrophenol in waste effluents from a parathion manufacturing plant (levels unspecified), in the lagoon waste water from a chemical plant (1.4 mg/L), and in the potable water supply of Ames, Iowa (0.2 mg/L) (reviewed in U.S. EPA, 1980). Measurable, but probably transient, environmental levels of mononitrophenols may also occur in areas where organophosphate pesticides are in use (U.S. EPA, 1980).

3.2. Human Exposure

p-Nitrophenol is a product of the microbial and hydrolytic degradation of the pesticides parathion, methyl parathion and fluorodifen (U.S. EPA, 1985a, cited in U.S. EPA, 1985b). Direct exposure to the skin may occur among workers who handle crops treated with these pesticides (U.S. EPA, 1985a, cited in U.S. EPA, 1985b) and among individuals, particularly Army personnel, wearing *p*-nitrophenol-treated footwear. The identification of *p*-nitrophenol on spinach and bean plants treated with parathion suggests potential exposure to the general public through the ingestion of food containing *p*-nitrophenol residues.

In the atmosphere, *p*-nitrophenol is a product of the photochemical reaction between benzene or toluene and nitrogen monoxide (U.S. EPA, 1980). The chemical has been associated with urban atmospheric particulates, indicating potential exposure to the general population by inhalation (U.S. EPA, 1985a, cited in U.S. EPA, 1985b; U.S. EPA, 1980). Also, Nojima et al. (1976), who detected *p*-nitrophenol in rain in the vicinity of Yokohama, Japan, suggested that the nitrophenols produced by photochemical reactions dissolve in rain, and in areas where severe photochemical smog exists humans may be exposed to substantial levels of mononitrophenols. However, the low vapor pressure of *p*-nitrophenol reduces the likelihood of inhalation exposure (U.S. EPA, 1985b).

p-Nitrophenol is present in the soil at Army ammunition plants at concentrations of 40 mg/kg (Hovatter, 1992), suggesting possible exposure of military and/or hazardous waste clean-up personnel. *p*-Nitrophenol would adsorb to the soil to some extent, (K_{OC}, 236 [CHEMFATE, 1992]), but the low volatility and high water solubility of the chemical would favor some leaching to groundwater.

Kutz et al. (1978, cited in U.S. EPA, 1980) analyzed 416 samples of urine collected from the general population and found *p*-nitrophenol (mean urinary level, 10 µg/L) in 1% of the population. These levels do not necessarily reflect direct exposure to *p*-nitrophenol, but probably result from the *in vivo* metabolic degradation of pesticides (U.S. EPA, 1980).

4. ENVIRONMENTAL FATE

p-Nitrophenol in the atmosphere may be removed by wet and dry deposition, by direct photolysis, or by reaction with photochemically generated hydroxyl radicals (U.S. EPA, 1985a, cited in U.S. EPA, 1985b). The estimated half-life for the atmospheric removal of the chemical due to rainfall is 3 weeks (U.S. EPA, 1985a, cited in U.S. EPA, 1985b).

p-Nitrophenol in water undergoes biodegradation and, in the presence of sunlight, rapid reaction with hydroxyl radicals (U.S. EPA, 1985a, cited in U.S. EPA, 1985b). One laboratory study demonstrated that 100% of *p*-nitrophenol is degraded by activated sludge in 15 days without acclimation and in 5 days with acclimation (Dojlido, 1979, cited in CHEMFATE, 1992); another reported rapid degradation (100% degradation in 96 hours) using inocula from enriched soil cultures (Sudhakar-Barik and Sethunathan, 1978, cited in CHEMFATE, 1992); and another reported 100% anaerobic degradation in 1 week using sewage sludge inoculum (Boyd et al., 1983, cited in CHEMFATE, 1992). The by-products of the biodegradation of *p*-nitrophenol include *p*-nitrocatechol, hydroquinone and 2-amino-7-chloro-3H-phenoxazin-3-one (CHEMFATE, 1992).
The observed photolytic half-life values for *p*-nitrophenol in aqueous solution are: from 16 hours to 5.7 days at pH 5, 6.7 days at pH 7, and 13 days at pH 11.5 (U.S. EPA, 1985a, cited in U.S. EPA, 1985b). Products of photolysis include *p*-nitrocatechol, hydroquinone and a "nonvolatile dark polymer" (N[illegible]gawa and Crosby, 1974, cited in CHEMFATE, 1992).

5. TOXICOKINETICS

5.1. Absorption

Data specific to the absorption of mononitrophenols by humans were not available; however, studies in animals, demonstrating that *p*-nitrophenol undergoes rapid clearance from the blood and urine (U.S. EPA, 1980; Arterberry et al, 1961; Lawford et al., 1954, both cited in U.S. EPA, 1980), suggest efficient gastric absorption. The systemic toxicity of *p*-nitrophenol in humans (Section 6.1.1.1.) is another indication that gastric absorption of the chemical occurs. *In vitro* studies using human skin from autopsies demonstrated that *p*-nitrophenol permeates the epidermis (Roberts et al., 1977, cited in U.S. EPA, 1980). The chemical also penetrated skin explants from hairless mice (Hinz et al., 1991).

5.2. Distribution

Data specific to the tissue distribution of the mononitrophenols by humans were not available. However, based on the rapid urinary elimination of the mononitrophenols, U.S. EPA (1980) theorized that the compounds may be restricted mainly to the blood and urine following absorption.

5.3. Metabolism

The major route of mononitrophenol metabolism in humans is most likely via conjugation and the ensuing formation of either glucuronide or sulfate conjugates (U.S. EPA, 1980). Experimental studies demonstrated that glucuronide conjugation of *p*-nitrophenol occurs in the liver, lung, and kidneys of rats, mice, rabbits, hamsters, and guinea pigs (Litterst et al., 1975, cited in U.S. EPA, 1980). Other possible routes of metabolism include the reduction of amino-compounds or oxidation to dihydric-nitrophenols (U.S. EPA, 1980).

5.4. Excretion

Data specific to the excretion of mononitrophenols by humans were not found. However, it appears that humans do excrete *p*-nitrophenol rapidly via the urinary tract following exposure to parathion. In one study, the chemical disappeared from the urine within 48 hours after parathion exposure ended (Arterberry et al., 1961, cited in U.S. EPA, 1980). Another study examined the excretion of *p*-nitrophenol given directly to animals. Elimination of the chemical from the blood of

monkeys was complete within 5 hours after oral and i.p. doses of 20 mg/kg (Lawford et al., 1954, cited in U.S. EPA 1980). Elimination of the chemical from the blood of mice, rats, rabbits, and guinea pigs was even more rapid (route of administration not clear, most likely oral and/or i.p.), occurring within two hours of administration.

6. HEALTH EFFECTS

6.1. Noncancer Effects

6.1.1. Oral Exposure

6.1.1.1. Human. In humans, the symptoms of toxicity resulting from ingestion of *p*-nitrophenol include headaches, drowsiness, nausea, and respiratory depression and cyanosis, indicative of methemoglobinemia (NTP, Draft).

6.1.1.2. Animal. LD_{50} values for various animal species exposed orally to *p*-nitrophenol are listed in Table 19.

Grant (1959, cited in U.S. EPA, 1980) observed a 15-30% increase in respiratory volume in anesthetized rats following oral intubation of *o*-, *m*-, or *p*-nitrophenol. Doses of *p*-nitrophenol ranged from 7-12 mg/kg. Orally administered *p*-nitrophenol (doses not given) did not produce methemoglobinemia in rats (Grant, 1959, cited in U.S. EPA, 1980). Seven-day-old chickens fed 0.25% *p*-nitrophenol in the diet for 3 weeks did not develop cataracts (Dietrich and Beutner, 1946, cited in U.S. EPA, 1980).

Oral doses of 400 mg/kg/day *p*-nitrophenol administered to pregnant mice (10/group) on days 7-14 of gestation had no adverse effects on fetal survival, birth weights or incidence of gross malformations (Plasterer et al., 1985). However, the same doses were toxic to the dams, as evidenced by significantly decreased survival and weight gain.

6.1.2. Other Exposure Routes

6.1.2.1. Human. Symptoms of toxicity resulting from inhalation or absorption through intact skin include headaches, drowsiness, nausea, and respiratory depression and cyanosis, indicative of methemoglobinemia (NTP, draft).

6.1.2.2. Animal. Limited data indicate that the inhalation toxicity of *p*-nitrophenol sodium salts is relatively low. Acute and repeated exposure of male rats to concentrations of 0, 0.34 or 2.47 mg/L caused methemoglobinemia, dark urine, proteinuria, and elevated creatinine and SGOT levels in the treated animals; exposure to 2.47 mg/L also caused elevated erythrocyte count, hemoglobin, and hematocrit. Histopathologic changes were not observed (Smith et al., 1988, cited in NTP, draft).

In an NTP (Draft) bioassay, Swiss-Webster mice (60 males and 60 females/group) were treated with *p*-nitrophenol by interscapular applications to the skin. Doses of 0, 40, 80, or 160 mg/kg were administered to the animals 3 days/week for 78 weeks. Reduced survival, mainly attributed to

TABLE 19. ORAL LD_{50} VALUES FOR ANIMALS

Species	Route	LD_{50}	Reference
Rat	oral	250 mg/kg	RTECS, 1992
Rat	oral	350 mg/kg	Fairchild, 1977 (cited in U.S. EPA, 1980)
Rat	oral	620 mg/kg	Vernot et al., 1977
Mouse	oral	380 mg/kg	RTECS, 1992
Mouse	oral	470 mg/kg	Vernot et al., 1977
"Mammal"	oral	247 mg/kg	RTECS, 1992

amyloidosis and secondary kidney failure, occurred in all groups. No biologically significant lesions were observed that were related to the dermal administration of *p*-nitrophenol.

Angerhofer (1985) examined the reproductive effects of *p*-nitrophenol in rats. Male and female Sprague-Dawley rats received dermal applications of 50, 100, and 250 mg/kg *p*-nitrophenol in ethanol 5 days/week for up to 42 weeks. There were no significant differences in mating, pregnancy, behavior, and growth in parents or two subsequent generations compared with controls. All exposed rats exhibited skin irritation (erythema, scaling and crusting).

von Oettingen (1941, cited in U.S. EPA, 1985b) and Smith et al. (1967, cited in U.S. EPA, 1985b) reported the formation of methemoglobin in cats and mice, respectively. Smith et al. (1967, cited in U.S. EPA, 1980) also reported the formation of methemoglobin in female mice by reduction products of *p*-nitrophenol, 2- and 4-aminophenol. (Experimental details for these studies were not given in the secondary source.)

An abstract of a Russian report listed alterations of neurohumoral regulation, gastritis, enteritis, colitis, hepatitis, neuritis, splenic hyperplasia and inhibited oxidation as "cumulative" effects of exposure to *p*-nitrophenol (Makhinya, 1969, cited in U.S. EPA, 1980). In this study, the limiting dose for the disruption of conditioned reflex activity was 0.00125 mg/kg (0.0025 mg/L of water). U.S. EPA (1980) considered these results to be questionable because experimental details and a complete description of biological effects were not available.

Increased CO_2 output and an inhibition of chloride transport in erythrocytes (RBC) have been associated with exposure to *p*-nitrophenol (Cameron, 1958; Motais et al., 1978, cited in U.S. EPA, 1985b). These results provide limited evidence that (1) *p*-nitrophenol is probably not a potent uncoupler of oxidative phosphorylation (CO_2 output) and (2) mechanistically, *p*-nitrophenol acts directly on the cell membrane (RBC effects) (U.S. EPA 1980).

6.2. Carcinogenicity

6.2.1. Oral Exposure

6.2.2.1. Human. No information was found in the available literature.

6.2.2.2. Animal. No information was found in the available literature.

6.3. Other Exposure Routes

6.3.1. Human

No information was found in the available literature.

6.3.2. Animal

In an NTP (Draft) bioassay, Swiss-Webster mice (60 males and 60 females/group) received *p*-nitrophenol by interscapular applications to the skin. Doses of 0, 40, 80, or 160 mg/kg were administered to the animals 3 days/week for 78 weeks. Reduced survival, attributed to amyloidosis and secondary kidney failure, occurred in all groups. Under the conditions of these studies, there was no evidence of carcinogenic activity in male or female Swiss-Webster mice. NTP conducted this study at the request of the U.S. Army; there was concern for the high risk of exposure to

fungicides (containing approximately 7% nitrophenol), resulting from their use in the manufactur of approximately 3 million pairs of boots and shoes per year for Army and other military personnel

A skin painting study conducted by Boutwell and Bosch (1959, cited in U.S. EPA, 1985b) wa deemed inadequate for the assessment of oncogenic potency by U.S. EPA (1985a, cited in U.S EPA, 1985b). Female mice receiving skin applications of 25 µL of *p*-nitrophenol twice weekly for 1 weeks did not exhibit increased tumor incidence.

6.4. Genotoxicity

p-Nitrophenol induced DNA damage in *Escherichia coli* (50 µmol/L), DNA repair in *Bacillu subtilis* (500 µg/disc), gene conversion and mitotic recombination in *Saccharomyces cerevisiae* (2 mmol/L) (RTECS, 1992), and chromosomal aberrations (with metabolic activation) in Chines hamster ovary cells (NTP, draft). *p*-Nitrophenol did not induce sister chromatid exchanges in hamste ovary cells (with or without metabolic activation) (NTP, draft) or streptomycin independence i streptomycin-independent *E. coli* (Szybalski, 1958, cited in U.S. EPA, 1980), and was not mutageni in a host-mediated assay, a dominant lethal assay (Buselmaier et al., 1976), in *Salmonell typhimurium* (with and without metabolic activation), or in *Drosophila melanogaster* (NTP, Draf McCann et al., 1975).

7. EXISTING STANDARDS, CRITERIA, GUIDANCE

7.1. EPA RfDs, RfCs, CRAVE Classifications

RfD:	None established
RfC:	None established
Oral Slope Factor:	None established
Drinking Water Unit Risk:	None established
Inhalation Slope Factor:	None established
Inhalation Unit Risk:	None established
U.S. EPA CRAVE Cancer Classification:	Not established

7.2. IARC Carcinogenicity Classification

Not established

7.3. OSHA, ACGIH, and NIOSH Standards and Criteria

OSHA (8-hr TWA):	None established
OSHA STEL:	None established
OSHA Ceiling Limit:	None established
ACGIH (8-hr TWA):	None established
ACGIH STEL:	None established
NIOSH RELs:	None established

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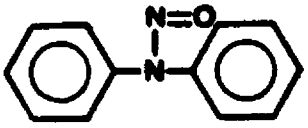
1. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Water, provides information on the health effects and other useful data that can aid in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. The EPA has an ongoing cooperative agreement with the Department of the Army to prepare drinking water Health Advisories (HA) for munitions and other environmental contaminants. Drinking water Toxicological Profiles are short summaries of the pertinent mammalian health effects literature, and are used by the Office of Water to determine if a data base is sufficient to allow the development of HAs. The following data bases were searched for information on *N*-nitrosodiphenylamine: TOXLINE, TOXLINE65, TOXLIT, TOXLIT65, CANCERLINE, DART, EMICBACK, CHEMFATE, ENVIROLINE, DTIC and RTECS. Secondary sources were also used.

This Drinking Water Toxicological Profile summarizes information on *N*-nitrosodiphenylamine (CAS No. 86-30-6). *N*-Nitrosodiphenylamine is used as an intermediate in the synthesis of *p*-nitrosodiphenylamine, as an anti-scorching agent or vulcanization retarder in rubber processing, and in the manufacture of pesticides (U.S. EPA, 1980; USAF, 1989). Nitrosamines (including *N*-nitrosodiphenylamine) are also found in a variety of foods (Fine, 1982).

The toxicology and health effects of *N*-nitrosodiphenylamine have been reviewed by ATSDR (ATSDR, 1988) and the U.S. EPA (1987). The structure of *N*-nitrosodiphenylamine is shown below.



N-nitrosodiphenylamine

2. SELECTED GENERAL INFORMATION

Physicochemical data and registry numbers for *N*-nitrosodiphenylamine are presented in Table 20.

TABLE 20. PHYSICOCHEMICAL DATA

Common name	*N*-nitrosodiphenylamine	
Synonyms	*N*-nitroso-*n*-phenylbenzamine; diphenylnitrosamine; benzenamine; diphenyl-*N*-nitrosamine	USAF, 1989 RTECS, 1986
CAS Registry No.	86-30-6	
RTECS No.	JJ9800000	RTECS, 1986
Chemical formula	$C_{12}H_{10}N_2O$	USAF, 1989
Molecular weight	198.2	USAF, 1989
Physical state	amorphous solid	IARC, 1982
Vapor pressure	6.69×10^{-4} mm Hg	SRC, 1988
Specific gravity	1.23 at 20°C	USAF, 1989
Melting/boiling/flash point	66.50°C/153°C/ND[a]	USAF, 1989
Solubility in water	1.13×10^2 mg/L at 25°C	USAF, 1989
Log K_{ow}	3.13	Banerjee et al., 1980
Bioconcentration factor (BCF)	2.34	Barrows et al., 1980
Conversion factors in air	1 mg/m^3 = 0.12 ppm 1 ppm = 8.1 mg/m^3	ATSDR, 1988
Odor threshold	ND	
Henrys' Law constant	1.40×10^{-6} atm·m^3/mol at 25°C	USAF, 1989

[a]ND: no data

3. SOURCES OF EXPOSURE

3.1. Occurrence in Water

N-Nitrosodiphenylamine has been found in raw waste samples and secondary effluent from textile plants at concentrations of 2 to 20 μg/L (IARC, 1982). *N*-Nitrosodiphenylamine has been found in the soil and groundwater at concentrations of 0.8 mg/kg and 11 - 14 μg/L, respectively, at U.S. Army ammunition plants (Hovatter, 1992).

3.2. Human Exposure

Specific data were not available. However, it may be assumed that the primary source of human exposure would be in occupational settings.

4. ENVIRONMENTAL FATE

N-Nitrosodiphenylamine is resistant to rapid hydrolysis but may slowly biodegrade (USAF, 1989). Because *N*-nitrosodiphenylamine is resistent to hydrolysis and the extent of its biodegradation uncertain, this chemical may be expected to persist in water for months to years (USAF, 1989). No data were available regarding degradation products of *N*-nitrosodiphenylamine.

5. TOXICOKINETICS

5.1. Absorption

Although no data were available specifically regarding the absorption of *N*-nitrosodiphenylamine, its absorption following oral exposure may be implied by metabolism and urinary excretion data.

5.2. Distribution

No information was located in the available literature.

5.3. Metabolism

N-Nitrosodiphenylamine is denitrosated to nitric oxide and diphenylamine and ultimately converted to nitrite and nitrate in the rat (Appel et al., 1984a,b). *N*-Nitrosodiphenylamine is not susceptible to oxidative bioactivation and, therefore, denitrosation may be the bioactivation pathway for this compound.

5.4. Excretion

Appel et al. (1984a,b) reported the urinary excretion of parent compound and several metabolites by rats administered *N*-nitrosodiphenylamine orally.

6. HEALTH EFFECTS

6.1. Noncancer Effects

6.1.1. Oral Exposure

6.1.1.1. Human. No information was located in the available literature.

6.1.1.2. Animal. Oral LD_{50} values of 1650 and 3850 mg/kg for the rat and mouse, respectively, are reported in RTECS (1986). Subchronic exposure (8 to 11 weeks) of F344 rats and $B6C3F_1$ mice to dietary *N*-nitrosodiphenylamine at concentrations up to 46,000 mg/kg diet resulted in decreased survival of female rats and decreased body weight gain in female rats (NCI, 1979).

6.1.2. Other Exposure Routes

6.1.2.1. Human. No information was located in the available literature.

6.1.2.2. Animal. No information was located in the available literature.

6.2. Carcinogenicity

6.2.1. Oral Exposure

6.2.1.1. Human. No information was located in the available literature.

6.2.1.2. Animal. Long-term exposure of male and female F344 rats to *N*-nitrosodiphenylamine in feed (4000 mg/kg diet/day for 100 weeks) resulted in an increased incidence (36% and 81% for males and females, respectively) of transitional cell carcinomas of the urinary bladder (NCI, 1979). A dose-related increase in the incidence of fibromas of the skin was also observed for male rats. $B6C3F_1$ mice exposed to dietary concentrations up to 20,000 mg/kg diet did not exhibit a carcinogenic response (NCI, 1979). Additional oral exposure studies, all with various degrees of deficiencies, are summarized in Table 21.

6.2.2. Other Exposure Routes

6.2.2.1. Human. No information was located in the available literature.

6.2.2.2. Animal. Both dermal and intraperitoneal exposure studies have been conducted (USAF, 1989). Although both showed positive responses (lung adenomas in the dermal exposure study, and hepatomas and pituitary adenomas in the injection study), both studies used inadequate experimental protocols.

6.3. Genotoxicity

Available data indicate equivocal genotoxicity. Mutagenicity without activation, oncogenetic transformations, unscheduled DNA synthesis, and sister chromatid exchanges have been

TABLE 21. CARCINOGENICITY OF *N*-NITROSODIPHENYLAMINE IN EXPERIMENTAL ANIMALS

Species and Number	Dose, Route, Duration	Result	IARC Comment (IARC, 1982)
18 (C57BL/6 x C3H/Anf)F_1 mice of each sex	100 mg/kg/day in DMSO (gavage) for 4 weeks followed by 3769 mg/kg/day (diet) for 75 weeks	no increase in tumor incidence	inadequate sample size
25 male Wistar rats	1070 µg/kg, 5 days/week by gavage for 49 weeks	no increase in tumor incidence	low dose and duration
16 male and 24 female hairless hr/hr Oslo mice	20 weekly dermal applications of 0.1 mL of a 1% solution in NDPA[a]	3 lung adenomas in males	no appropriate controls
24 male CB rats	25 mg/kg (one i.p. injection/week) in polyethylene glycol 400 for 2 years	1 hepatoma and pituitary adenoma; 1 hepatoma in controls	low dose used; poor survival (21%)

[a] NDPA: *N*-nitrosodiphenylamine

Source: USAF, 1989

reported for *N*-nitrosodiphenylamine (RTECS, 1986). Other reports indicate the absence of genotoxicity in bacterial test strains (IARC, 1982).

7. EXISTING STANDARDS, CRITERIA, GUIDANCE

7.1. EPA RfDs, RfCs, CRAVE Classifications

RfD:	None established
RfC:	None established
Oral Slope Factor:	4.9E-3/mg/kg/day(IRIS, 1990)
Drinking Water Unit Risk:	1.4E-7/μg/L (IRIS, 1990)
Inhalation Slope Factor:	None established
Inhalation Unit Risk:	None established
U.S. EPA CRAVE Cancer Classification:	Group B2; probable human carcinogen (IRIS, 1990)

The U.S. EPA has developed an ambient water criterion for the protection of human health (for 10^{-5} risk level) of 49 μg/L for *N*-nitrosodiphenylamine (U.S. EPA, 1980).

7.2. IARC Carcinogenicity Classification

IARC (1987) has classified *N*-nitrosodiphenylamine in Group 3; not classifiable as to its carcinogenicity in humans.

7.3. OSHA, ACGIH, and NIOSH Standards and Criteria

OSHA TWA (8-hr):	None established
ACGIH TLV (8-hr TWA):	None established
STEL:	None established
NIOSH RELs:	None established

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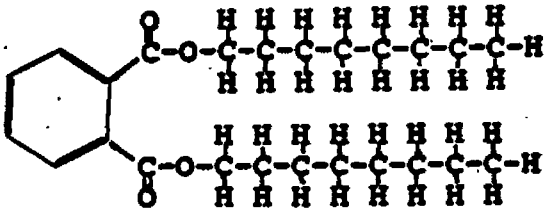
1. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Water, provides information on the health effects and other useful data that can aid in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. The EPA has an ongoing cooperative agreement with the Department of the Army to prepare drinking water Health Advisories (HA) for munitions and other environmental contaminants. Drinking water Toxicological Profiles are short summaries of the pertinent mammalian health effects literature, and are used by the Office of Water to determine if a data base is sufficient to allow the development of HAs. The following data bases were searched for information on di-*n*-octyl phthalate: TOXLINE, TOXLINE65, TOXLIT, TOXLIT65, CANCERLINE, DART, EMICBACK, CHEMFATE, ENVIROLINE, DTIC and RTECS. Secondary sources were also used.

This Drinking Water Toxicological Profile summarizes information on di-*n*-octyl phthalate which is the di-*n*-ocytl ester of 1,2-benzenedicarboxylic acid. It is one of several similar esters primarily used in the plastics industry. Di-*n*-octyl phthalate is specifically used as a plasticizer in the manufacture of polystyrene and vinyl plastics. It is, therefore commonly found in household and medical products including carpetback coating, food packaging, and medical tubing and blood containers (Autian, 1973; U.S. EPA, 1987a). It is also a registered ingredient in some pesticides (U.S. EPA, 1987a). The structure of di-*n*-octyl phthalate is shown below.



Di-*n*-octyl phthalate

2. SELECTED GENERAL INFORMATION

General information, physical and chemical data are presented in Table 22.

TABLE 22. PHYSICOCHEMICAL DATA

Common name	di-*n*-octyl phthalate	
Synonyms	1,2-benzene dicarboxylic acid, di-*n*-octyl ester; *n*-octyl phthalate; DOP; DNOP; dinopol NOP; celluflex DOP; polycizer 162	Sax and Lewis, 1989 Sandmeyer and Kirwin, 1978 U.S. EPA, 1987a
CAS registry no.	117-84-0	
RTECS no.	TI1925000	RTECS, 1987
Chemical formula	$C_{24}H_{38}O_4$	Sax and Lewis, 1989
Molecular weight	390.62	Sax and Lewis, 1989
Physical state	clear oily liquid	Sandmeyer and Kirwin, 1978
Vapor pressure	1.44×10^{-4} mm Hg at 25°C <0.2 mmHg at 150°C	Mabey et al., 1981 Sandmeyer and Kirwin, 1978
Specific gravity	0.978 at 20°	U.S. EPA, 1987b
Melting/Boiling/Flash point (°C)	-30/230 at 5 mmHg/219	Sax and Lewis, 1989
Solubility in water	3.0 mg/L at 25°	Wolfe et al., 1980
Log K_{ow}	5.22	Hansch and Leo, 1985
Bioconcentration factor (BCF)	9400 fish *Gambusia affinis* (water conc. 0.064 µg/L, exposure time 33 days.)	Sanborn et al., 1975
	1.16 fish *Gambusia affinis* (water conc. 3.45 µg/L, exposure time 3 days.)	Sanborn et al., 1975
	333 (calculated according to: log BCF = 2,791-0.564 X log water solubility in ppm)	Lyman et al., 1982 U.S. EPA, 1987b
Conversion factors in air	1 ppm = 15.94 mg/m^3 1 mg/m^3 = 0.06 ppm	Calculated[a]
Henrys' law constant	2.4×10^{-5} atm. m^3/mol	U.S. EPA, 1987b

[a] Formula: $\text{ppm by volume} = \text{mg/m}^3 \times \frac{24.45}{\text{mol. wt. in grams}}$

3. SOURCES OF EXPOSURE

3.1. Occurrence in Water

Di-*n*-octyl phthalate has been reported in wastewater from petroleum refineries, chemical plants, paper manufacturing, and sewage treatment plants. It has also been found in runoff water, river water and ground water across the U.S. and in several other countries. The concentrations usually reported range from 2 to 39 μg/L (U.S. EPA, 1987b). It has also been found in ground water (2 to 19 mg/L), in surface water (410 mg/L), and in soil (0.4 to 0.7 mg/kg) at U.S. ammunition plants that are national priorities list superfund cleanup sites (Hovatter, 1992).

3.2. Human Exposure

Humans are exposed to di-*n*-octyl phthalate, usually mixed with other phthalate esters, in food and drinking water, in the air and, in some cases, by skin contact. Its extensive use in the plastics industry leads to human exposure from polystyrene and vinyl packaging used in the food and medical products. The most common route of exposure is by ingestion. Inhalation and dermal routes of exposure are thought to be minor, however, intravenous exposure has been shown to occur as a result of leaching of phthalate esters from plastic tubing and containers used for medical applications (Sandmeyer and Kirwin, 1978).

4. ENVIRONMENTAL FATE

Di-*n*-octyl phthalate was found to degrade slowly over a period of about three weeks in surface water followed by a rapid biodegradation. Over 90% of the di-*n*-octyl phthalate was removed in seven days following the initial three week period (Tabak et al., 1981). A $T_{1/2}$ of about five days was determined for removal of di-*n*-octyl phthalate from water in a model ecosystem (Sanborn, 1975).

Di-*n*-octyl phthalate undergoes enzymatic hydrolysis by microorganisms in water first to the monoester then to phthalic acid (Tabak et al., 1981). The most common by-products found in the water are mono-octyl phthalate and phthalic acid. The monoester is further hydrolyzed to phthalic acid which is degraded to carbon dioxide and water (Sanborn, 1975; U.S. EPA, 1987a).

5. TOXICOKINETICS

5.1. Absorption

Specific studies on the absorption of di-*n*-octyl phthalate were not available. Studies on related phthalate diesters would indicate that it may be absorbed by ingestion, inhalation and by skin contact. The most prominent route of exposure is probably oral. It can be inferred from the effects observed in toxicity studies using di-*n*-octyl phthalate that the ester and/or it's degradation products are probably well absorbed from the gastrointestinal tract (U.S. EPA, 1987a).

5.2. Distribution

Judging from the presence of the phthalate esters and their metabolites in the blood and the observed effects in different organ systems, phthalate esters as a group are carried by the blood to all parts of the body and become widely distributed. Specific effects of di-*n*-octyl phthalate have been observed in the liver, kidney, and immune system (See section 6). Other phthalate

di-esters, but not di-*n*-octyl phthalate, are known to effect the fetus and, thus, may be able to cross the placenta (U.S. EPA, 1987b).

5.3. Metabolism

Similar to other phthalate diesters, the hydrolysis of di-*n*-octyl phthalate to the monoester has been shown to occur in the intestine before absorption, however, hydrolysis can also occur intracellularly in the intestinal mucosal cells and in other tissues (Kluwe, 1982; Rowland, 1974; U.S. EPA, 1987b).

5.4. Excretion

Specific studies on the excretion of di-*n*-octyl phthalate were not available. However, animal studies have shown that it's isomer, diisooctyl phthalate, is excreted in the urine, feces and bile primarily as the monoester. The primary route depends on the test animal, but excretion half-lives of 1.2 and 5.4 hours have been reported (Ikeda et al., 1978). Similar results have been seen with di-n butyl phthalate and *bis*(2-ethylhexyl)phthalate (U.S. EPA, 1987a). In humans, a glucuronide conjugate is usually formed with the monoester derivative before excretion. The molecule can also be hydrolyzed to phthalic acid or oxidized and excreted (Kluwe, 1982).

6. HEALTH EFFECTS

6.1. Noncancer Effects

6.1.1. Oral Exposure

6.1.1.1. Human. Specific human studies with di-*n*-octyl phthalate were not available, however acute exposure to related compounds have caused irritation of mucous membranes and gastrointestinal disturbances (Sandmeyer and Kirwin, 1978).

6.1.1.2. Animal. An acute oral LD_{50} for a rat was reported to be greater than 13 g/kg di-*n*-octyl phthalate (Sandmeyer and Kirwin, 1978). Decreased resistance to viral, bacterial, and protozoan infections have been reported in mice and rats following short term (5 days) oral exposure to di-*n*-octyl phthalate at 0.05 to 0.2 times the LD_{50} dose. The mean survival time of the animals was reduced (Dogra et al., 1987; 1989).

Mann et al. (1985) observed increased liver weight with centrilobular fat accumulation and mild necrosis in male Wistar rats fed 20,000 ppm di-*n*-octyl phthalate in their diet for 21 days. There was little effect on liver peroxizomes. Hinton et al. (1986) fed 2000 mg/kg/day di-*n*-octyl phthalate to rats for up to 21 days and reported increased liver weight with centrilobular fat accumulations. Histological examination of the thyroid revealed an increase in the number and size of lysosomes and an enlarged Golgi apparatus with altered mitochondria in treated animals.

Heindel et al. (1989) fed groups of 20 male and 20 female mice 0, 1.25, 2.5, or 5% di-*n*-octyl phthalate in their diet for 106 days in an experiment designed to test for reproductive toxicity. The only effect reported was a statistically significant increase in liver weights with no effect on reproductive function.

Longer term (48 week) oral studies have shown dose dependent nephrotoxicity in rats and mice exposed to 500 and 1000 ppm di-*n*-octyl phthalate in the diet. All treated mice and 50% of the rats developed interstitial nephritis with the high dose (Nagasaki et al., 1974). Piekacz (1971) exposed rats to dietary levels of 3500 ppm for 7 to 12 months and observed increased liver and kidney weights in females and increased SGOT and SGPT levels in both sexes (U.S. EPA, 1987a).

Oral exposure to most phthalic acid di-esters can cause testicular atrophy, decreased testicular weight with histological evidence of degeneration. However, di-*n*-octyl phthalate exposure at equimolar concentrations has no apparent testicular effect (Cater et al., 1977; Gray and Butterworth, 1980; U.S. EPA, 1987a). In metabolic experiments, the di-*n*-octyl ester had no effect, whereas, the mono-*n*-octyl ester, a principle metabolite of di-*n*-octyl phthalate, was observed to inhibit the respiratory functions of the Sertoli cell mitochondria. Other tested di-phthalate esters except for the di-*n*-octyl ester also inhibited Sertoli cell respiration. The inhibited Sertoli cell respiration has been proposed as a possible mechanism for the testicular damage (Oishi, 1990).

6.1.2. Other Exposure Routes

6.1.2.1. Human. Acute exposures are reported to be irritating to the skin and eyes. If di-*n*-octyl phthalate is heated to combustion, acrid, irritating smoke and fumes are emitted (Sax and Lewis, 1989). Workers who handle mixtures of plasticizers containing di-*n*-octyl phthalate have been reported to develop polyneuritis, a decline in olfactory excitability, and decreased hemoglobin and numbers of thrombocytes and leukocytes. Air concentrations of phthalate esters ranged from 1 to 60 mg/m^3. Exposure time in one study averaged 4.5 years (Milkov et al., 1973; Gilioli et al., 1978).

6.1.2.2. Animal. A dermal LD_{50} value of 75 ml di-*n*-octyl phthalate/kg has been reported for guinea pigs (Sandmeyer and Kirwin, 1978). Subchronic (90-day) exposure by intraperitoneal injection caused dose dependent histological changes in the testis of rats that persisted after 45 days of no treatment. The initial injury appeared to be to the Sertoli cells (Khanna et al., 1989). Khanna et al. (1990) in a similar 90-day intraperitoneal injection experiment demonstrated dose dependent injury to the kidneys of rats including tubular epithelial degeneration and infiltration of chronic inflammatory cells in the interstitial area which also persisted after 45 days of no treatment. Di-*n*-octyl phthalate (5 or 10 ml/kg) given on the 5th, 10th and 15th days of gestation by intraperitoneal injection to pregnant rats resulted in decreased fetal weight and skeletal malformations in a study investigating the teratogenicity of six phthalate esters. Di-*n*-octyl phthalate was one of the least fetotoxic of the tested compounds (Singh et al., 1972; Dillingham and Autian, 1973).

6.2. Carcinogenicity

6.2.1. Oral Exposure

6.2.2.1. Human. No information on human carcinogenicity of di-*n*-octyl phthalate was available.

6.2.2.2. Animal. Di-*n*-octyl phthalate has been reported to enhance the development of preneoplastic lesions and hepatocellular carcinomas in the male rat. Thus, while not mutagenic or apparently carcinogenic, di-*n*-octyl phthalate promotes diethylnitrosamine-induced liver cancer (DeAngelo et al., 1986; 1989).

6.2.2. Other Exposure Routes

6.2.2.1. Human. No information was located in the available literature.

6.2.2.2. Animal. No information was located in the available literature.

6.3. Genotoxicity

Di-*n*-octyl phthalate has not been found to be mutagenic in any of the tested *Salmonella* strains (Zeiger et al., 1985).

7. EXISTING STANDARDS, CRITERIA, GUIDANCE

7.1. EPA RfDs, RfCs, CRAVE Classifications

Subchronic RfD:	2.00×10^{-2} mg/kg/day (U.S. EPA 1992)
Chronic RfD:	2.00×10^{-2} mg/kg/day (U.S. EPA 1992)
Oral slope factor:	None established
Oral unit risk:	None established
Inhalation slope factor:	None established
Inhalation unit risk:	None established
EPA CRAVE Cancer Classification:	D, Inadequate data (U.S. EPA, 1987a)

7.2. IARC Carcinogenicity Classification

Not evaluated

7.3 ACGIH, OSHA, and NIOSH Standards and Criteria

OSHA (8-hr TWA):	None established
OSHA STEL:	None established
OSHA Ceiling Limit:	None established
ACGIH (8-hr TWA):	None established
NIOSH RELs:	None established

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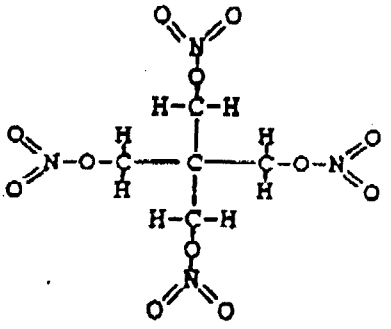
1. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Water, provides information on the health effects and other useful data that can aid in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. The EPA has an ongoing cooperative agreement with the Department of the Army to prepare drinking water Health Advisories (HA) for munitions and other environmental contaminants. Drinking water Toxicological Profiles are short summaries of the pertinent mammalian health effects literature, and are used by the Office of Water to determine if a data base is sufficient to allow the development of HAs. The following data bases were searched for information on pentaerythritol tetranitrate: TOXLINE, TOXLINE65, TOXLIT, TOXLIT65, CANCERLINE, DART, EMICBACK, CHEMFATE, ENVIROLINE, DTIC and RTECS. Secondary sources were also used.

This Drinking Water Toxicological Profile summarizes information on pentaerythritol tetranitrate (PETN). PETN is a class A explosive used as a component of the explosive charge in small caliber cartridges and grenades (Sax and Lewis, 1989). It is also used in detonators and fuses and as a booster charge in other weaponry (Budavari et al., 1989; Stokinger, 1978). PETN is stored, shipped and handled wet (40% water) and is stable in storage up to 18 months at 65°C. Small amounts of free acid or alkali (0.01%) accelerate deterioration (Stokinger, 1978; Sax and Lewis, 1989). When mixed with plasticizers and stabilizers in explosive composites, however, it is reported to have a shelf life of 65 to 164 years (Asthana et al., 1990).

PETN explodes at 215°C and releases toxic fumes of NO_x upon decomposition (Sax and Lewis, 1989). The structure of pentaerythritol tetranitrate is shown below.



Pentaerythritol tetranitrate

2. SELECTED GENERAL INFORMATION

General information, physical and chemical data are presented in Table 23.

TABLE 23. PHYSICOCHEMICAL DATA

Common name	pentaerythritol tetranitrate	
Synonyms	PETN; 2,2-*bis*(hydroxymethyl)-1,3-propanediol tetranitrate; 2,2-*bis*[(nitrooxy)-methyl]-1,3-propanediol dinitrate; nitropentaerythritol; penthrit; erinit; niperyt; lentrat; hasethrol; peritrate; mycardol; nitropenton; pentral 80; terpate; pentanitrine; subicard; tranite D-lay; vasodiatol; angicap; metranil	Sax and Lewis, 1989 Budavari et al., 1989
CAS registry no.	78-11-5	
RTECS no.	RZ2620000	RTECS, 1987
Chemical formula	$C_5H_8N_4O_{12}$	Sax and Lewis, 1989
Molecular weight	316.15	Stokinger, 1978 Budavari et al., 1989
Physical state	tetragonal holohedra crystals	Budavari et al., 1989
Vapor pressure	ND[a]	
Specific gravity	1.765	Stokinger, 1978
Melting/Boiling/ Flash point (°C)	138-140/180 at 50 mmHg/explodes at 205-215°C	Stokinger, 1978 Sax and Lewis, 1989
Solubility in water	43.0 mg/L at 25°C	Stokinger, 1978
Log K_{ow}	ND	
Bioconcentration factor (BCF)	ND	
Conversion factors in air	1 ppm = 12.90 mg/m^3 at 25°C 1 mg/m^3 = 0.077 ppm at 25°C	Calculated[b]
Odor/taste threshold	ND	
Henrys' law constant	ND	

[a]ND: no data

[b]Formula: ppm by volume = mg/m^3 $\times \frac{24.45}{\text{mol. wt. in grams}}$

3. SOURCES OF EXPOSURE

3.1. Occurrence in Water

Although PETN is only sparingly soluble in water, the compound has been found in waste effluents from munitions manufacturing. Experiments designed to test the toxicity of these effluents to aquatic organisms have shown that the only effects observed were due to the high pH resulting from the desensitization process and not from compound toxicity (Bentley et al., 1975).

3.2. Human Exposure

Workers in the munitions industry are subject to accidental PETN exposure. Possible exposure could occur by oral, dermal or inhalation routes (Stokinger, 1978). PETN is used medically as a vasodilator in angina patients. It is usually given orally, but can be administered sublingually or by injection (Lewis et al., 1981; AMA, 1983).

4. ENVIRONMENTAL FATE

No quantitative information is available, however, intestinal bacteria are known to remove the nitrate groups from the molecule resulting in pentaerythritol and the mono- di- and trinitrate derivatives (Carter and Goldman, 1976). It is reasonable to expect the same process to occur with similar bacteria in the environment.

5. TOXICOKINETICS

5.1. Absorption

Accidental exposure can occur by oral, dermal or inhalation routes, although dermal absorption has been reported to be minimal (Stokinger, 1978). No quantitative information on inhalation absorption is available, however, effects have been reported in workers exposed to an atmosphere contaminated with PETN (Kuzelova et al., 1984). PETN is used medically as a vasodilator in angina patients. It is usually given orally, but can be administered sublingually or by injection (Lewis et al., 1981; AMA, 1983). Earlier experiments indicated limited absorption from the gastrointestinal tract of rats (Lawton et al., 1944). Later experiments with [^{14}C] PETN demonstrated that the molecule could be readily absorbed from the rat gastrointestinal tract, but was rapidly degraded resulting in the presence of seven metabolites in the blood and marginally detectable levels of PETN (Crew et al., 1975; King and Fung, 1986). Studies utilizing [^{14}C] PETN in humans show rapid gastrointestinal absorption; radioactive label appeared in the blood 15 min. after ingestion. Chemical analysis of the blood detected only polyerythritol, polyerythritol dihydrate, and polyerythritol monohydrate (Davidson et al., 1971).

5.2. Distribution

No quantitative distribution data was located, however, it can be inferred from effects on the nervous and cardiovascular systems (See section 6) that PETN and metabolites are generally distributed by the blood throughout the body (AMA, 1983; Lewis et al., 1981).

5.3. Metabolism

Given orally, PETN does not generate nitrites under the acidic conditions in the stomach (Boring et al., 1983). However, the intestinal flora is thought to remove nitrate groups from the molecule, and may play a critical role degrading the mononitrate derivative (Carter and Goldman, 1976). Once absorbed, PETN is rapidly degraded to polyerythritol trinitrate, polyerythritol dinitrate, polyerythritol mononitrate and polyerythritol. The dinitrate metabolite was reported to have peak blood concentration in 15 min. and the mononitrate metabolite in 180 min. following ingestion in humans (Neurath and Duenger, 1977). A number of human tissues have been shown in vitro to have PETN degradative activity including intestinal mucosa, kidney, liver, and blood. The PETN degradative activity in human intestinal mucosa was shown to be four times higher than in liver (Posadas del Rio et al., 1988). PETN and metabolites bind to elements in the plasma and erythrocytes (DiCarlo et al., 1965). Degradation of PETN in the rat has been shown to be 10 times higher in the erythrocyte than in plasma. The half-life of PETN in whole blood following arterial injection in rats was 15 min. (King and Fung, 1986). Glucuronide conjugates of PETN and its trinitrate metabolite were reported in rat blood following oral administration of [^{14}C] PETN. The presence of the conjugates may explain the extended half lives of 2 hour and 3 hours for PETN and the trinitrate metabolite, respectively (Crew et al., 1975).

5.4. Excretion

Experiments utilizing [^{14}C] PETN have shown that 92% of an oral dose (20 or 40 mg) was excreted by humans in the feces and urine within 48 hours. The amount of label found in urine accounted for 60% of the low dose and 50% of the high dose. The primary metabolites excreted include polyerythritol, polyerythritol mononitrate, and polyerythritol dinitrate (Davidson et al., 1971). A large percentage of the metabolites in humans were shown to be excreted in the urine as glucuronide conjugates (Neurath and Duenger, 1977).

6. HEALTH EFFECTS

6.1. Noncancer Effects

6.1.1. Oral Exposure

6.1.1.1. Human. Some cases of mild illness and dermatitis have been reported as a result of industrial PETN exposure (Stokinger, 1978). PETN has been used medically for its antispasmodic and vasodilatation action on smooth muscle of coronary blood vessels. It is usually given orally but can also be injected. Oral doses range from 40 to 160 mg/day (0.6 to 2.3 mg/kg for a 70 kg human) (Murad, 1990). Adverse reactions reported among people taking the drug have included headaches, gastrointestinal distress, dermatitis and hypotension. The dermatitis can become severe requiring discontinuation of the drug. Alcohol aggravates the hypotension and can cause collapse (Lewis et al., 1981).

6.1.1.2. Animal. Anesthetized dogs given a single dose of 5 mg PETN in 10% acetone solution/kg by gavage developed a 28% decrease in blood pressure, a slight increase in venous pressure and an increased respiratory rate. All of the effects returned to normal within 1.5 hours (von Oettingen and Donahue, 1944). No evidence of toxicity was seen in F344 rats or $B6C3F_1$ mice fed up to 10,000 ppm PETN in their diet for 14 days. Female rats had lower weight gain after 13 weeks on a diet containing 5,000 or 10,000 ppm PETN. No toxic effects were seen in mice (50/group) or male rats (50/group) on diets containing 5,000 to 10,000 ppm PETN or in female rats (50/group) given 1,240 to 2,500 ppm PETN for up to two years (Bucher et al., 1990). Donahue (1944) fed 2 mg PETN/kg/day to rats for 1 year and saw no effects on growth, blood, vascular walls, lungs, liver, kidneys spleen, brain, or femurs.

6.1.2. Other Exposure Routes

6.1.2.1. Human. Workers exposed to air concentrations of 1 to 2 mg/m^3 of a mixture of nitrate esters including PETN for a mean of 11.5 years reported irritability, sleep disturbance, digestive trouble and intolerance to alcohol. Altered EEG recordings were observed in 11% of the workers (Kuzelova 1984). Such long term exposure has also resulted in withdrawal complications consisting of transient angina symptoms upon leaving the industrial environment (Lewis et al., 1981). There is apparently no appreciable dermal absorption of PETN. Patch tests on up to 20 people have also shown no skin irritation or sensitization (Stokinger, 1978). PETN has been used medically for its antispasmodic action on smooth muscle of coronary blood vessels. It is usually given orally but can also be injected. A patient who had been taking PETN and glyceryl trinitrate by injection for angina symptoms for about 10 years developed a serious dermatitis (Ryan, 1972).

6.1.2.2. Animal. No information was located in the available literature.

6.2. Carcinogenicity

6.2.1. Oral Exposure

6.2.2.1. Human. No information on human carcinogenicity of PETN was located in the available literature.

6.2.2.2. Animal. PETN was given to F344 rats or $B6C3F_1$ mice in their diets at levels of 5,000 to 10,000 ppm (mice and male rats) and 1,240 to 2,500 ppm (female rats) in a two-year carcinogenicity study. No evidence of carcinogenicity or toxicity was observed in any of the animal groups. Neoplasms of the Zymbal gland were seen at low incidences in both sexes of rats, but were not attributed to PETN treatment (Bucher et al., 1990).

6.2.2. Other Exposure Routes

6.2.2.1. Human. No information was located in the available literature.

6.2.2.2. Animal. No information was located in the available literature.

6.3. Genotoxicity

PETN was negative in mutagenicity tests with *Salmonella typhimurium* with or without a rat liver activation system (Whong et al., 1980).

7. EXISTING STANDARDS, CRITERIA, GUIDANCE

7.1. EPA RfDs, RfCs, CRAVE Classifications

RfD:	None established
RfC:	None established
Oral slope factor:	None established
Oral unit risk:	None established
Inhalation slope factor:	None established
Inhalation unit risk:	None established
EPA CRAVE Cancer Classification:	Not classified

7.2. IARC Carcinogenicity Classification

Not evaluated

7.3 ACGIH, OSHA, and NIOSH Standards and Criteria

OSHA (8-hr TWA):	None established
OSHA STEL:	None established
OSHA Ceiling Limit:	None established
ACGIH (8-hr TWA):	None established
NIOSH RELs:	None established

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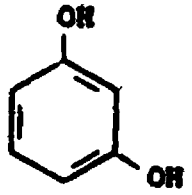
1. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Water, provides information on the health effects and other useful data that can aid in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. The EPA has an ongoing cooperative agreement with the Department of the Army to prepare drinking water Health Advisories (HA) for munitions and other environmental contaminants. Drinking Water Toxicological Profiles are short summaries of the pertinent mammalian health effects literature, and are used by the Office of Water to determine if a data base is sufficient to allow the development of HAs. The following data bases were searched for information on resorcinol: TOXLINE, TOXLINE65, TOXLIT, TOXLIT65, CANCERLINE, DART, EMICBACK, CHEMFATE, ENVIROLINE, DTIC and RTECS. Secondary sources were also used.

This Drinking Water Toxicological Profile summarizes information on resorcinol. Resorcinol is a crystalline compound and is classified as a hazardous waste by the U.S. EPA (Sittig, 1985). The chemical is used for the production of various adhesives, and in the preparation of dyes, uv absorbers, and pharmaceuticals (Mark et al., 1978). Resorcinol is also a component of cigarette smoke, skin care products, and hair dyes (Sittig, 1985). The chemical structure of resorcinol is shown below.



Resorcinol

2. SELECTED GENERAL INFORMATION

Physicochemical data and registry numbers for resorcinol are presented in Table 24.

TABLE 24. PHYSICOCHEMICAL DATA

Common name	Resorcinol	
Synonyms	1,3 benzenediol, *m*-dihydroxybenzene, *m*-hydroxyphenol, 1,3-dihydro-oxybenzene, resorcin	Budavari et al., 1989
CAS Registry No.	108-46-3	
RTECS No.	VG9625000	RTECS, 1986
Chemical formula	$C_6H_6O_2$	Budavari et al., 1989
Molecular weight	110.11	Budavari et al., 1989
Physical state	crystal	Budavari et al., 1989
Vapor pressure	5 mm Hg at 138°C	Verschueren, 1983
Specific gravity	1.285	Verscheuren, 1983
Melting/boiling/flash point	109-111°C/280°C/ND[a]	Weiss, 1980
Solubility in water	840 g/L at 0°C; 2,290 g/L at 30°C	Verscheuren, 1983
Log K_{ow}	0.80	Hansch and Leo, 1981
Bioconcentration factor (BCF)	Little or no potential for bioconcentration; rapidly degraded	Weiss, 1980; Verschueren, 1983
Conversion factors in air	1 mg/m^3 = 0.222 ppm 1 ppm = 4.5 mg/m^3	Calculated[b]
Odor threshold	ND; faint, aromatic odor	Mark et al., 1978
Henrys' Law constant	ND	

[a]ND: No data

[b]Formula: $\text{ppm by volume} = \text{mg/m}^3 \times \frac{24.45}{\text{mol. wt. in grams}}$

3. SOURCES OF EXPOSURE

3.1. Occurrence in Water

Specific data on the occurrence of resorcinol in water was not located in the searched literature. Based upon reports of its rapid degradation, resorcinol is not likely to be persistent in surface or groundwater systems.

3.2. Human Exposure

Human exposure to resorcinol is most likely to occur in occupational situations and would likely involve primarily inhalation and/or dermal exposure.

4. ENVIRONMENTAL FATE

Resorcinol undergoes auto-oxidation at 25°C with a half-time of 1612 hours at a pH of 9.0 (Verscheuren, 1983). Degradation by a variety of species of soil microbes has been reported (Larway and Evans, 1965; Chapman and Ribbons, 1976; Groseclose and Ribbons, 1981). Based upon data confirming its rapid degradation, resorcinol is not likely to be persistent in groundwater or surface water systems. Degradation of resorcinol by soil microbes may result in maleylacetate (Chapman and Ribbons, 1976) and pyrogallol (Groseclose and Ribbons, 1981).

5. TOXICOKINETICS

5.1. Absorption

Although no data were available regarding the absorption of resorcinol, its absorption may be inferred from the metabolism and excretion data noted below.

5.2. Distribution

No information was located in the available literature.

5.3. Metabolism

A glucuronide conjugate of resorcinol has been identified as a urinary excretion product (species not specified) thereby implying metabolism of the chemical (La Du et al., 1981).

5.4. Excretion

La Du et al. (1981) noted that resorcinol may be excreted as a glucuronide conjugate in the urine.

6. HEALTH EFFECTS

6.1. Noncancer Effects

6.1.1. Oral Exposure

6.1.1.1. Human. Oral exposure to resorcinol may result in tachycardia, dizziness, hepatomegaly, jaundice, unconsciousness and coma (Sittig, 1985). RTECS (1986) lists a human LDLo of 29 mg/kg for resorcinol.

6.1.1.2. Animal. Approximate lethal doses of resorcinol for rats and guinea pigs is 370 mg/kg, and for rabbits is 750 mg/kg (Verschueren, 1983). An oral LD_{50} of 301 mg/kg has been reported for rats (RTECS, 1986)

6.1.2. Other Exposure Routes

6.1.2.1. Human. Inhalation and dermal exposure are the most likely routes of exposure to resorcinol for humans. Contact dermatitis has been reported for pharmaceuticals and skin care products containing resorcinol, especially in workers such as hairdressers (Vilaplana et al., 1991), who have routine contact with the products. Occupational settings are responsible for most long-term exposures to this chemical. Although quantifiable data are lacking, workers in tire manufacturing facilities have reported health effects following long-term exposure to resorcinol (Sittig, 1985). Health effects resulting from various routes of exposure include dizziness, eye and respiratory tract irritation, and dermatitis (Sittig, 1985).

6.1.2.2. Animal. Noncancer toxicity data resulting from other than oral exposure to resorcinol was limited to a dermal LD_{50} of 3360 mg/kg for rabbits (RTECS, 1986).

6.2. Carcinogenicity

6.2.1. Oral Exposure

6.2.1.1. Human. No information was located in the available literature.

6.2.1.2. Animal. A gavage exposure study in male and female rats and mice showed no evidence of resorcinol-induced carcinogenicity (NTP, 1992). However, at this time no specific data were available from NTP regarding this study.

6.2.2. Other Exposure Routes

6.2.2.1. Human. No information was located in the available literature.

6.2.2.2. Animal. No information was located in the available literature.

6.3. Genotoxicity

Genotoxic activity has been reported for resorcinol. Resorcinol was shown to induce single-strand breaks in the DNA of isolated hepatocytes (Walles, 1992) and was also mutagenic (with activation) in *Salmonella typhimurium* TA98 and *Escherichia coli* B/r WP2 (Hosono et al., 1991).

7. EXISTING STANDARDS, CRITERIA, GUIDANCE

7.1. EPA RfDs, RfCs, CRAVE Classifications

RfD:	None established
RfC:	None established
Oral Slope Factor:	None established
Drinking Water Unit Risk:	None established
Inhalation Slope Factor:	None established
Inhalation Unit Risk:	None established
U.S. EPA CRAVE Cancer Classification:	U.S. EPA has not evaluated the carcinogenicity of resorcinol

7.2. IARC Carcinogenicity Classification

IARC (1987) has determined that resorcinol is not classifiable as to its carcinogenicity to humans.

7.3. OSHA, ACGIH, and NIOSH Standards and Criteria

OSHA (8-hr TWA):	None established
OSHA STEL:	None established
ACGIH TLV (8-hr TWA):	10 ppm (45 mg/m^3); skin notation (ACGIH, 1992)
STEL:	20 ppm (90 mg/m^3)
NIOSH RELs:	None established

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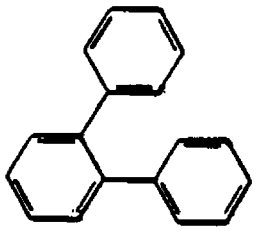
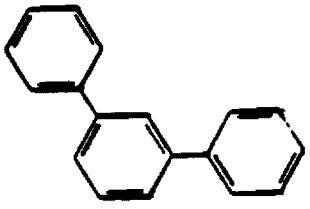
1. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Water, provides information on the health effects and other useful data that can aid in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. The EPA has an ongoing cooperative agreement with the Department of the Army to prepare drinking water Health Advisories (HA) for munitions and other environmental contaminants. Drinking water Toxicological Profiles are short summaries of the pertinent mammalian health effects literature, and are used by the Office of Water to determine if a data base is sufficient to allow the development of HAs. The following databases were searched for information on terphenyl: CANCERLINE, CHEMFATE, DART, DTIC, EMICBACK, ENVIROLINE RTECS, TOXLINE, TOXLINE65, TOXLIT, and TOXLIT65. Secondary sources were also used.

This Drinking Water Toxicological Profile summarizes information on terphenyl (CAS No. 26140-60-3). Terphenyls are aromatic hydrocarbons, members of the family of polyphenyls in which benzene rings are attached to one another in a chain-like manner (Weaver et al., 1978). Terphenyls occur naturally in petroleum oil; commercial preparations consist of mixtures of three isomers, the *ortho*-terphenyl (CAS No. 84-15-1), *meta*-terphenyl (CAS No. 92-06-8), and *para*-terphenyl (CAS No. 92-94-4) (Sandmeyer, 1981; RTECS, 1987). Terphenyls are used as heat transfer fluids and reactor coolants (ACGIH, 1986). A Japanese patent describes terphenyl as one of the active ingredients in pest-repellant compositions (Narasaki and Morita, 1991). Abstracts from the DTIC (1992) online data base suggest that the military may use terphenyls as laser dyes and heat transfer fluids, and in the synthesis of intermediates for the production of heat-resistant explosives. The structures of the three isomers of terphenyl are shown below.



ortho-Terphenyl



meta-Terphenyl

para-Terphenyl

2. SELECTED GENERAL INFORMATION

Physicochemical data for terphenyl are presented in Table 25.

TABLE 25. PHYSICOCHEMICAL DATA

Common name	terphenyl (D-14)	
Synonyms	terphenyl; Delowax OM; Delowas S; diphenylbenzene; diphenyl benzenes; triphenyls	RTECS, 1992 ACGIH, 1986
CAS Registry no.	26140-60-3	RTECS, 1992
RTECS No.	WZ6450000	RTECS, 1987
Chemical formula	$C_{18}H_{14}$	RTECS, 1992
Molecular weight	230.32	RTECS, 1992
Physical state	solid at room temp.	Sandmeyer, 1981
Vapor pressure	1.2 mm Hg at 149°C (commercial mixture)	Weaver et al., 1981
Specific gravity	1.14 (*o*-), 1.16 (*m*-), 1.24 (*p*-) at 25 °C	Sandmeyer, 1981
Melting/Boiling/Flash point	56.2°C (*o*-), 87.4°C (*m*-), 212.7 °C (*p*-)/332-381°C/ 163°C (*o*-), 135°C (*m*-), 240°C (*p*-)	ACGIH, 1986; Sandmeyer, 1981
	ND/60-145°C/364°C (commercial mixture)	Weaver et al., 1981
Solubility in water	insoluble	ACGIH, 1986
Log K_{OW}	ND[a]	
Bioconcentration factor (BCF)	ND	
Conversion factors in air	1 mg/m^3 = 0.106 ppm 1 ppm = 9.42 mg/m^3	Sandmeyer, 1981
Odor threshold	ND	
Henry's Law constant	ND	

[a]ND: no data

3. SOURCES OF EXPOSURE

3.1. Occurrence in Water

Smith and Maher (1984) reported concentrations of *m*-terphenyl ranging from 0.2-0.3 µg/L in coastal waters of Australia. These presumably resulted from oil spills.

3.2. Human Exposure

According to the National Occupational Hazard Survey of 1983 (RTECS, 1992) 14,872 workers, employed in 299 facilities, were potentially exposed to terphenyls. Adamson and Weeks (1973) reported that approximately 10^{-7} gm/liter of HB-40[1] were present in the atmosphere at a Canadian reactor site.

4. ENVIRONMENTAL FATE

No information was found in the available literature regarding the environmental fate of mixed terphenyls. *Pseudomonas desmolyticum* grows on *m*-terphenyl and degrades it (Catelani et al., 1970), suggesting that the mixture may also undergo biodegradation.

5. TOXICOKINETICS

5.1. Absorption

The rate of percutaneous absorption, estimated for terphenyl applied to rat tail 3 hours/day for 4-8 weeks, was 0.23 g/12 cm^2 skin/3 hours (Verkkala and Savolainen, 1983). The rate could be altered by changing skin contact time.

Scozzafava and Gerbaulet (1971) reported that, for rats and rabbits, an intragastric dose of ^{14}C-labeled o-terphenyl was rapidly absorbed, distributed and almost completely excreted within 48 hours.

5.2. Distribution

In the mouse, terphenyl (form not specified) accumulated in the liver, peaking at 4.5 hours (Adamson and Furlong, 1974).

5.3. Metabolism

No information was found in the available literature.

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[1]HB-40 is a 40% hydrogenated terphenyl mixture that is used as a coolant for nuclear reactors. The nonirradiated coolant contains o-, m-, and p-terphenyls and a small concentration of higher polymers (Adamson and Weeks, 1973). Reactor conditions alter the composition of the coolant, and irradiated HB-40 contains a reduced proportion of the terphenyl isomers, a small percentage of biphenyl and phenylcyclohexane, and an increased concentration of high polymers.

5.4. Excretion

Scoppa and Gerbaulet (1971, cited in Sandmeyer, 1981) reported that an intragastric dose of ^{14}C-labeled o-terphenyl was almost completely excreted within 48 hours. For the rat, excretion was mainly via the bile and for the rabbit, mainly in the urine.

In the mouse, terphenyl (form not specified) was completely cleared in 1 week (Adamson and Furlong, 1974).

6. HEALTH EFFECTS

6.1. Noncancer Effects

6.1.1. Oral Exposure

6.1.1.1. Human. No information was found in the available literature.

6.1.1.2. Animal. Oral LD_{50} values and systemic effects from subacute and subchronic studies of orally administered terphenyls are summarized in Tables 26 and 27. The physiologic responses of test animals vary according to the individual isomer and whether or not the test chemical was irradiated. (Toxicity data are presented for irradiated terphenyls to represent coolants for nuclear reactors that have undergone changes in composition under reactor conditions; see the discussion in the footnote on the preceding page.) The LD_{50} data of Adamson and Weeks (1973) indicate that, for rats, the irradiated terphenyl is approximately three times more toxic than the nonirradiated mixture, which appears to be practically nontoxic. Also, the individual isomers are generally more toxic than the mixture. Chronic oral studies in mice and rats with nonirradiated mixed and individual terphenyls, respectively, identified the kidney and liver as potential target organs for cumulative toxicity (Adamson and Weeks, 1973; Weeks et al., 1970; Khromenko et al., 1972).

Adamson and Weeks (1973) administered nonirradiated and irradiated HB-40 to male JAX mice by oral intubation at doses ranging from 20-2000 mg/kg body weight/day, 1-2 times/week for up to 16 weeks. The animals were killed at various times up to 6 months after exposure; changes were considered irreversible if they persisted for 6 months. Renal effects were dose-related, and the irradiated compound appeared to be more toxic. Table 26 shows the doses at which renal lesions were produced after 16 weeks of dosing. Both forms of HB-40 produced ultrastructural effects in the liver at doses $\geq$250 mg/kg, but the severity of the effects did not increase with dose or duration of exposure, and the changes were reversible. Thererfore, their clinical significance was not clear.

6.1.2. Other Exposure Routes

6.1.2.1. Human. The inhalation toxicity of the terphenyls appears to be relatively low in humans (Sandmeyer, 1981; Table 28). Both acute and chronic effects are reversible

TABLE 26. ORAL LD_{50} VALUES FOR TERPHENYLS IN RODENTS

Species/Sex	Material	Route	LD_{50}	Reference
Rats, male	terphenyl[a]	oral	17.5 g/kg	Adamson and Weeks, 1973
Rats, male	terphenyl (irradiated)[b]	oral	6.0 g/kg	Adamson and Weeks, 1973
Rats	*o*-terphenyl	oral	1.9 g/kg	Cornish et al., 1962
Rat	*m*-terphenyl	oral	2.4 g/kg	Cornish et al., 1962
Rat	*p*-terphenyl	oral	>10 g/kg	Cornish et al., 1962
Rat	hydroterphenyl	oral	6.6 g/kg	Khromenko et al., 1972
Mouse	terphenyl	oral	13.2 g/kg	RTECS, 1992
Mice, male	terphenyl (nonirradiated)	oral	12.5 g/kg	Adamson and Weeks, 1973
Mice, male	terphenyl (irradiated)	oral	6.0 g/kg	Adamson and Weeks, 1973
Mouse	hydroterphenyl[c]	oral	4.2 g/kg	Khromenko et al., 1972

[a]Chemicals called terphenyl or terphenyls are assumed to be a mixture of the three isomers unless otherwise indicated.
[b]Mixtures of terphenyls are used as coolants in nuclear reactors; the finding of terphenyls in the atmosphere at a reactor site prompted the testing of irradiated, as well as nonirradiated terphenyls.
[c]Partially hydrogenated terphenyls are derivatives of terphenyl.

TABLE 27. PHYSIOLOGIC RESPONSE TO ORALLY ADMINISTERED TERPHENYLS

Species/Sex	Material	Effect Level/Route	Effects	Reference
JAX mice, 10 males/group	terphenyl (mixed, nonirradiated and mixed, irradiated)	≥250 mg/kg/day x 8 weeks by intubation	changes in cytoplasm of hepatocytes - reversible[a]	Adamson and Weeks, 1973
JAX mice, 10 males/group	terphenyl (mixed, nonirradiated)	600 mg/kg/day x 16 weeks by intubation	changes in proximal tubules of kidneys - reversible	Adamson and Weeks, 1973
JAX mice, 10 males/group	terphenyl (mixed, irradiated)	600 mg/kg/day x 16 weeks by intubation	interstitial nephritis - irreversible	Adamson and Weeks, 1973
JAX mice, 10 males/group	terphenyl (mixed, nonirradiated)	1200 mg/kg/day x 16 weeks	interstitial nephritis - irreversible	Adamson and Weeks, 1973
JAX mice, 10 males/group	terphenyl (mixed, irradiated)[b]	1200 mg/kg/day x 16 weeks	death	Adamson and Weeks, 1973
Rat	*o*-terphenyl	250-500 mg/kg/day x 30 days	increased liver and kidney to body weight ratios	Weeks et al., 1970
Rat	*m*-terphenyl	250-500 mg/kg/day x 30 days	increased liver to body weight ratios	Weeks et al., 1970
Rat	*p*-terphenyl	2500-5000 mg/kg/day x 1 month	"insignificant weight decreases, intensification of antitoxic functions of the liver"	Khromenko, 1972

[a]Doses <250 mg/kg/day produced no lesions.
[b]Mixtures of terphenyls are used as coolants in nuclear reactors; the finding of terphenyls in the atmosphere at a reactor site prompted the testing of irradiated, as well as nonirradiated terphenyls.

TABLE 28. PHYSIOLOGIC RESPONSE TO TERPHENYLS ADMINISTERED VIA INHALATION AND SKIN APPLICATION

Species	Material	Route	Dose/Concentration	Effects	Reference
Human	terphenyl	inhalation	spills with short-term exposure	headaches and sore throat, reversible within 24 hours	Weeks et al., 1970
Human	terphenyl	inhalation	0.01-0.94 ppm (0.094-0.89 mg/m^3) (chronic)	no significant effect on blood pressure, pulmonary function, or isocitric dehydrogenase	Weeks et al., 1970
Human	terphenyl	skin	0.01-0.94 ppm (0.094-0.89 mg/m^3) (chronic)	nonspecific skin rashes in 6/200; no skin sensitization	Weeks et al., 1970
Rat	terphenyl	inhalation	100 ppm (0.94 g/m^3) (acute)	no mortality; pulmonary pathology after 1-hour exposure	Amdur and Creasia, 1966
Rat	terphenyl	inhalation	320 ppm (3.01 g/m^3) (acute)	4/8 deaths due to asphyxiation death caused by crystalline plugs in the trachea	Amdur and Creasia, 1966
Rat	HB-40[a]	inhalation	50 mg/m^3 7 hours/day for up to 8 days	increased number of vacuolated mitochondria (v.m.) in pulmonary cells (transient effect; number of v.m. directly related to exposure duration)	Adamson et al., 1969
Rat	terphenyl	skin application	applied to the rat tail 3 hours/day for 4-8 weeks	interference with nerve-muscle interaction in the tail	Verkkala and Savolainen, 1983
Laboratory animals	*p*-terphenyl	inhalation	0.3 ppm (3 mg/m^3) for 1 month	no effect	Khromenko, 1972
Laboratory animals	*p*-terphenyl	inhalation	3.7 ppm (35 mg/m^3) for 1 month	functional and morphological changes (target organ not identified)	Khromenko, 1972
Laboratory animals	*p*-terphenyl	inhalation	212 ppm (2000 mg/m^3) 4 hr/day, 5 days/week for 8 weeks	Cell debris in lungs, but rapidly cleared	Adamson, 1973

[a]Nonirradiated mixture of hydrogenated terphenyls used as an organic coolant in reactors.

(Weeks et al., 1970). Concentrations of terphenyls above 10 mg/m^3 have been associated with eye and respiratory irritation in workers (ACGIH, 1986).

Weeks and Lentle (1970) conducted a clinical survey of 47 workers constantly exposed to HB-40 concentrations ranging from 0.094 to 0.89 mg/m^3 and exposure durations ranging from 6 months to 7 years. With the exception of skin irritation, which was particularly apparent among workers wearing protective clothing that increased the moistness of the skin, there was no evidence of adverse effects.

6.1.2.2. Animal. The effects of terphenyls administered to rats via inhalation and to the skin are summarized in Table 28. Short-term inhalation of 100 ppm for 1 hour resulted in pulmonary pathology; 320 ppm (acute exposure, exact duration not given) caused death by asphyxiation, attributed to crystalline plugs in the trachea (Amdur and Creasia, 1966; Table 28). Inhalation of *p*-terphenyl produced no adverse effects at 0.3 ppm (1 month), functional and morphological changes at 3.7 ppm (1 month; target organ not identified) (Khromenko, 1972), and cell debris in the lungs at 212 ppm (2 months) (Adamson, 1973). Terphenyl applied to the skin had neuromuscular effects in one study (Verkkala and Savolainen, 1983).

6.2. Carcinogenicity

6.2.1. Oral Exposure

6.2.1.1. Human. No information was found in the available literature.

6.2.1.2. Animal. No information was found in the available literature.

6.2.2. Other Exposure Routes

6.2.2.1. Human. In the study of Weeks and Lentle (1970; described above), 47 workers constantly exposed to HB-40 (0.094 to 0.89 mg/m^3) for 6 months to 7 years did not develop skin tumors.

6.2.2.2. Animal. Sandmeyer (1981) briefly alluded to the finding of one papilloma in a chronic skin study that suggested cocarcinogenic potential for terphenyls, similar to that of tars (Henderson and Weeks, 1973). No other information was found in the available literature.

6.4. Genotoxicity

No information was found in the available literature.

7. EXISTING STANDARDS, CRITERIA, GUIDANCE

7.1. EPA RfDs, RfCs, CRAVE Classifications

RfD:	None established
RfC:	None established
Oral slope factor:	None established
Drinking Water Unit Risk:	None established
Inhalation Slope Factor:	None established
Inhalation Unit Risk:	None established
EPA CRAVE Cancer Classification:	Not established

7.2. IARC Carcinogenicity Classification

Not established

7.3. OSHA, ACGIH, and NIOSH Standards and Criteria

OSHA (8-hr TWA):	None established
OSHA STEL:	None established
OSHA Ceiling Limit:	0.5 ppm (≈5 mg/m^3) (OSHA, 1989)
ACGIH (8-hr TWA):	None established
ACGIH Ceiling Limit:	0.5 ppm (≈5 mg/m^3) (ACGIH, 1986)
NIOSH RELs:	None established

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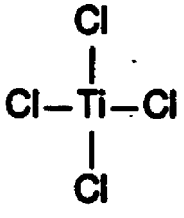
1. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Water, provides information on the health effects and other useful data that can aid in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. The EPA has an ongoing cooperative agreement with the Department of the Army to prepare drinking water Health Advisories (HA) for munitions and other environmental contaminants. Drinking water Toxicological Profiles are short summaries of the pertinent mammalian health effects literature, and are used by the Office of Water to determine if a data base is sufficient to allow the development of HAs. The following databases were searched for information on titanium tetrachloride: CANCERLINE, CHEMFATE, DART, DTIC, EMICBACK, ENVIROLINE, RTECS, TOXLINE, TOXLINE65, TOXLIT, and TOXLIT65. Secondary sources were also used.

This Drinking Water Toxicological Profile summarizes information on titanium tetrachloride, a metal halide in the +4 oxidation state. A commercially important compound, titanium tetrachloride is used as a polymerization catalyst and in the production of titanium metal and pigments (such as titanium dioxide and titanous chloride) (Stokinger, 1981; Nordman and Berlin, 1986). Titanium tetrachloride is the starting material for the substitution of chloride by alcohols to give polymeric alcoholates or mixed substitution products with amines (Wennig and Kirsch, 1988) and has been used as a mordant dye, and in the manufacture of iridescent glass and artificial pearls (Budavari et al., 1989). Titanium tetrachloride fumes in moist air, forming a dense, persistent white cloud (Budavari et al., 1989); the military uses the chemical in smoke screens and smoke trails (DTIC, 1992). The military has also used titanium tetrachloride in experimental electro- and photodeposition studies, and as an intermediate in the synthesis of organic titanium compounds (DTIC, 1992). The structure for titanium tetrachloride is shown below.



Titanium tetrachloride

2. SELECTED GENERAL INFORMATION

Physicochemical data for titanium tetrachloride are presented in Table 29. Heated to decomposition, it liberates toxic fumes of Cl^- and HCl (Sax, 1984).

TABLE 29. PHYSICOCHEMICAL DATA

Common name	titanium tetrachloride	Budavari et al., 1989
Synonyms	titanium chloride	RTECS, 1987
CAS Registry No.	7550-45-0	RTECS, 1987
RTECS No.	XR1925000	RTECS, 1987
Chemical formula	$TiCl_4$	RTECS, 1987
Molecular weight	189.70	RTECS, 1987
Physical state	colorless liquid	Budavari et al., 1989
Vapor pressure	10 mm Hg at 21.3°C	Sax, 1984
Specific gravity	1.772 at 25°C/25°C[a]	Sax, 1984
Melting/boiling/flash point	-25°C/136.4°C/ND	Stokinger, 1981
Solubility in water	soluble in cold water (quantitatative data not found)	Budavari et al., 1989
Log K_{ow}	ND[b]	
Bioconcentration factor (BCF)	ND	
Conversion factors in air	1 mg/m^3 = 0.1289 ppm 1 ppm = 7.76 mg/m^3	Calculated[c]
Odor threshold	ND; penetrating acid odor	Budavari et al., 1989
Henry's Law constant	ND	

[a]Density of liquid at 25°C relative to the density of water at 25°C
[b]ND = no data

[c]Formula: $\text{ppm by volume} = \text{mg/m}^3 \times \frac{24.45}{\text{mol. wt. in grams}}$

3. SOURCES OF EXPOSURE

3.1. Occurrence in Water

Titanium tetrachloride hydrolyzes rapidly in water (U.S. EPA, 1988); therefore, it would not be expected to occur in drinking or ambient water.

3.2. Human Exposure

Titanium is not an essential element for humans (Stokinger et al., 1981). However, it is a ubiquitous element and its distribution in the body is general in all organs and tissues, but in low concentrations (Stokinger et al., 1981). The body burden for titanium is approximately 15 mg, most of which is stored in the lungs, probably the result of inhalation exposure (Goyer, 1986; Wennig and Kirsch, 1988).

Exposure of workers to fumes and vapors of titanium tetrachloride can occur during the handling of titanium tetrachloride and in the chlorinating department during production of titanium dioxide (Stokinger et al., 1981; Nordman and Berlin, 1986; Sax, 1984). However, U.S. EPA (1988) assumes that, because titanium tetrachloride hydrolyzes rapidly in water and fumes in the presence of moist air, inhalation exposure would be limited primarily to its hydrolysis products. Splashing of the skin and eyes with the liquid titanium tetrachloride has occurred in the workplace (Nordman and Berlin, 1986).

Smokes comprise another potential source of exposure to titanium tetrachloride. The compound is a product of the combustion of titanium dioxide-hexachloroethane mixtures that are used to make smokes (Karlsson et al., 1968).

4. ENVIRONMENTAL FATE

Titanium tetrachloride hydrolyzes rapidly in water and fumes in the presence of moist air; its proposed hydrolysis products include $TiOCl_2$ and HCl (Stokinger, 1981; Sax, 1984, respectively). No data were found to estimate the residence time for titanium tetrachloride in water or air.

5. TOXICOKINETICS

5.1. Absorption

No data were found for the absorption of titanium tetrachloride. Titanium compounds are generally considered to be poorly absorbed via ingestion and inhalation (Nordman and Berlin, 1986); approximately 3% of an oral dose of titanium is absorbed (Goyer, 1986). However, studies

in mice that were exposed to 5 mg/L potassium titanium oxalate in the drinking water for up to 268 days suggest that soluble titanium compounds are readily absorbed from the G.I. tract (Schroeder et al., 1963).

5.2. Distribution

No data were found for the distribution of titanium tetrachloride. In the general population, it appears that low concentrations of titanium are distributed to all organs and tissues; titanium accumulates in the lungs with age, but has no special affinity for other internal organs (Stokinger et al., 1981). An estimated one-third of inhaled titanium is retained in the lungs (Goyer, 1986). The experiments (described above) with soluble potassium titanium oxalate in mice showed that, compared with controls, titanium levels in the exposed animals were 4 times greater in the lungs and heart, 15 times greater in the kidney, 7.5 times greater in the liver, and 4.7 times greater in the spleen (Schroeder et al., 1963). Ferrin (1971) reported that the amount of titanium dioxide (unlike titanium tetrachloride, this compound is insoluble in water) deposited in the lungs of rats was dose-related.

5.3. Metabolism

No information was found in the available literature. Generally, soluble salts of Group IV metals such as titanium undergo hydrolysis and subsequent olation at tissue pH levels (Luckey and Venugopal, 1977). Based on this and the rapid hydrolysis of titanium tetrachloride in water, the compound (if it remains intact long enough) would be expected to undergo hydrolysis in biological tissues.

5.4. Excretion

No information specific to titanium tetrachloride was found in the available literature. About 3% of an oral dose of titanium is absorbed; the bulk of the absorbed dose is excreted in the urine (Goyer, 1986). About one-third of inhaled titanium remains in the lung, probably for long periods of time.

6. HEALTH EFFECTS

6.1. Noncancer Effects

The high acute toxicity of titanium tetrachloride is attributed to the hydrochloric acid liberated by the hydrolysis of the chemical (Wennig and Kirsch, 1988).

6.1.1. Oral Exposure

6.1.1.1. Human. No information was found in the available literature.

6.1.1.2. Animal. No information was found in the available literature.

6.1.2. Other Exposure Routes

6.1.2.1. Human. Titanium tetrachloride is highly irritating to the skin, eyes, mucous membranes and by inhalation (Sax, 1984).

A worker inhaled the vapor from a cloud that formed when a glass pipe broke, releasing titanium tetrachloride to the air (Park et al., 1984). He developed progressive carbon-dioxide retention and respiratory insufficiency; bronchoscopy revealed 35-40 fleshy polyps on both sides of the bronchial tree, some occluding the bronchi upon inspiration. Biopsy of the lesions demonstrated granulation tissue with acute inflammation. The authors concluded that the polyps were part of the response to the titanium tetrachloride-induced tracheobronchial injury.

Workers producing titanium tetrachloride exhibited hyperemia and thinning of the mucosa of the respiratory tract as well as bronchitis (Kokorev et al., 1960). The investigators presumed that exposure to titanium tetrachloride and its hydrolysis product had caused these effects. Ten workers exposed to low concentrations of titanium tetrachloride for 4 or more years did not appear to have developed any progressive pulmonary lesions or dysfunction (Lawson, 1961).

An epidemiological study examined lung cancer mortality and other respiratory parameters in workers exposed to titanium tetrachloride (Fayerweather et al., 1992). The results of the cancer study are discussed in Section 6.3.1. A total of 2477 employees from two titanium dioxide plants comprised the study. The titanium tetrachloride workers showed no statistically significant increase in fatal respiratory diseases (cohort analysis) and no statistically significant association between cancer, chronic respiratory disease, and chest x-ray abnormalities (nested case-control analysis). There were no cases of pulmonary fibrosis.

Two Russian studies reported systemic effects resulting from occupational exposure to titanium tetrachloride. In the first study, a group of workers exposed to the chemical for 3 to 5 years exhibited increased levels of urinary delta-aminolevulinic acid and coproporphyrin levels; the results in humans were supported by studies in experimental animals exposed for 120 days (concentrations were not given) (Beloslyudtseva, 1974). Another group of workers experienced chronic respiratory tract disorders (such as bronchitis), myocardial dystrophy, metabolic disorders, and blood and nervous system changes (Beloskurskaya, 1976). No other details were available.

6.1.2.2. Animal. The LC_{Lo} for titanium tetrachloride in the mouse is 10 mg/m^3 for a 20 hour inhalation exposure (Stokinger et al., 1981), and in mice and rats, LC_{50} values were 100 mg/m^3/2 h and 460 mg/m^3/4 h, respectively (RTECS, 1987). Sprague-Dawley rats exposed to titanium tetrachloride at concentrations of 370-2900 mg/m^3 for 10 minutes showed signs of irritation, but did not die (Karlsson et al., 1986).

Dogs inhaling titanium tetrachloride fumes for 1 to 2 hours per day, for three exposures spread over several days (concentration not measured), showed respiratory distress with vomiting during and after each exposure (Zapp, 1949a). One dog collapsed (but recovered) after the second exposure and one died after the third exposure (4 days after the second exposure).

Death resulted from severe bronchitis and edema, attributed to the inhalation of HCl. Another dog, sacrificed 4 days after the third exposure, had focal congestion and hemorrhage of the lungs and deposits of titanium particles in the alveoli. A continuation of this study examined the chronic effects from inhaling titanium tetrachloride (Zapp, 1949b). Four dogs were exposed 6 hours/day, 5 days per week for 9 weeks to average atmospheric titanium concentrations of 8.4 ppm and volatile chloride levels averaging 6.8 ppm. The dogs had increased leukocyte counts and microscopic lesions of the lungs. These lesions consisted of titanium and monocytes grouped around the bronchi. The foci contained masses of necrotic cells associated with proliferation of connective tissue cells, a lesion that results in scar tissue formation, reduced pulmonary capacity, and increased susceptibility to infection over extended exposure.

In a chronic toxicity study, Lee et al. (1986) exposed Charles River (CD) rats to vapors of the hydrolysis products of titanium tetrachloride. These products formed when titanium tetrachloride vapors, directed by a nitrogen stream into exposure chambers, reacted with the air in the chambers. The animals (100 males, 100 females/group) inhaled 0, 0.1, 1.0 or 10.0 mg/m^3 of the hydrolysis products 6 hours/day, 5 days/week for 2 years. Dose-related effects of the treatment included the following: degeneration of alveolar macrophages (significant at 10 mg/m^3); increased cholesterol granulomas (significant at 10 mg/m^3); damage to type I alveolar pneumocytes, thought to have triggered hyperplasia of type II pneumocytes in the alveolar walls (significant at all concentrations); transformation of ciliated columnar cells into epithelial cells (significant at 10 mg/m^3); increased lung weights (statistically significant at 10 mg/m^3); appearance of yellow foci on surface of lungs (significant at 1.0 and 10 mg/m^3); and lymphocytopenia and erythrocytosis (statistically significant at 10 mg/m^3).

Liquid titanium tetrachloride applied to the clipped skin of albino guinea pigs twice per day for three successive days resulted in the destruction of the outer layers of the skin, comparable to a second-degree thermal burn (Zapp, 1949a).

6.2. Carcinogenicity

6.2.1. Oral Exposure

6.2.2.1. Human. No information was found in the available literature.
6.2.2.2. Animal. No information was found in the available literature.

6.3. Other Exposure Routes

6.3.1. Human

An epidemiological study examined lung cancer mortality in workers exposed to titanium tetrachloride (Fayerweather et al., 1992). A total of 2477 employees from two titanium dioxide plants comprised the study. Of those, 969 employees were observed for cancer incidence from 1956 through 1985 and for mortality from 1935 through 1983. In comparison to the reference group, the titanium tetrachloride workers showed no statistically significant increase in lung

cancer (cohort analysis) and no statistically significant association between lung cancer, chronic respiratory disease, and chest x-ray abnormalities (nested case-control analysis).

6.3.2. Animal

Lee et al. (1986) exposed Charles River (CD) rats (100/group) to vapors of the hydrolysis products of titanium tetrachloride. The animals (100 males, 100 females/group) inhaled 0, 0.1, 1.0 or 10.0 mg/m^3 of the hydrolysis products 6 hours/day, 5 days/week for 2 years. Squamous cell carcinomas developed in the alveoli of 2/69 male and 3/74 female rats exposed to 10 mg/m^3. U.S. EPA (1988) questioned the relevance of these tumors, which may result from chronic tissue irritation from dust cells and cellular debris, to titanium tetrachloride-induced lung tumors in humans. Squamous cell carcinomas develop in the bronchi of humans, not in the alveoli, and cystic keratinizing squamous cell carcinoma is a unique chemically-induced lung tumor in rats that does not usually occur spontaneously in other animals or humans. Lee et al. (1986) recommended additional studies to determine if the lesions were neoplastic or metaplastic.

6.4. Genotoxicity

Titanium tetrachloride was negative in the rec-assay with *Bacillus subtilis* (Kada et al., 1980).

7. EXISTING STANDARDS, CRITERIA, GUIDANCE

7.1. EPA RfDs, RfCs, CRAVE Classifications

RfD:	None established
RfC:	None established
Oral slope factor:	None established
Drinking Water Unit Risk:	None established
Inhalation Slope Factor:	None established
Inhalation Unit Risk:	None established
EPA CRAVE Cancer Classification:	Not established
Chronic Reportable Quantity(RQ):	100 (U.S. EPA, 1988) (for hydrolysis products; found no evidence that this is a final value)

7.2. IARC Carcinogenicity Classification

Not established

7.3. OSHA, ACGIH, and NIOSH Standards and Criteria

OSHA (8-hr TWA):	None established
OSHA STEL:	None established
OSHA Ceiling Limit:	None established
ACGIH (8-hr TWA):	None established
ACGIH Ceiling Limit:	None established
NIOSH RELs:	None established

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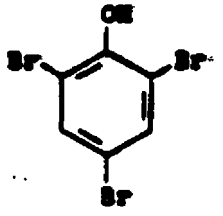
1. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Water, provides information on the health effects and other useful data that can aid in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. The EPA has an ongoing cooperative agreement with the Department of the Army to prepare drinking water Health Advisories (HA) for munitions and other environmental contaminants. Drinking Water Toxicological Profiles are short summaries of the pertinent mammalian health effects literature, and are used by the Office of Water to determine if a data base is sufficient to allow the development of HAs. The following data bases were searched for information on 2,4,6-tribromophenol: CANCERLINE, CHEMFATE, DART, DTIC, EMICBACK, ENVIROLINE, RTECS, TOXLINE, TOXLINE65, TOXLIT, AND TOXLIT65. Secondary sources were also used.

This Drinking Water Toxicological Profile summarizes information on 2,4,6-tribromophenol, an organic bromine compound, prepared by controlled bromination of phenol (Budavari et al., 1989). It is soluble in alcohol, chloroform, ether, and caustic alkaline solution, and has a sweet taste and penetrating bromine odor (Sax and Lewis, 1987). When heated to decomposition, it emits toxic fumes of bromide ion (Sax, 1984). 2,4,6-Tribromophenol is used as a fire retardant, antiseptic, germicide, and fungicide (Stenger, 1978). The structural formula for 2,4,6-tribromophenol is shown below.



2,4,6-Tribromophenol

2. SELECTED GENERAL INFORMATION

Physicochemical data for 2,4,6-tribromophenol are presented in Table 30.

TABLE 30. PHYSICOCHEMICAL DATA

Common name	2,4,6,-tribromophenol	
Synonyms	tribromophenol, bromol	RTECS, 1992
CAS Registry No.	118-79-6	
RTECS No.	SN1225000	RTECS, 1992
Chemical formula	$C_6H_2Br_3OH$	Budavari et al., 1989
Molecular weight	330.83	Budavari et al., 1989
Physical state	crystalline solid	Budavari et al., 1989
Vapor pressure	ND[a]	
Specific gravity	2.55 at 20°C/20°C[b]	Sax and Lewis, 1987
Melting/Boiling/Flash point	96°C(sublimes)/244°C/ND	Sax and Lewis, 1987
Solubility in water	almost insoluble; soluble in 70 mg/L at 15°C	Sax and Lewis, 1987; Budavari et al., 1989
Log K_{ow}	3.34	Velsicol Chem. Corp., 1990a
Bioconcentration factor (BCF)	203 (calculated)	Lyman et al., 1982
Conversion factors in air	1 ppm = 13.53 mg/m^3 1 mg/m^3 = 0.074 ppm	calculated[c]
Odor threshold	ND	
Henrys' Law constant	ND	

[a]ND: no data
[b]Density of liquid at 20°C relative to the density of water at 20°C

[c]Formula: $\text{ppm by volume} = \text{mg/m}^3 \times \frac{24.45}{\text{mol. wt. in grams}}$

3. SOURCES OF EXPOSURE

3.1. Occurrence in Water

2,4,6-Tribromophenol is a potential drinking water pollutant (Devillers and Chambon, 1988; Sithole and Williams, 1986). Low levels of the compound have been detected in estuarine sediments of the river Rhone in France (Tolosa et al., 1991) and in river and marine sediments in Japan (Tolosa et al., 1991; Watanabe et al., 1985). The observed seaward negative gradient of concentrations in the river Rhone suggested a land-based discharge as the principal source, probably originating in automotive emissions washed out to the river by urban runoff (Tolosa et al., 1991). There were no data regarding the concentrations of 2,4,6-tribromophenol in U.S. surface or drinking water.

Bench-scale experiments showed that chlorination of distilled water containing bromide ion and phenol resulted in the formation of 2,4,6-tribromophenol (Sweetman and Simmons, 1980). Low levels of brominated phenols, including 2,4,6-tribromophenol, were are also formed under normal chlorination conditions of drinking water or wastewater (Ventura and Rivera, 1986; Watanabe et al., 1985; Watanabe et al., 1984).

3.2. Human Exposure

The extent of occupational or environmental exposure to 2,4,6-tribromophenol is not known, although its potential use a flame retardant and as a component of germicides or fungicides suggests the likelihood of environmental release. Automotive emissions from leaded gasoline containing additives such as dibromoethane are another potential source of 2,4,6-tribromophenol exposure. Radical halogenation of aromatic phenols during combustion may result in the formation of 2,4,6-tribromophenol and other halogenated compounds (Muller and Buser, 1986).

4. ENVIRONMENTAL FATE

Bacteria encountered in a sewage treatment plant were ineffective in biodegrading 2,4,6-tribromophenol (Velsicol Chem. Corp., 1990b). However, the compound was biodegraded by *Pseudomonas* at a concentration of 200 mg/L at 30°C, with 14% ring disruption occurring in 120 hours (Verschueren, 1983). Progressive dehalogenation was the primary degradation process in anoxic marine sediments incubated with halogenated phenols, including bromophenols (Abrahamsson and Klick, 1991).

Photodegradation of 2,4,6-tribromophenol in aqueous solution was biphasic, with half-lives of 1 hour and 11.5 hours for the first and second phases, respectively. 3,5-Dibromo-1,2-dihydroxybenzene was a major degradation product, other degradation products included monobromodihydroxybenzene and carbon dioxide (Velsicol Chem. Corp., 1990c).

A screening study for potential flame retardants showed that thermal decomposition of 2,4,6-tribromophenol occurs at temperatures far above ambient levels, i.e., 600°C, resulting in the releases of benzenes and dibenzodioxins (Thoma and Hutzinger, 1989).

5. TOXICOKINETICS

5.1. Absorption

Quantitative data on absorption of 2,4,6-tribromophenol were not available. The compound is rapidly absorbed from the gastrointestinal tract (Deichmann and Keplinger, 1981) and is also absorbed through the skin (Sax, 1984). Absorption of 2,4,6-tribromophenol following inhalation exposure may be inferred from toxicity and excretion data (Intl. Res. and Dev. Corp., 1990b; Indust. Bio-Test Labs., 1990b).

5.2. Distribution

Rats administered oral doses of 4-5 mg/kg of 2,4,6-tribromophenol retained only 0.005% of the dose after 48 hours, with residues occurring in the kidneys, liver, and lungs. The retention half-life in blood was 2 hours and ranged from 1.45 to 2.3 hours in other tissues (Velsicol Chem. Corp., 1990d). 2,4,6-Tribromophenol was detected in fatty tissue of rats fed 1000 ppm for 1-3 weeks, but was not detected after a 14-day recovery period (Ind. Biotest Labs., 1990a).

5.3. Metabolism

No information was found in the available literature.

5.4. Excretion

Following oral administration, rats excreted 50-92% of the dose in the urine and 4-14% in feces (Velsicol Chem. Corp., 1990d).

6. HEALTH EFFECTS

6.1. Noncancer Effects

6.1.1. Oral Exposure

6.1.1.1. Human. No information was found in the available literature.

6.1.1.2. Animal. Oral LD_{50} values for rats range from 200 mg/kg (Sax, 1984) to 5012 mg/kg (Intl. Res. Dev. Corp., 1990a). Acute exposure produced increased respiratory rate and amplitude followed by loss of muscle tone, collapse, and death (Deichmann and Keplinger, 1981). Pathological changes were most marked in the lungs as manifested by congestion and hemorrhages. Large doses of 2,4,6-tribromophenol also produced inflammation of the mucous membranes of the pylorus and fundus of the stomach with corrosion and hemorrhages.

In a teratology study, six groups of five pregnant rats were treated by gavage with 2,4,6-tribromophenol at dose levels of 10, 30, 300, 1000, or 3000 mg/kg/day on days 6 through 15 of gestation (Velsicol, 1990e). There were no treatment-related effects on maternal body weights, food consumption, number of corpora lutea, viable or nonviable fetuses, resorptions, or

implantations at doses of ≤300 mg/kg. Exposure to 1000 mg/kg/day produced decreased weight gain, increased postimplantation losses, and a slight decrease in the number of viable fetuses. Increased mortality occurred at 3000 mg/kg. Terata were not observed at any dose level.

6.1.2. Other Exposure Routes

6.1.2.1. Human. 2,4,6-Tribromophenol is a strong irritant to skin, eyes, and mucous membranes (Sax, 1984).

6.1.2.2. Animal. Decreased motor activity, eye squint, slight dyspnea, erythema, and ocular porphyrin discharge was observed in rats exposed by inhalation to 50,000 mg/m^3 for 4 hours (Intl. Res. and Dev. Corp., 1990b). Inhalation exposure of male and female rats to 100 or 1000 mg/m^3 of 2,4,6-tribromophenol dust (6 hours/day, 5 days/week) for 3 weeks produced hypoactivity, salivation, lacrimation, and red nasal discharge. Compared with controls, lower body weight gains were seen in females exposed to 100 mg/m^3 and in both sexes exposed to 1000 mg/m^3 (Indust. Bio-Test Labs., 1990b).

Intradermal injection of a 0.1% solution of 2,4,6-tribromophenol in saline induced slight sensitization in guinea pigs (Intl. Res. and Dev. Corp., 1990c). Application of 100, 300, or 1000 mg/kg of 2,4,6-tribromophenol to the skin of rabbits (5 days/week) for 4 weeks produced slight skin irritation, but no other adverse effects (Indust. Bio-Test Labs., 1990c).

6.2. Carcinogenicity

6.2.1. Oral Exposure

6.2.1.1. Human. No information was found in the available literature.

6.2.1.2. Animal. No information was found in the available literature.

6.2.2. Other Exposure Routes

6.2.2.1. Human. No information was found in the available literature.

6.2.2.2. Animal. No information was found in the available literature.

6.3. Genotoxicity

2,4,6-Tribromophenol was not mutagenic in several *Salmonella* strains in the presence or absence of metabolic activation (Zeiger et al., 1987).

7. EXISTING STANDARDS, CRITERIA, GUIDANCE

7.1. EPA RfDs, RfCs, CRAVE Classifications

RfD:	None established
RfC:	None established
Oral slope factor:	None established
Drinking Water Unit Risk:	None established
Inhalation Slope Factor:	None established
Inhalation Unit Risk:	None established
EPA CRAVE Cancer Classification:	Not evaluated

7.2. IARC Carcinogenicity Classification

Not evaluated

7.3. OSHA, ACGIH, and NIOSH Standards and Criteria

OSHA (8-hr TWA):	None established
OSHA STEL:	None established
OSHA Ceiling Limit:	None established
ACGIH (8-hr TWA):	None established
NIOSH RELs:	None established

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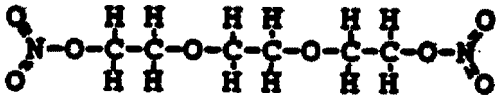
1. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Water, provides information on the health effects and other useful data that can aid in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. The EPA has an ongoing cooperative agreement with the Department of the Army to prepare drinking water Health Advisories (HA) for munitions and other environmental contaminants. Drinking water Toxicological Profiles are short summaries of the pertinent mammalian health effects literature, and are used by the Office of Water to determine if a data base is sufficient to allow the development of HAs. The following data bases were searched for information on triethylene glycol dinitrate: TOXLINE, TOXLINE65, TOXLIT, TOXLIT65, CANCERLINE, DART, EMICBACK, CHEMFATE, ENVIROLINE, DTIC and RTECS. Secondary sources were also used.

This Drinking Water Toxicological Profile summarizes information on triethylene glycol dinitrate (TEGDN). TEGDN, one of the more versatile glycol nitrates, has a variety of military uses. It appears to be most commonly used as an energetic plasticizer in warheads and solid rocket propellent mixtures (Macy and Saffitz, 1947; Wells, 1977), and it is also used as a component of illuminating flares (Handler and Sbrocca, 1972) and can also be used as the primary explosive charge in mines (Heathcote, 1976). The structure of triethylene glycol dinitrate is shown below:



Triethylene glycol dinitrate

2. SELECTED GENERAL INFORMATION

General information, physical and chemical data are presented in Table 31.

TABLE 31. PHYSICOCHEMICAL DATA

Common name	triethylene glycol dinitrate	
Synonyms	TEGDN; ethanol, 2,2'-[1,2-ethanediyl*bis*(oxy)]*bis*-dinitrate	Sax and Lewis, 1989 Rowe and Wolf, 1978
CAS registry no.	111-22-8	
RTECS no.	YE5500000	RTECS, 1987
Chemical formula	$C_6H_{12}N_2O_8$	Rowe and Wolf, 1978
Molecular weight	240.20	Sax and Lewis, 1989
Physical state	liquid	Forbes and Coleburn, 1973
Vapor pressure	ND[a]	
Specific gravity	ND	
Melting/boiling/flash point (°C)	ND	
Solubility in water	slight	Macy and Saffitz, 1947
Log K_{ow}	ND	
Bioconcentration factor (BCF)	ND	
Conversion factors in air	1 ppm = 9.80 mg/m^3 1 mg/m^3 = 0.102 ppm	calculated[b]
Henrys' law constant	ND	

[a] ND: No data

[b] Formula: $\text{ppm by volume} = \text{mg/m}^3 \times \frac{24.45}{\text{mol. wt. in grams}}$

3. SOURCES OF EXPOSURE

3.1. Occurrence in Water

No information was located in the available literature.

3.2. Human Exposure

Exposure to TEGDN is primarily limited to workers in the munitions industry where the compound is increasingly being used (Hiatt and Korte, 1989). Possible exposure routes are oral, inhalation and dermal.

4. ENVIRONMENTAL FATE

TEGDN is slightly soluble in water where it is hydrolyzed to the mononitrate (Macy and Saffitz, 1947). It has been shown to undergo biodegradation resulting in the sequential cleaving of the nitrate groups in the presence of an activated sludge inoculum containing mineral salts and ethanol as an additional carbon source (Cornell et al., 1981).

5. TOXICOKINETICS

5.1. Absorption

Specific studies on the absorption of TEGDN were not available. The effects observed in animal studies (see section 6), however, indicate that it is readily absorbed from the gastrointestinal tract (Hiatt et al., 1989; Morgan et al., 1989) and by respiration (Mattsson et al., 1977). Systemic effects were also seen with repeated dermal exposure (Andersen and Mehl, 1973) indicating that TEGDN can also be absorbed through the skin (see section 6).

5.2. Distribution

Specific studies on the distribution of TEGDN were not available, however, the presence of systemic neurological effects would indicate widespread distribution of TEGDN after absorption (see section 6)(Andersen and Mehl, 1973).

5.3. Metabolism

TEGDN oxidizes hemoglobin and in turn is converted to the mononitrate and nitrite (Andersen and Mehl, 1973; Andersen and Smith, 1973).

5.4. Excretion

Specific studies on the excretion of TEGDN were not available.

6. HEALTH EFFECTS

6.1. Noncancer Effects

6.1.1. Oral Exposure

6.1.1.1. Human. No information was located in the available literature.

6.1.1.2. Animal. Andersen and Mehl (1973) reported 24-hour oral LD_{50} of 1000 mg/kg in male Sprague-Dawley rats. Hiatt et al. (1989) gave male and female Sprague-Dawley rats single doses of TEGDN by gavage and determined median lethal doses of 1330 and 1116 mg/kg for male and female rats, respectively. The clinical signs observed were hunched posture, inactivity, tremors, twitching and hypotonia. The signs appeared within two hours of treatment and the animals either died or were free of the clinical signs in 72 hours. Morgan et al. (1989) determined median lethal single gavage doses of 2036.5 and 1866.3 mg/kg for male and female ICR mice, respectively. Signs of toxicity, which appeared within two hours of dosing, included hunched posture, squinting, increased startle reflex, depression of grasping and righting reflexes, tremors, jumping, twitching, and convulsions. Guinea pigs fed 0, 100, 200, or 400 mg TEGDN/kg for 15 days had dose related decreased weight gain that was related to a concurrent decrease in food intake (Andersen and Mehl, 1973).

Certain symptoms are reported that are independent of route of administration and test species. A hypotensive response, typical of glycol dinitrates, is seen with comparatively low doses (see section 6.1.2.2.). Nervous system toxicity is reported that appears to be caused by a blockage of cholinergic neurotransmission in treated animals (Andersen and Mehl, 1973; Andersen et al., 1976). TEGDN also oxidizes hemoglobin resulting in methemoglobinemia. Death is thought to be caused by a combination of these toxic effects (Andersen and Mehl, 1973).

6.1.2. Other Exposure Routes

6.1.2.1. Human. No information was located in the available literature.

6.1.2.2. Animal. Andersen and Mehl (1973) determined LD_{50} values of 945, 700 and 796 mg/kg by intraperitoneal injection for male mice, male guinea pigs and male rats, respectively. The same authors also reported an LD_{50} of 2520 mg TEGDN/kg by subcutaneous injection in male rats. Much lower doses (2.4 mg/kg) injected intravenously into male rats resulted in a hypotensive response. The blood pressure dropped from 90 to 49 mm Hg immediately and slowly recovered over the next 15 min. to 96 mm Hg.

TEGDN was tested for dermal sensitization and irritation. No evidence of sensitization was reported after repeated dermal applications of TEGDN to male guinea pigs (Brown and Korte, 1989a). A slight erythema was reported in rabbits treated with a single application of 2 ml TEGDN/kg to the skin under a semi-occlusive wrap for 24 hours. The erythema cleared in seven of eight animals by 72 hours, and no evidence of systemic toxicity was observed (Brown and

Korte, 1989b; Morgan and Korte, 1989). Repeated daily application of 21 mmole/kg TEGDN (about 5 mg/kg) to the skin of rabbits resulted in the death of nine of eleven animals in an average treatment time of 17 days. The TEGDN-treated rabbits lost 20 to 30% of their body weight during the treatment (Andersen and Mehl, 1973). TEGDN was tested for eye irritation by a modified Draize method using New Zealand White rabbits. A slight conjunctival vasodilation indicative of mild inflammation was reported. The authors concluded that TEGDN is not a primary eye irritant (Hiatt and Korte, 1989). Mattsson et al. (1977) treated one male rhesus monkey for two and four hours with a 2.4 ppm TEGDN aerosol and reported changes in behavior as measured by an increased response rate and by the Sidman avoidance task.

6.2. Carcinogenicity

6.2.1. Oral Exposure

6.2.2.1. Human. No information was located in the available literature.

6.2.2.2. Animal. No information was located in the available literature.

6.2.2. Other Exposure Routes

6.2.2.1. Human. No information was located in the available literature.

6.2.2.2. Animal. No information was located in the available literature.

6.3. Genotoxicity

No information was located in the available literature.

7. EXISTING STANDARDS, CRITERIA, GUIDANCE

7.1. EPA RfDs, RfCs, CRAVE Classifications

RfD:	None established
Oral slope factor:	None established
Oral unit risk:	None established
Inhalation slope factor:	None established
Inhalation unit risk:	None established
EPA CRAVE Cancer Classification:	Not classified

7.2. IARC Carcinogenicity Classification

Not evaluated

7.3 ACGIH, OSHA, and NIOSH Standards and Criteria

OSHA (8-hr TWA):	None established
OSHA STEL:	None established
OSHA Ceiling Limit:	None established
ACGIH (8-hr TWA):	None established
NIOSH RELs:	None established

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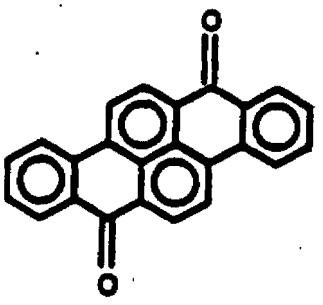
1. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Water, provides information on the health effects and other useful data that can aid in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. The EPA has an ongoing cooperative agreement with the Department of the Army to prepare drinking water Health Advisories (HA) for munitions and other environmental contaminants. Drinking Water Toxicological Profiles are short summaries of the pertinent mammalian health effects literature, and are used by the Office of Water to determine if a data base is sufficient to allow the development of HAs. The following data bases were searched for information on Vat Yellow 4: TOXLINE, TOXLINE65, TOXLIT, TOXLIT65, CANCERLINE, DART, EMICBACK, CHEMFATE, ENVIROLINE, DTIC and RTECS. Secondary sources were also used.

This Drinking Water Toxicological Profile summarizes information on Vat Yellow 4, a commercially produced anthraquinone vat dye (Chung and Farris, 1979). Vat Yellow 4 is produced and used as a mixture of chemicals, with dibenzo(b,def)chrysene-7,14-dione as the principal color component. The dye has been used by the military to color smoke screens and as a signalling agent (IARC, 1990). It is also used as a dye for cotton, silk, wool, and paper (NCI, 1978). The structural formula for Vat Yellow 4 is shown below.



Vat Yellow 4

2. SELECTED GENERAL INFORMATION

Commercial grade Vat Yellow 4 contains approximately 18% dibenzo(b,def)chrysene-7,14-dione, 31% sorbitol, 6% dispersant, 3% glycerin, and 43% water. Impurities include dibenzochrysene, dibenzochrysenedione, benzanthrone, and three ketones. U.S. military specifications limit the content of dibenzochrysene in Vat Yellow 4 used for smoke screen formulations to a maximum of 0.1% (IARC, 1990). Physicochemical data for Vat Yellow 4 are presented in Table 32.

TABLE 32. PHYSICOCHEMICAL DATA

Common Name	Vat Yellow 4	
Synonyms	dibenzo[*b,def*]chrysene-7,14-dione; dibenzo[*a,b*]pyrene-7,14-dione; Anthravat Golden Yellow; C.I. Vat Yellow 4; C.I. 59100; Indanthrene Golden Yellow	RTECS, 1992
CAS Registry No.	128-66-5	
RTECS No.	HO7030000	RTECS, 1992
Chemical formula	$C_{24}H_{12}O_2$	SRC, 1988
Molecular weight	332.36	SRC, 1988
Physical state	solid	
Vapor pressure	ND[a]	
Specific gravity	ND	
Melting/Boiling/Flash Point	385°C (dye)/ND/ND	IARC, 1990
Solubility in water	0.08 mg/L at 25°C	SRC, 1988
Log K_{ow}	5.339	SRC, 1988
Bioconcentration factor (log BCF)	3.83	SRC, 1988
Conversion factors in air	1 ppm = 13.59 mg/m^3 1 mg/m^3 = 0.074 ppm	calculated[b]
Odor threshold	ND	
Henrys' Law constant	ND	

[a]ND: no data

[b]Formula: $\text{ppm by volume} = \text{mg/m}^3 \times \frac{24.45}{\text{mol. wt. in grams}}$

3. SOURCES OF EXPOSURE

3.1. Occurrence in Water

No information was found in the available literature.

3.2. Human Exposure

During the 1940s and 1950s, military personnel were exposed to chemical smoke screens containing Vat Yellow 4. Data on exposure levels were not available (IARC, 1990). The dye is also used to color cellulose fibers, some cellulose synthetics, wool, silk and paper (NCI, 1979). Inhalation and/or dermal contact are the most likely routes of human exposure.

4. ENVIRONMENTAL FATE

No information was found in the available literature.

5. TOXICOKINETICS

5.1. Absorption

No quantitative information was found in the available literature, however the results observed in mice and rats fed Vat Yellow 4 during carcinogenicity studies indicate that some absorption from the gastrointestinal tract does occur (see sections 6 and 7)(NCI, 1979).

5.2. Distribution.

No quantitative information was found in the available literature, however a dose-related increase in lymphomas and hepatocellular carcinomas was reported in male mice (see section 7). This indicates that Vat Yellow 4, a component or metabolite has at least a limited distribution in mice.

5.3. Metabolism.

No information was found in the available literature.

5.4. Excretion.

No information was found in the available literature.

6. HEALTH EFFECTS

6.1. Noncancer Effects

6.1.1. Oral Exposure

6.1.1.1. Human. No information was found in the available literature.

6.1.1.2. Animal. Male and female Fischer 344 rats were fed diets containing 3500 or 7000 ppm commercial Vat Yellow 4 for 104 weeks in a carcinogenicity study. Decreased body weights were reported in all treated rats, however no effect was seen on survival. No effect was seen on survival or body weight gain in male mice fed diets containing 25,000 or 50,000 ppm commercial Vat Yellow 4 or in female mice fed diets containing 12,500 or 25,000 ppm. Commercial Vat Yellow 4 contains approximately 18% dibenzo[b,def]chrysene-7,14-dione (NCI, 1979).

6.1.2. Other exposure routes

6.1.2.1. Human. No information was found in the available literature.

6.1.2.2. Animal. No information was found in the available literature.

6.2. Carcinogenicity

6.2.1. Oral Exposure

6.2.1.1. Human. No information was found in the available literature.

6.2.1.2. Animal. The tumor incidence in 50 male and 50 female Fischer 344 rats fed a diet containing 3500 ppm or 7000 ppm of commercial Vat Yellow 4 for 106 weeks was not higher than that of controls. Commercial Vat Yellow 4 contains approximately 18% dibenzo(b,def)chrysene-7,14-dione (NCI, 1978). Groups of 50 B6C3F_1 mice were fed diets containing 25,000 or 50,000 ppm (males) and 12,500 or 25,000 ppm (females) commercial Vat Yellow 4 for 106 weeks. Male mice exhibited a significant dose-related increase of lymphomas and an increase of hepatocellular carcinomas compared with controls. The tumor incidence in female mice was not significantly increased (NCI, 1979).

6.2.2. Other Exposure Routes

6.2.2.1. Human. No information was found in the available literature.

6.2.2.1. Animal. No information was found in the available literature.

6.3. Genotoxicity

Vat Yellow 4 was not mutagenic in four *Salmonella typhimurium* strains in the presence or absence of metabolic activation (Zeiger et al., 1987), but gave a weak positive response in the mouse lymphoma assay with metabolic activation, possibly due to mutagenic contaminants (Harrington-Brock, 1991).

7. EXISTING STANDARDS, CRITERIA, GUIDANCE

7.1. EPA RfDs, RfCs, CRAVE Classifications

RfD:	None established
RfC:	None established
Oral slope factor:	None established
Drinking Water Unit Risk:	None established
Inhalation Slope Factor:	None established
Inhalation Unit Risk:	None established
EPA CRAVE Cancer Classification:	Not evaluated

7.2. IARC Carcinogenicity Classification

Group 3 (not classifiable as to its carcinogenicity to humans) IARC, 1990

7.3. OSHA, ACGIH, and NIOSH Standards and Criteria

OSHA (8-hr TWA):	None established
OSHA STEL:	None established
OSHA Ceiling Limit:	None established
ACGIH (8-hr TWA):	None established
NIOSH RELs:	None established

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1. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Water, provides information on the health effects and other useful data that can aid in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. The EPA has an ongoing cooperative agreement with the Department of the Army to prepare drinking water Health Advisories (HA) for munitions and other environmental contaminants. Drinking Water Toxicological Profiles are short summaries of the pertinent mammalian health effects literature, and are used by the Office of Water to determine if a data base is sufficient to allow the development of HAs. The following data bases were searched for information on zinc naphthenate: CANCERLINE, CHEMFATE, DART, DTIC, EMICBACK, ENVIROLINE, RTECS, TOXLINE, TOXLINE65, TOXLIT, AND TOXLIT65. Secondary sources were also used.

This Drinking Water Toxicological Profile summarizes information on zinc naphthenate, an organic zinc salt that is derived by fusion of zinc oxide or hydroxide and naphthenic acid, or by precipitation from a mixture of soluble zinc salts and sodium naphthenate. It exists as an amber, viscous, basic liquid containing 8-10% zinc or as a basic solid containing 16% zinc. It is soluble in hydrocarbons and acids (Lloyd, 1984) and very soluble in acetone (Sax and Lewis, 1987). Zinc naphthenate presents a slight fire hazard when exposed to heat or flame (Sax, 1984). It is used as a drier and wetting agent in paints, varnishes, and resins; insecticide, fungicide, and mildew preventive; wood preservative; waterproofing agent for textiles; and in insulating materials (Sax and Lewis, 1987). The structural formula for zinc naphthenate, a naphthenic acid salt, was not available. The structure of naphthenic acid is shown below.

Naphthenic acid

2. SELECTED GENERAL INFORMATION

Physicochemical data for zinc naphthenate are presented in Table 33.

TABLE 33. PHYSICOCHEMICAL DATA

Common name	zinc naphthenate	
Synonyms	naphthenic acid, zinc salt; zinc uversol; Fungitrol zinc 8% fungicide	RTECS, 1992; Bioresearch, Inc., 1980
CAS Registry No.	12001-85-3	
RTECS No.	QK9275000	RTECS, 1992
Chemical formula	$Zn(C_6H_5COO)_2$	Sax and Lewis, 1987
Molecular weight	307.61	
Physical state	liquid or solid	Sax and Lewis, 1987
Vapor pressure	ND[a]	
Specific gravity	ND	
Melting/Boiling/Flash Point	ND	
Solubility in water	insoluble	Lloyd, 1984
Log K_{ow}	ND	
Bioconcentration factor (BCF)	ND	
Conversion factors in air	1 ppm = 12.58 mg/m^3 1 mg/m^3 = 0.08 ppm	calculated[b]
Odor threshold	ND	
Henrys' Law constant	ND	

[a]ND: no data

[b]Formula: $\text{ppm by volume} = mg/m^3 \times \frac{24.45}{\text{mol. wt. in grams}}$

3. SOURCES OF EXPOSURE

3.1. Occurrence in Water. No information was found in the available literature.

3.2. Human Exposure

The extent of human exposure to zinc naphthenate is not known, although its potential uses as a component of wood preservatives, paints, insecticides, fungicides, waterproofing agents, and insulating materials suggest the likelihood of environmental release.

4. ENVIRONMENTAL FATE

No information was found in the available literature.

5. TOXICOKINETICS

5.1. Absorption

No information was found in the available literature.

5.2. Distribution

No information was found in the available literature.

5.3. Metabolism

No information was found in the available literature.

5.4. Excretion

No information was found in the available literature.

6. HEALTH EFFECTS

6.1. Noncancer Effects

6.1.1. Oral Exposure

6.1.1.1. Human. No information was found in the available literature.

6.1.1.2. Animal. Oral LD_{50} values for rats are 4.92 g/kg (Bushy Run Research Center, 1953) and >5.0 g/kg, indicating that the compound is only slightly toxic via the oral route according to the Gosselin et al. (1984) scale.

Rats fed 0.5% zinc naphthenate for an unspecified time period experienced a significant weight loss. This weight loss had no effect on mating or viability of offspring over two generations of rats (Michie et al., 1988). Tests on the potential developmental or teratogenic hazards associated with the use of zinc naphthenate as a wood preservative showed that administration of 94 or 188 mg/kg/day during the period of organogenesis did not adversely affect dams or developing fetuses (Angerhofer et al., 1991). A dose of 938 mg/kg/day produced transient maternal toxicity, a higher incidence of resorptions, and lower fetal body weights.

6.1.2. Other exposure routes

6.1.2.1. Human. No information was found in the available literature.

6.1.2.2. Animal. The inhalation LC_{50} for rats is 11.6 mg/L for exposure to a 50% w/v suspension in mineral spirits over a 4-hour period. The acute dermal LD_{50} in rabbits is >2.0 g/kg. The compound is a primary skin irritant in rabbits and guinea pigs, and possibly a sensitizing agent in guinea pigs. It is not a primary eye irritant in rabbits (Bioresearch, Inc., 1980).

6.2. Carcinogenicity

6.2.1. Oral Exposure

6.2.1.1. Human. No information was found in the available literature.

6.2.1.2. Animal. No information was found in the available literature.

6.2.2. Other Exposure Routes

6.2.2.1. Human. No information was found in the available literature.

6.2.2.2. Animal. No information was found in the available literature.

6.3. Genotoxicity. No information was found in the available literature.

7. EXISTING STANDARDS, CRITERIA, GUIDANCE

7.1. EPA RfDs, RfCs, CRAVE Classifications

RfD:	None established
RfC:	None established
Oral slope factor:	None established
Drinking Water Unit Risk:	None established
Inhalation Slope Factor:	None established
Inhalation Unit Risk:	None established
EPA CRAVE Cancer Classification:	Not evaluated

7.2. IARC Carcinogenicity Classification

Not evaluated

7.3. OSHA, ACGIH, and NIOSH Standards and Criteria

OSHA (8-hr TWA):	None established
OSHA STEL:	None established
OSHA Ceiling Limit:	None established
ACGIH (8-hr TWA):	None established
NIOSH RELs:	None established

8. REFERENCES

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