SCIENTIFIC SUPPORT DOCUMENTATION

FOR

CYCLE 9

REVISIONS OF NR 140.10

GROUNDWATER ENFORCEMENT STANDARD

&

PREVENTIVE ACTION LIMIT

RECOMMENDATIONS

Prepared by:

Lynda Knobeloch, Ph.D., Toxicologist

Wisconsin Department of Health Services
Division of Public Health

May 2009

CONTENTS

ABBREVIATIONS

AA	= Atomic absorption spectrophotometry
cm	= centimeter
DHFS	= Wisconsin Department of Health and Family Services
DNR	= Wisconsin Department of Natural Resources
EPA	= Environmental Protection Agency
ES	= Enforcement Standard
g	= gram
HSDB	= Hazardous Substances Data Bank (a computerized database distributed by the National Library of Medicine)
ICP	= inductively-coupled plasma absorption emission spectrophotometry
IRIS	= Integrated Risk Information System (a computerized database distributed by the USEPA)
kg	= kilogram
L	= Liter
LC_{50}	= Lethal Concentration for 50% of Exposed Animals (inhalation exposure)
LD_{50}	= Lethal Dose for 50% of Exposed Animals (oral exposure)
LOAEL	= Lowest Observed Adverse Effect Level
LOEL	= Lowest Observed Effect Level
MCL	= Maximum Contaminant Level
MCLG	= Maximum Contaminant Level Goal
mg	= milligram
MRID	= Master Record Identification (number)
NOAEL	= No Observed Adverse Effect Level
NOEL	= No Observed Effect Level
PAL	= Preventive Action Level
ppb	= parts per billion
ppm	= parts per million
RfD	= Reference Dose
RSC	= Relative Source Contribution
UF	= Uncertainty Factor
USEPA	= United States Environmental Protection Agency
µg	= microgram (0.000001 gram)

INTRODUCTION

This document contains recommendations for the establishment of groundwater enforcement standards (ES) and preventive action limits (PAL) for five substances (Table 1).

The recommendations found in this document contain background information on the chemistry, uses, possible routes of human exposure and occurrence in Wisconsin groundwater of each chemical proposed for regulation. In addition, DHS has included a brief literature review of the important health effects, acute and chronic toxicity, and environmental fate of each substance. Based upon its review, DHS has calculated proposals for enforcement standards and preventive action limits using the risk assessment methods and assumptions provided by s.s. NR Ch. 160.

This statute directs the Department of Natural Resources (DNR) to identify and rank substances which may contaminate Wisconsin groundwater. The Department of Health Services (DHS) then develops recommendations for ES and PALs for these substances. Since 1986, Public Health Groundwater Quality Standards for 123 substances have been adopted under Chapter NR 140, the Wisconsin Administrative Code for Groundwater Quality.

TABLE 1. Recommended Enforcement Standards and Preventive Action Limits

Revisions (15)

	Current	Proposed	
	ES	ES	PAL
Substance	**ug/L**	**ug/L**	**ug/L**
1,3-Dichlorobenzene	1,250	600	120
1,3-Dichloropropene	0.2	0.4	0.04
Acetone	1,000	9,000	1,800
Boron	960	1,000	200
Carbaryl	960	40	4
Chloromethane	3	30	3
Dibutyl Phthalate	100	1,000	100
Ethylene glycol	7,000	14,000	2,800
Methyl ethyl ketone	460	4,000	800
Metolachlor	15	100	10
Metribuzin	250	70	14
Phenol	6,000	2,000	400
Prometon	90	100	20
Toluene	1,000	800	160
Xylene	10,000	2,000	400

New Standards (15)	**Proposed standards**	
	ES	**PAL**
Substance	**ug/L**	**ug/L**
1,4-Dioxane	3	0.3
Acetochlor	1	0.1
Acetochlor ESA and OXA	230	46
Aluminum	170	17
Ammonia	9,700	970
Chlorodifluoromethane	7,000	700
Chlorpyrifos	2	0.4
Dimethenamid	50	5
Dinitrotoluenes	0.05	0.005
Ethyl ether	1,000	100
Manganese	300	60
Metolachlor ESA and OXA	1,300	260
Perchlorate	7	0.7
Propazine	10	2
Tertiary Butyl Alcohol	12	1.2

STRUCTURE OF THE STANDARDS DOCUMENTS

Introduction: A brief description of the uses of the chemical, if any.

Chemical Profile: A list of the important properties of the substance, including chemical structure, molecular weight, specific gravity and synonyms.

Occurrence: Description of quantities estimated to enter the environment through industrial production and/or waste generation. Includes results of groundwater testing by state and federal agencies.

Human Exposure Routes: Description of observed and potential routes of human exposure, including the estimated contribution of drinking water to total exposure.

Toxicity

> **Acute.** LD_{50}s or LC_{50}s in rats and mice. The LD_{50} is the oral dose which causes lethality in half the exposed animals, while the LC_{50} is a corresponding air concentration from inhalation studies.
>
> **Subchronic.** Results of animal studies of durations from 90 days to 1 year.
>
> **Chronic.** Results of animal or human studies lasting longer than 1 year.
>
> **Carcinogenicity.** Results of animal or human studies on the ability of the chemical to cause cancer..
>
> **Mutagenicity.** Results of any short-term mutagenicity assays, such as the Ames test or the mouse lymphoma forward mutation assay, on the chemical.
>
> **Reproductive and Developmental Effects.** Reports of any effects of the chemical on reproduction or development.
>
> **Interactive Effects.** Results of experiments in which the chemical was administered in combination with other chemicals, or a discussion of concerns related to simultaneous exposure to other chemicals.

Environmental Fate: Description of the stability of the chemical in air, soil, surface water or groundwater, including the chemical's tendency to move from soil to groundwater.

Analytical Laboratory Methods: A brief description of the methods used to detect the chemical, including the current limit of detection.

USEPA Regulatory Position: Availability of toxicity values published by the US EPA.

> **Maximum Contaminant Level (MCL).** The maximum allowable concentration of a chemical allowed in drinking water under the Safe Drinking Water Act. The MCL takes into account cost of remediation and analytical capabilities in addition to potential health effects.

Maximum Contaminant Level Goal (MCLG). The maximum allowable concentration of a chemical allowed in drinking water if only health effects are considered.

Lifetime Health Advisory (LHA). An EPA standard used for health-based guidance for substances for which MCLs and MCLGs have not been promulgated.

For noncarcinogens, the following parameters may be reported.

No Observed Adverse Effect Level (NOAEL). The highest dose of a chemical which produced no adverse effects in experimental animals or humans.

No Observed Effect Level (NOEL). The highest dose of a chemical at which no exposure-related effects were observed.

Lowest Observed Adverse Effect Level (LOAEL). The lowest dose which produced adverse effects in experimental animals or humans.

Lowest Observed Effect Level (LOEL). The lowest dose of a chemical at which no exposure-related effects were observed.

Uncertainty Factor (UF). Divisor applied to a NOAEL or LOAEL to obtain an acceptable human dose for daily exposure.

Reference Dose (RfD). The RfD is an estimate of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. RfDs are derived on the basis of a NOAEL, LOAEL or benchmark dose, with uncertainty factors applied to reflect limitations of the data used.

Drinking Water Equivalent Level (DWEL). Drinking water concentration derived on the basis of an RfD. Calculations use assumptions of a 70-kg adult human body weight, consumption of 2 liters of water a day and 100% exposure to the chemical occurring via drinking water.

For carcinogens, the following parameters may be reported.

Cancer Potency Factor. U.S. EPA concludes that a chemical is carcinogenic if animals form tumors in a dose-related manner upon exposure. Data on doses and numbers of tumors are entered into a complex computer program and an estimate of the slope of the line is called the cancer potency factor.

10^{-6} Risk Level. The concentration in water calculated to produce an excess cancer risk of 1 in 1,000,000 assuming lifetime exposure to a 70 kg person drinking 2 L/day of water.

Other Toxicology Information: Any other information pertinent to development of groundwater standards.

Recommendations and Conclusions: The following discussion briefly summarizes the procedure by which DHFS is directed to develop recommendations for enforcement standards and preventive action limits:

- If a single federal number exists for a substance, the federal number shall be the enforcement standard;
- If more than one federal number exists for a substance, the most recently established federal number representing the most current data shall be the enforcement standard.
- If no federal number exists for a substance, but there is a state drinking water standard, the state drinking water standard shall be the enforcement standard.
- If neither a federal number nor a state drinking water standard exists for a substance, [DHFS] shall develop a recommended enforcement standard using the methodology under s. 160.13."

In this process, DHFS is directed to use a 'federal number' if one exists. In Ch. 160.01(3), the term "federal number" is defined as "a numerical expression of the concentration of a substance in water, established as:

(a) A drinking water standard or maximum contaminant level, by the federal environmental protection agency;
(b) A suggested no-adverse-response level, by the federal environmental protection agency; or
(c) For oncogenic substances, a concentration based on a risk level determination by the federal environmental protection agency or a concentration based on a probability of risk model determined by the national academy of sciences."

For those substances for which neither a federal number nor a state standard exists, DHFS is directed to determine the acceptable daily intake (ADI) for the substance and to convert that value into a numerical drinking water concentration by applying a daily water consumption rate of 1 L/day and a body weight of 10 kg (s. 160.13(2)(c)).

For non-carcinogens, if DHFS finds no serious flaws in the methodology used to derive the RfD, which constitutes a suggested no-observed-effect level from EPA (based on EPA's NOAEL or LOAEL and UF), DHFS is directed to use this value as a basis for setting the enforcement standard. If no RfD exists, or the RfD is determined by DHFS to be based on data that do not accurately reflect current scientific knowledge on the chemical, DHFS is directed to make an independent determination as to a NOEL or LOEL and a UF. In such cases, DHFS uses the assumptions that 1 L (0.9 qt) of this water is consumed by a 10 kg (22 lb) child, and that all (100%) of the chemical consumed by the child comes from drinking water. From this information, a drinking water concentration is calculated using the following formula:

$$\frac{\text{NOEL or LOEL (mg/kg/day)} \times 10\text{ kg} \times 100\%}{\text{UF} \times 1\text{ L}} = \text{ES}$$

For carcinogens, DHFS determines the concentration of the chemical at which lifetime consumption of the chemical would be assumed to cause one excess cancer case among 10,000 to 1,000,000 exposed persons as compared to unexposed persons. The concentration in water associated with a 1 in 10,000 to 1 in 1,000,000 (the "cancer risk") is determined by assuming a 70-year lifetime exposure, a 70-kg (154 lb.) human, 2 L (1.8 qt) water consumption per day and that 100% of exposure to that chemical comes from drinking water. The calculations are as follows:

$$\frac{70\text{ kg} \times \text{cancer risk}}{\text{Cancer potency factor} \times 2\text{ L/day}} = \text{ES}$$

Significant figures: All enforcement standards and preventive action limits have been rounded to contain no more than two significant figures.

USEPA CANCER CLASSIFICATIONS

The USEPA has classified environmental chemicals according to their suspected carcinogenicity. The classifications are as follows:

Group A--Human Carcinogen

Sufficient evidence in epidemiologic studies to support causal association between exposure and cancer.

Group B--Probable Human Carcinogen

Limited evidence in epidemiologic studies (Group B1) and/or sufficient evidence in animal studies (Group B2).

Group C--Possible Human Carcinogen

Limited or equivocal evidence from animal studies and inadequate or no data in humans.

Group D--Not Classified

Inadequate or no human and animal evidence of carcinogenicity.

Group E--No Evidence of Carcinogenicity for Humans

No evidence of carcinogenicity in at least two adequate animal tests in different species or in adequate epidemiologic and animal studies.

UNCERTAINTY FACTORS

As described in Ch. 160 Stats., an uncertainty factor is applied to a NOEL or LOEL to obtain a dose level or concentration assumed safe for long-term exposure to human populations. UFs are applied to account for sources of variability which might otherwise cause the observed concentration to be insufficiently protective. Among the most common sources of variability and uncertainty that are addressed by the use of UFs are biological variability among species, biological variability within a species, the lack of an experimental NOEL for a substance, the lack of a chronic health study for a substance, and the lack of data needed to adequately assess effects that could be anticipated based on knowledge of related chemicals or chemical structure, such as carcinogenicity or developmental toxicity.

Typically, uncertainty factors ranging from 10 to 10,000 are used. Low uncertainty factors are common in cases where there is an experimental NOEL based on a chronic health study, especially when the NOEL is derived from experience with human exposure. Higher uncertainty factors are more common when only limited or incomplete chronic or subchronic toxicity data are available, or when experimental data on endpoints of particular concern are unavailable.

METABOLITES

The Department of Health and Family Services recognizes that many substances degrade in the environment to metabolites which may also contaminate groundwater. In the absence of adequate toxicological information, we believe that these breakdown products should be considered to have biological effects similar to those of the parent compound. Under this assumption, these breakdown products, or metabolites, can be regulated using existing groundwater standards which were developed based on the toxicological profile of the parent compound.

We recommend that when a metabolite is detected in the groundwater, and a groundwater standard exists for the parent compound but not for the metabolite, the existing groundwater standard should be used to regulate the sum of any parent and metabolite detected. If the metabolite weighs significantly more or less than the parent compound, a molecular weight conversion should be conducted since the toxicity assumption is based on molecular equivalency.

DNR HEARINGS PROCESS

DNR staff review the DHS recommended standards and hold public hearings for comment on the appropriateness of the proposed numerical standards. After completing the review process, public comments will be incorporated into the technical support document and any changes made will be written into the final text. The DNR Board, after reviewing the recommended groundwater standards document (including responses to public comments), will vote to accept or reject the original or modified risk assessments. Standards accepted by the DNR Board are sent to the Wisconsin State Legislature for their review and approval. Upon acceptance, these standards become law and are printed in the Wisconsin Administrative Code.

1,3-DICHLOROBENZENE (Revision)

1,3-Dichlorobenzene is one of three isomers of dichlorobenzene. It is a colorless liquid which is practically insoluble in water, but soluble in alcohol and ether. The three dichlorobenzene isomers are 1,2-dichlorobenzene, 1,3-dichlorobenzene, and 1,4-dichlorobenzene (also referred to as ortho-, meta-, and para-dichlorobenzene, respectively). Dichlorobenzenes are produced from the reaction of liquid benzene with chlorine gas in the presence of a catalyst.

CAS No	541-73-1
Molecular formula	C6H4Cl2
Molecular weight	147.1
Water solubility	123 mg/L
Physical state	Colorless liquid
Specific gravity	1.28
Synonyms	m-Dichlorobenzene, m-DCB, 2,6-Dichlorobenzene

Production of 1,3-dichlorobenzene in the United States during 1983 was less than 500 tons (IARC, 1999). 1,3-Dichlorobenzene is used in the production of herbicides, insecticides, pharmaceuticals, and dyes (IARC, 1999; U.S. EPA, 1981). Dichlorobenzenes are readily absorbed from the gastrointestinal tract. Following absorption by the gastrointestinal or respiratory tract, dichlorobenzenes are rapidly metabolized and eliminated in the urine. Excretion via exhaled breath or feces represents minor pathways. Dichlorobenzenes are not likely to bioaccumulate.

Occurrence

1,3 Dichlorobenzene is rarely detected in the environment. Federal surveys of drinking water supplies have failed to identify the meta isomer. Human biomonitoring studies have failed to identify this isomer in blood and breast milk samples, as well, although 1,2 and 1,4 dichlorobenzene were detected in the majority of samples.

Acute Toxicity

Rat LC50 = 500 mg/kg

Inhalation exposure to 1,3-dichlorobenzene can cause symptoms of sore throat, cough, drowsiness, nausea and vomiting. Ingestion causes gastric burning, diarrhea, nausea and vomiting. Concentrated product is irritating to skin, eyes and mucous membranes.

Chronic Toxicity

The oral toxicity database contains only one subchronic rat study (McCauley et al., 1995) and one developmental toxicity study that was reported in abstract form (Ruddick et al., 1983). The developmental toxicity study revealed no maternal or developmental toxicity at doses as high as 200 mg/kg-day. In the subchronic toxicity study, rats were exposed to doses of 9, 37, 147, or 588 mg/kg-day 1,3-dichlorobenzene for 90 days. Effects were seen in the thyroid, pituitary, and liver at all tested dose levels. This study was used by the EPA to derive an oral reference dose (EPA, 2003). The thyroid and pituitary effects seen in rats are assumed to be relevant to humans who may be chronically exposed to 1,3-dichlorobenzene. Little is known about the mechanisms responsible for the long-term oral toxicity of 1,3-

dichlorobenzene, but the available evidence suggests that hepatic metabolism to a reactive intermediate is involved.

Potential points of departure were derived by benchmark dose analysis of the thyroid and pituitary data. Modeled BMDLs for thyroid (1.9 mg/kg-day) and pituitary lesions (3.3 mg/kg-day) were similar and since these effects may be related, the average of these values was chosen as the point of departure. The average BMDL of 2.6 mg/kg-day was divided by an uncertainty factor of 3000 to derive a draft reference dose of 0.9 ug/kg/day (EPA, 2003). However, this draft risk assessment was reviewed and withdrawn by the agency in 2006 at which time the EPA determined that there was too much uncertainty to support the development of a reference dose for this substance.

ATSDR has derived an MRL of 0.02 mg/kg/day for intermediate-duration oral exposure to 1,3-Dichlorobenzene. The intermediate oral MRL is based on benchmark dose analysis of incidences of pituitary lesions in male rats administered 1,3-dichlorobenzene by daily oral gavage for 90 days (McCauley et al. 1995). The resulting BMDL10 of 2.1 mg/kg/day was divided by an uncertainty factor of 100 (10 for extrapolating from animals to humans and 10 for human variability).

US EPA Cancer Classification

Class D: Not classifiable.

Both the International Agency for Research on Cancer (IARC) and the EPA have concluded that 1,2- and 1,3- dichlorobenzene are not classifiable as to human carcinogenicity.

Regulatory Summary

Reference Dose	None
MCL	None
MCLG	None
NOAEL	None
LOAEL	9 mg/kg/day
DWEL	3 mg/L
Lifetime Health Advisory	0.6 mg/L*
Cancer Class	D, not classifiable*

*2006 Drinking Water and Health Advisory Tables, US EPA Office of Water.

State Drinking Water or Groundwater Quality Standards and Guidelines

Arizona	620 µg/L
California	130 µg/L
Florida	10 µg/L
Idaho	600 µg/L
New Jersey	600 µg/L
Vermont	600 ug/L
Wisconsin	1,250 µg/L

Recommendations and Conclusions

The Department of Health Services recommends that the existing groundwater enforcement standard be lowered from 1,250 ug/L to 600 ug/L to reflect the EPA's Lifetime Health Advisory. Since 1,3-dichlorobenzene is not known to cause cancer or mutations, a 20% PAL is proposed.

Recommended enforcement standard	600 µg/L
Recommended preventive action limit	120 µg/L

References

IARC (International Agency for Research on Cancer). (1999) *ortho*- and *para*-Dichlorobenzenes. 14 In: IARC Summaries & Evaluations. Vol. 73:

International Occupational Safety and Health Information Center, accessed online at http://www.ilo.org/public/english/protection/safework/cis/products/icsc/dtasht/_icsc10/icsc1095.htm Nov 12, 2008.

McCauley, P.T., M. Robinson, F.B. Daniel and G.R. Olson. (1995) Toxicity studies of 1,3-dichlorobenzene in Sprague-Dawley rats. Drug Chem. Toxicol. 18(2&3):201-221.

Ruddick, J.A., W.D. Black, D.C. Villeneuve and V.E. Valle. (1983) A teratological evaluation 12 following oral administration of trichloro- and dichlorobenzene isomers to the rat. Teratology. 13 27(2):73A-74A.

US EPA Office of Water. 2006. Drinking Water Standards and Health Advisories.

USEPA. 2003. Draft Toxicological Review of Dichlorobenzenes. Docket no. EPA/635/R-03/015.

USEPA. 2006. Toxicological Review of Dichlorobenzenes. Revised Final Draft. Docket no. EPA/635/R-03/015.

cis, trans 1,3-DICHLOROPROPENE (Revision)

1,3-Dichloropropene (DCP), or Telone, is used in 95% solutions as a soil fumigant for the control of root nematodes as follows: cotton and potatoes, 48%; vegetables, tobacco and sugar beets, 38%; floral, ornamental, fruit trees and miscellaneous, 14%. The principal US manufacturer is Dow Chemical. Dichloropropene is highly irritating to the skin, eyes and mucous membranes. Inhalation causes severe lung damage. The technical product is a mixture of the *cis* and *trans* isomers.

CAS No.	542-75-6
Molecular weight:	110.98
Physical state:	Liquid with chloroform-like odor
Water solubility:	2,700 mg/l at 25^{o}C
Specific gravity:	1.22
Synonyms:	Dichloropropylene, chloroallyl chloride, Telone.

Occurrence

The cis- isomer has been detected in 35 of 5732 wells tested in Wisconsin. The trans- isomer has been detected in 31 of 5684 Wisconsin wells tested.

DCP has been found in 41 of 1,088 surface water samples analyzed and in 10 of 3,949 ground-water samples. Samples were collected in 800 surface water locations and 2,506 ground-water locations. DCP was identified in water samples from 13 states.

In occupational settings humans can be exposed to 1,3-dichloropropene both via inhalation and dermal exposures. These exposures are most often linked to field application of this chemical as a soil fumigant. The general public can be exposed via inhalation near source areas and from contaminated drinking water.

Toxicity

1,3-Dichloropropene is very toxic with an oral lethal dose of between 1 teaspoon and 1 ounce for an adult.

Stott et al. (1995) fed male and female Fischer 344 rats (50/sex/dose) a microencapsulated formulation of Telone II (96% 1,3-dichloropropene) in the diet at doses of 0, 2.5, 12.5, or 25 mg/kg/day for 24 months. Satellite groups of rats (10/sex/dose) were administered Telone II for 12 months. Standard bioassay data including body weights, food consumption, clinical chemistry, hematology, urine analysis, organ weights, pathology, and histopathology were collected. Body weights were decreased in a dose-dependent manner in treated animals. Decreases were statistically and toxicologically significant in both sexes at 25 mg/kg/day. Average organ weight changes in males and females were associated with decreased body weight. The only histopathology observed was in the forestomach which exhibited a mild basal cell hyperplasia of the mucosal lining. The incidence of forestomach lesions was statistically increased in both sexes at 12.5 mg/kg/day and higher. The forestomach hyperplasia is believed to be a manifestation of chronic irritation, which is consistent with the observation of primary dermal irritation (Nater and Gooskens, 1976) and other portal-of-entry effects from 1,3-dichloropropene exposure (Haut et al. 1996; Lomax et al. 1989; Linnett et al. 1988; Stott et al. 1988). Of the two critical effects, body weight decrease and chronic irritation (as evidenced by the forestomach hyperplasia), data from the most sensitive effect, chronic irritation, were used to develop the RfD.

Carcinogenicity

USEPA classification: B2, probable human carcinogen

In an NTP (1985) study, F344 rats of each sex were gavaged with Telone II (92% 1,3-dichloropropene, 1% epichlorohydrin) in corn oil at doses of 0, 25, and 50 mg/kg 3 times/week while B6C3F1 mice of each sex were gavaged with 0, 50, and 100 mg/kg 3 times/ week for 104 weeks. In rats, elevated incidences of forestomach squamous cell papillomas and carcinomas and liver adenomas/carcinomas were observed at 50 mg/kg:. This dose level approximated a maximum tolerated dose level. Elevated incidences of forestomach papillomas and carcinomas; squamous cell carcinomas ; urinary bladder transitional cell carcinomas; and lung adenomas/ carcinomas were observed in mice.

In feeding studies, Fischer 344 rats (50/sex/dose) were administered Telone II (96% 1,3-dichloropropene without epichlorohydrin) in the diet at 0, 2.5, 12.5, or 25 mg/kg/day for 24 months (Stott et al., 1995) while B6C3F1 mice (50/sex/dose) received doses of 0, 2.5, 25, or 50 mg/kg/day for 24 months (Redmond et al., 1995). In rats, a statistically significant increase in the incidence of benign liver cell tumors was observed in males in the 25 mg/kg/day group. No increases in tumor incidence were observed in treated mice of either gender.

Quantitative estimate of carcinogenic risk from oral exposure (US EPA, 2000)

Drinking water unit risk	3E-6 per (µg/L) (NTP, 1985; urinary bladder tumors)
Oral slope factor	1E-1 per (mg/kg)/day (NTP, 1985; urinary bladder tumors)

Risk level vs Drinking Water Concentration

Risk level	Concentration
1 in 10,000	40 µg/l
1 in 100,000	4 µg/l
1 in 1,000,000	0.4 µg/l

Mutagenicity

Telone II was a direct acting mutagen in several Salmonella strains and is structurally related to other short chain halogenated hydrocarbons that are known oncogens. These include ethylene dibromide which produces forestomach squamous cell carcinomas in rats and mice after oral administration and vinyl chloride monomer which produces lung adenomas and adenocarcinoma in rats following inhalation exposure (US EPA, 2000).

Reproductive Effects

1,3-Dichloropropene has been evaluated for potential reproductive effects in rats and rabbits exposed via inhalation 6 hrs/day during gestation days 6-15 (rats) or 6-18 (rabbits). No evidence of a teratogenic or embryotoxic response was observed in either species at any exposure level up to 120 ppm tested (US EPA, 2000).

1,3-Dichloropropene was administered by intraperitoneal injections of 0 to 75 mg/kg/day for 5 days had no effect on sperm count, sperm morphology or testicular weights in mice.

Environmental Fate

Aquatic

If released to water 1,3-dichloropropene will be lost primarily due to volatilization (half-life about 4 hr in model river). Hydrolysis and microbial degradation may occur but these process are slow. Adsorption to sediment will not be an important pathway.

Atmospheric
When released into air, 1,3-dichloropropene will degrade by reaction with photochemically generated hydroxyl radicals.

Terrestrial
1,3-Dichloropropene is hydrolyzed in soil to form 3-chlorallyl alcohol. The half-life for this conversion ranges from 3 to more than 69 days.

Eight months after soil fumigant containing 1,3-dichloropropene was applied to muck and sandy loam soils in August during field studies, residues of 1.8 and 4.8 ppm of the cis and trans isomers were found in the muck soil and 0.03 and 0.39 ppm were found in the sandy loam.

Regulatory Summary

EPA regulatory information was obtained from IRIS. This database was last updated on 5/25/2000.

MCL and MCLG	None proposed
BMDL	3.4 mg/kg/day
Oral reference dose	0.03 mg/kg/day
Carcinogen Classification	B2, probable human carcinogen
Oral slope factor	0.1 per mg/kg/day

State Drinking Water Standards and Advisories

California	0.5 ug/L
Florida	0.4 ug/l
Massachusetts	0.5 ug/l
Maine	2 ug/l
Minnesota	2 ug/l
Wisconsin	0.2 ug/l

Recommendations and Conclusions

In 2000, the US EPA revised the cancer potency estimate for 1,3-Dichloropropene. The new slope factor equates a one-in-a-million lifetime cancer risk with a drinking water concentration of 0.4 ug/L. The previous slope factor equated the same risk to a water concentration of 0.2 ug/L. The Department of Health Services recommends that the groundwater enforcement standard and preventive action limit be revised to reflect this change in the federal risk assessment for 1,3-Dichloropropene.

Recommended Groundwater Enforcement Standard	0.4 µg/L
Recommended Preventive Action Limit	0.04 µg/L

References

Hanley T.R., et al. 1987. Funda Appl Toxicol 8(4):562-70.

Hanley, TR, Jr.; John-Greene, JA; Young, JT; et al. (1988) Evaluation of the effects of inhalation exposure to 1,3-dichloropropene on fetal development in rats and rabbits. Fundam Appl Toxicol 8:562-570.

Haut, KT; Stebbins, KE; Johnson, KA; et al. (1996) Subchronic toxicity of ingested 1,3-dichloropropene in rats and mice. Fundam Appl Toxicol 32:224-232.

Hernandez, AF; Martin-Rubi, JC; Ballesteros, JL; et al. (1994) Clinical and pathological findings in fatal 1,3-dichloropropene intoxication. Hum Exper Toxicol 13:303-306.

Hutson, DH; Moss, JA; Pickerine, BA. (1971) The excretion and retention of components of the soil fumigant D-D and their metabolites in the rat. Food Cosmet Toxicol 8:677-680.

Kenaga E.E. 1980. Ecotoxicol Environ Safety 4:26-38.

Linnett, SL; Clark, DG; Blair, D; et al. (1988) Effects of subchronic inhalation of D-D (1,3-dichloropropene/1,2-dichloropropene) on reproduction in male and female rats. Fundam Appl Toxicol 10:214-223.

Lomax, LG; Stott, WT; Johnson, KA; et al. (1989) The chronic toxicity and oncogenicity of inhaled technical grade 1,3-dichloropropene in rats and mice. Fundam Appl Toxicol 12:418-431.

Markovitz A, Crosby WH; Arch Int Med 144: 1409-11, 1984.

Nater, JP; Gooskens, VHJ. (1976) Occupational dermatosis due to a soil fumigant. Contact Dermatitis 2(4):227-229.

National Research Council. 1986. Drinking Water and Health, Vol. 6, Washington, D.C. National Academy Press. pg. 337.

NTP. 1985. Toxicology and Carcinogenesis Studies of Telone II in F344/N Rats and B6C3F1 Mice (Gavage Studies) Rpt No. 269.

Stott, WT; Johnson, KA; Jeffries, TK; et al. (1995) Telone II soil fumigant: two-year chronic toxicity/oncogenicity study in Fischer 344 rats. The Dow Chemical Company. Midland, Michigan. Study # M-003993-0311.

US Environmental Protection Agency. 1991. Integrated Risk Information System (IRIS) computerized data base: 1,3-dichloropropene.

US EPA. 2000. Toxicological Review of 1,3-Dichloropropene, EPA/635/R-00/001, May 2000.

USEPA. IRIS document for 1,3-Dichloropropene, 5/25/2000.

ACETONE (Revision)

Acetone is a popular industrial solvent for fats, oils, waxes, resins, rubber, plastics, lacquers, varnishes, rubber cements. It is also used in the manufacture of mesityl oxide, acetic acid, diacetone alcohol, chloroform, iodoform, bromoform, explosives, airplane dopes, rayon, isoprene, photographic films, storing acetylene gas it is useful for extraction of various substances from animal and plant tissues; in paint and varnish removers; purifying paraffin, and hardening and dehydrating tissues. Acetone is often found in the home in the form of nail polish or varnish remover.

Most acetone production in the USA is based on a process in which benzene and propylene are reacted to form cumene. Cumene is then oxidized with air to produce cumene hydroperoxide which is then decomposed or cleaved with an acid to yield phenol and acetone.

CAS No.	67-64-1
Chemical formula	C_3H_6O
Molecular weight	58.08
Physical state	Colorless, flammable liquid
Water solubility	Soluble
Specific gravity	0.7899 at 20^o
Synonyms	Dimethylformaldehyde, dimethyl ketone, propanone

Occurrence

No information is available on contamination incidents in Wisconsin involving acetone.

Human Exposure Routes

Human exposure often occurs as a result of occupational and home use of acetone as a solvent. Most exposure is likely via inhalation, however dermal absorption and incidental ingestion may also occur.

Toxicity

Acetone is moderately toxic with an oral lethal dose between 1 ounce and 1 pint for a 70-kg person (Gosselin et al, 1984) Toxic effects are similar to ethyl alcohol for equal blood levels, but the anesthetic potency is greater.

Groups of 10 male and 10 female F344/N rats were administered acetone in their drinking water at concentrations of 0, 2,500, 5,000, 10,000, 20,000, or 50,000 ppm for 13 weeks (NTP, 1991; Dietz et al., 1991). Time-weighted average doses for males were 0, 200, 400, 900, 1,700, and 3,400 mg/kg-day, respectively, and for females 0, 300, 600, 1,200, 1,600, and 3,100 mg/kg-day, respectively. Water consumption was decreased in high-dose males and in females given 20,000 and 50,000 ppm acetone. Mean final body weight of the high-dose males was 81% of the controls; body weights of the females were unaffected by treatment. At necropsy, statistically significant ($p <= 0.01$ or 0.05) increases kidney and liver weights were noted. In high-dose males, depressed sperm motility, caudal weight, epididymal weight and an increased incidence of abnormal sperm were seen. Males given the two highest concentrations of acetone had increases in the incidence and severity of nephropathy, indicating early onset and enhanced progression of the disease. The authors of the study identified kidney changes as the most prominent chemically-related effect. Pigment deposition in the spleen was observed in 10/10 males in the 20,000 and 50,000 ppm groups compared with 0/10 controls. In summary, the testis, kidney, and

hematologic system were identified by the study authors as target organs for male rats, with a LOAEL of 1,700 mg/kg-day and a NOAEL of 900 mg/kg-day.

Groups of 10 male and 10 female B6C3F1 mice were administered acetone in the drinking water at concentrations of 0, 1,250 (males only), 2,500, 5,000, 10,000, 20,000, or 50,000 (females only) ppm for 13 weeks (NTP, 1991; Dietz et al., 1991). The liver was identified as the target organ in males and females. The LOAELs for males and females were 4,900 and 11,000 mg/kg-day, respectively, and the NOAELs were 2,300 and 5,900 mg/kg-day, respectively.

A point of departure of 900 mg/kg-day was selected by the US EPA based on an increased incidence of mild nephropathy in male rats.

An overall uncertainty factor of 1,000 was applied to account for intra- and inter-species variation, use of a subchronic feeding study, and to account for a deficient database.

Carcinogenicity

Not classified.

In accordance with the Draft Revised Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1999) *data are inadequate for an assessment of the human carcinogenic potential* of acetone.

Mutagenicity

Acetone did not show mutagenic activity when tested in *Salmonella typhimurium* strains TA98 and TA100 or in *Schizosaccharomyces pombe* strain P1 either in the presence or absence of liver homogenates (McCann et al, 1975; Abbondandolo et al, 1980; Maron et al, 1981; Hallstrom et al, 1981) or in cell transformation systems (Freeman et al, 1973; Rhim et al, 1974; Quarles et al, 1979; Norppa, 1981). Furthermore, acetone gave negative results in assays for chromosomal aberrations and sister chromatid exchange (Norppa et al, 1981; Tates and Kriek, 1981) DNA binding (Kubinski, 1981), point mutation in mouse lymphoma cells (Amacher et al, 1980), and transfection of E. coli CR63 cells (Vasavada and Padayatty, 1981). In one study, however, acetone was reported to produce chromosomal aberrations but not sister chromatid exchanges (Kawachi et al, 1980).

Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to acetone. Reproductive effects were assessed in pregnant mice exposed by gavage to acetone during gestation (EHRT 1987). The reproductive index was significantly reduced ($p=0.05$) (number of females producing viable litters/number of surviving females that were ever pregnant; 24/31 treated compared with 34/36 controls). In addition, acetone treatment significantly ($p<0.01$) increased the duration of gestation from 18.1 days in controls to 18.5 days in treated mice.

No effects were observed on the fertility of male Wistar rats treated with drinking water containing acetone at 1,071 mg/kg/day for 6 weeks (Larsen et al. 1991). The indices of fertility examined were successful matings with untreated females, number of pregnancies, number of fetuses, testicular weight, seminiferous tubule diameter, and testicular lesions. However, male Sprague-Dawley rats treated with 3,400 mg/kg/day acetone in drinking water for 13 weeks had significantly increased ($p<0.01$) relative testis weight, probably because body weight was reduced, and significantly ($p<0.05$) decreased sperm motility, caudal weight and epididymal weight, and increased incidences of abnormal sperm (Dietz et al. 1991; NTP 1991). No testicular lesions were observed upon histological examination. Vaginal cytology

examinations of the female rats revealed no effects. No effects on sperm morphology and vaginal cytology were observed in mice similarly treated with drinking water containing acetone at doses <4,858 mg/kg/day in males and <11,298 mg/kg/day in females.

Interactions:

Inhalation and oral administration of acetone potentiate the liver toxicity of carbon tetrachloride (Charbonneau et al., 1986).

Environmental Fate

Aquatic
If released into water, acetone is expected to biodegrade. It is readily biodegradable in screening tests, although data from natural water are lacking. It will also be lost due to volatilization. It's estimated half-life from a river is 20 hours. Adsorption to sediment should not be significant.

Atmospheric
In the atmosphere, acetone will be lost by photolysis and reaction with photochemically produced hydroxyl radicals. Half-life estimates from these combined processes are 79 and 13 days in January and June, respectively, for an overall annual average of 22 days. Therefore considerable dispersion should occur. Being miscible in water, wash out by rain should be an important removal process. This process has been confirmed around Lake Shinsei-ko in Japan (Kato et al, 1980). There acetone was found in the air and rain as well as the lake and the amount of acetone in the rain is what would be expected from the air concentration and solubility.

Terrestrial
If released on soil, acetone will both volatilize and leach into the ground. Acetone readily biodegrades and there is evidence suggesting that it biodegrades fairly rapidly in soils.

Bioconcentration
The recommended log octanol/water partition coefficient for acetone is -0.24 (Hansch and Leo, 1985) and therefore its potential for bioconcentration in fish is negligible. One experimental study of bioconcentration in adult haddock at 7-9 deg C (static test), resulted in a BCF of 0.69.

Regulatory Summary

USEPA regulatory information was obtained from IRIS. This computerized database was updated 07/31/2003 (oral RfD).

LOAEL	1700 mg/kg/day
NOAEL	900 mg/kg/day
MCL	None
MCLG	None
DWEL	None
Oral reference dose	0.9 mg/kg/day (revised from 0.09 mg/kg/day in 2003)
Uncertainty factor	1000
Cancer classification	Not classifiable

State Drinking Water Standards and Health Advisories

Maryland	3,600 ug/L
Massachusetts	700 ug/L
Minnesota	700 ug/L
New Hampshire	700 ug/L
New Jersey	6,000 ug/L
Wisconsin	1,000 ug/L
Vermont	700 ug/L

Recommendations and Conclusions

The Department of Health Services recommends revision of the groundwater standards for acetone to reflect the current federal reference dose. Since acetone is not known to have carcinogenic, mutagenic or reproductive effects, a 20% preventive action limit is proposed.

$$\frac{0.9 \text{ mg/kg/day} \times 10\text{-kg} \times 100\%}{1 \text{ liter/day}} = 9 \text{ mg/L}$$

Recommended groundwater enforcement standard:	9,000 µg/L
Recommended preventive action limit:	1,800 µg/L

References

40 CFR 136 (7/1/86).

Abbondandolo A, Bonatti S, Corsi C, et al. 1980. The use of organic solvents in mutagenicity testing. Mutat. Res. 79: 141-150.

Amacher DE, Paillet SC, Turner GN, Ray VA and DS Salsburg. 1980. Point mutations at the thymidine kinase locus in L5178Y mouse lymphoma cells. 2. Test validation and interpretation. Mutat. Res. 72:447-474.

Charbonneau M. et al Toxicol Appl Pharmacol 84(2):286-294, 1986.

Freeman AE, Weisburger EK, Weisburger JH, Wolford RG, Maryak JM and RJ Huebner. 1973. Transformation of cell cultures as an indication of the carcinogenic potential of chemicals. J Natl Cancer Inst. 51(3):799-808.

Gosselin, Smith and Hodge. Clinical Toxicology of Commercial Products, 5th edition, 1984, Williams & Wilkins, Baltimore.

Hallstrom I, Sundvall A, Rannug U, Grafstrom R and C Ramel. 1981. The metabolism of drugs and carcinogens in isolated subcellular fractions of Drosophila melangaster. I. Activation of vinyl chloride, 2-amnioanthrecene and benzo(a)pyrene as measured by mutagenic effects in Salmonella typhimurium. Chem. Biol. Inter. 34: 129-143.

Hansch C and AJ Leo. MEDCHEM PROJECT Issue No. 26 Claremont CA Pomona College (1985)

Kato T et al; Bulletin of the Institute of Environmental Science and Technology, Yokohama National University 6: 11-20, 1980.

Kawachi T, Yahagi T, Kada T et al. 1980. Cooperative programme on short-term assays for carcinogenicity in Japan. In: Molecular and Cellular Aspects of Carcinogen Screening Tests. R. Montesano, ed. WHO, IARC, Lyon, France. p. 323-330.

Kubinski H, Gutzke GE and ZO Kubinski. 1981. DNA-cell-binding (DCB) assay for suspected carcinogens and mutagens. Mutat. Res. 89:95-136.

Lyman WJ et al; Handbook of Chem Property Estimation Methods McGraw-Hill NY pp. 5-1 to 5-30 (1982).

Maron D, Katzenellenbogen J and BN Ames. 1981. Compatability of organic solvents with the Salmonella/microsome test. Mutat. Res. 88: 343-350.

McCann J, Choi E, Yamasaki E and BN Ames. 1975. Detection of carcinogens as mutagens in the Salmonella/microsome test: Assay of 300 chemicals. Proc. Natl. Acad. Sci. 72(12): 5135-5139.

Norppa H. 1981. The in vitro induction of sister chromatid exchanges and chromosome aberrations in human lymphocytes by styrene derivatives. Carcinogenesis. 2(3): 237-242.

Norppa H, Hemminki K, Sorsa M and H Vainio. 1981. Effect of monosubstituted epoxides on chromosome aberrations and SCE in cultured human lymphocytes. Mutat. Res. 91: 243-250.

Quarles JM, Sega MW, Schenley CK and RW Tennant. 1979b. Rapid screening for chemical carcinogens: Transforming activity of selected nitroso compounds detected in a transplacental host-mediated culture system. Natl. Cancer Inst. Monogr. 51: 257-263.

Quarles, JM, Sega MW, Schenley CK and W Lijinsky. 1979a. Transformation of hamster fetal cells by nitrosated pesticides in a transplacental assay. Cancer Res. 39: 4525-4533.

Rhim JS, Park DK, Weisburger EK and JH Weisburger. 1974. Evaluation of an in vitro assay system for carcinogens based on prior infection of rodent cells with nontransforming RNA tumor virus. J Natl Cancer Inst. 52(4): 1167-1173.

Rustung E et al; Biochem Z 242: 366-76 (1931)

Tates, A.D. and E. Kriek. 1981. Induction of chromosomal aberrations and sister-chromatid exchanges in Chinese hamster cells in vitro by some proximate and ultimate carcinogenic acrylamide derivatives. Mutat. Res. 88: 397-410.

Vasavada, H.A. and J.D. Padayatty. 1981. Rapid transfection assay for screening mutagens and carcinogens. Mutat. Res. 91: 9-14.

US EPA. IRIS Document for Acetone accessed online January 13, 2009.

BORON (Revision)

Boron is an element that is commonly found in soil and rocks. In nature boron is rarely found as a pure element, but rather is found in combination with other substances to form borates, boric oxides or boric acid. Borates are used mostly in the production of glass. They are also used in the manufacture of leather tanners, fire-retardant materials, cosmetics, photographic materials, and in some high-energy fuels. Some pesticides used for cockroach control and wood preservatives also contain borates.

CAS No	7440-42-8
Atomic symbol	B
Atomic weight	10.81
Physical state	Solid
Density	2.35
Water solubility	Insoluble as pure element, soluble as salt or acid
Synonyms	None

Occurrence

Boron is widely distributed in nature. Its concentration in sea water averages about 4.5 mg/L. Fresh surface water samples collected in the United States had boron concentrations ranging from 0.001 to 5 mg/L with an average value of about 0.1 mg/L. Background boron levels in U.S. soils were reported at a geometric mean of 26 mg/kg with a maximum concentration of about 300 mg/kg.(ATSDR, 1992) According to the Wisconsin Groundwater Retrieval Network, 2,403 potable and non-potable wells in Wisconsin have been tested for boron. Of these wells, 113 potable wells and 1,986 non-potable wells had detects of boron with an average concentration of 29.7 µg/L and 7.4 µg/L, respectively (WDRN, 1997).

Human Exposure Routes

Human exposure to borates may occur through ingestion of food and water or contact with insecticides used to control roaches. Inhalation of boron-containing dusts or absorption of boron from cosmetics or medical preparations through mucous membranes or damaged skin. Occupational exposures may be higher. Workers may be exposed by inhalation of dusts or gaseous boron compounds. Dermal absorption may also occur but this is considered to be a minor exposure pathway.

Toxicity

LD_{50}(rat) Boric acid: 898 mg/kg; Borax: 642 mg/kg

Ingestion of large amounts of boron can be fatal. Infants who ingested formula accidentally prepared with 2.5% boric acid died within 3 days. It was estimated that the amount of boric acid consumed ranged from 4.51 to 14 g. Infants became lethargic and developed vomiting and diarrhea. Degenerative changes were seen in the liver, kidney, and brain. Acute exposure to dose levels of 895 mg boron per kg body weight as boric acid was not lethal in an adult.

Groups of 4 male and 4 female dogs were fed borax and boric acid in the diet for two years. The NOAEL was established at 8.8 mg B/kg/day which was the highest dose tested. In an additional study, dogs were fed doses of 29 mg B/kg/day for 38 weeks. At this dose, severe testicular atrophy and spermatogenic arrest occurred (Weir and Fisher, 1972). A recent review of pathological records from this study revealed evidence of similar histological abnormalities in three of four animals fed the control diet. The authors of the review concluded that this observation of testicular pathology in control animals rendered the study inadequate for use in quantitative risk assessment (Moore et al, 1997).

Groups of 35 male and 35 female rats were fed borax and boric acid in the diet for 2 years at boron-equivalent doses of 117, 350, and 1170 ppm (5.9, 17.5 or 58.5 mg B/kg/day). No treatment-related effects were seen at 5.9 or 17.5 mg/kg/day. The LOAEL was 58.5 mg B/kg/day, based on the following: significantly decreased testes weights and testes-to-body weight ratios; atrophied seminiferous epithelium; and decreased tubular size in the testes. Brain and brain-to-body weight ratios were also significantly decreased (Weir and Fisher 1972).

Schroeder and Mitchener (1975) reported a lifetime study in which mice were administered boron in drinking water at 8.1 mg B/kg/day. No effects were observed with regard to body weight, longevity or survival.

Carcinogenicity

Under the *Draft Revised Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1999), data are inadequate for an assessment of human carcinogenic potential for boron.

Mutagenicity

No studies were located regarding genotoxic effects of boron in humans or animals. Results were negative in bacterial assays and in the *in vitro* mammalian assays.

Reproductive/Developmental Effects

Groups of 26-29 female rats were fed boric acid in gestational days 0-20 to assess the toxicity of boric acid in prenatal development and to determine the persistence of effects in a 21-day postnatal period. In the prenatal phase, decreased fetal body weight on gestational day 20 was observed at doses of 74 and 145 mg boric acid/kg/day (13 and 25 mg B/kg/day). A statistically significant increase in the number of fetuses per litter with shortened rib XIII was also observed at both doses. In the postnatal phase, a statistically significant increase in the number of pups per litter with shortened rib XIII was observed at 145 mg boric acid/kg/day (25 mg B/kg/day). The authors identified the prenatal NOAEL as 55 mg boric acid/kg/day (9.6 mg B/kg/day) and the postnatal NOAEL as 74 mg boric acid/kg/day (13 mg B/kg/day) (Price et al, 1996).

Boron exposure resulted in testicular atrophy and reduced sperm counts in dogs, rats and mice. In addition, reduced sperm counts have been observed among occupationally exposed men. These results suggest that reproductive toxicity may be an area of concern following human exposure to boron.

Environmental Fate

Since boron is an element, it is not subject to decomposition and can remain in the environment indefinitely. Its mobility is dependent on its chemical form. Boron salts and acids are water soluble and have a tendency to leach from soils into ground and surface water. Boron dusts and gases discharged into the atmosphere may be carried great distances before removal by wet or dry deposition.

Regulatory Summary

$BMDL_{05}$	10.3 mg/kg/day
UF	66
Reference dose	0.2 mg/kg/day
DWEL	7 mg/L

Lifetime health advisory	1 mg/L
MCL	None
Cancer class	D - Not classifiable

Confidence in the oral Reference Dose: High

EPA's confidence in the data base is high due to the existence of numerous studies, including several subchronic studies; chronic feeding studies in dogs, rats, and mice; a multigeneration study in rats; a continuous breeding reproductive study in mice; and developmental studies in rats, mice, and rabbits. EPA's high confidence in the RfD follows.

Existing Drinking Water Standards

Florida	630 ug/L
Maine	630 ug/L
Minnesota	600 ug/L
New Hampshire	630 ug/L
EU	1,000 ug/L
Vermont	600 ug/L
Wisconsin	960 ug/L

Recommendations and Conclusions

The Department of Health Services recommends revision of Wisconsin's groundwater enforcement standard for boron from 960 to 1,000 µg/L. This revision will provide consistency with the federal advisory for public water supplies. Since boron has not demonstrated carcinogenic or mutagenic effects, a 20% preventive action limit is appropriate.

Recommended enforcement standard	1,000 µg/L
Recommended preventive action limit	200 µg/L

References

Agency for Toxic Substances and Disease Registry. Toxicological Profile for Boron. Prepared by Life Systems, Inc. July 1992.

Moore JA et al. (1997). Assessment of boric acid and borax using the IEHR Evaluative Process for assessing human developmental and reproductive toxicity of agents. Reprod Toxicol 11: 123-160.

National Toxicology Program. (1987). Technical report series no. TR324 on the toxicology and carcinogenesis studies of boric acid in B6C3F1 mice (feed studies).

Price CJ, Strong PL, Marr MC, Myers CB and Murray FJ. (1996) Developmental toxicity NOAEL and postnatal recovery in rats fed boric acid during gestation. Fundam Appl Toxicol 32: 179-193.

Schroeder HA and Mitchener M. (1975). Life-term effects of mercury, methyl mercury and nine other trace metals in mice. J. Nutr. 105:452-458.

Ward AF et al. Environ Anal (Paper presented at the annual meeting of the Federation of Analytical Chemical Spectroscopy Society) 3rd, 1977.

Weir RJ Jr, and Fisher RS. (1972). Toxicological studies on borax and boric acid. Toxicol. Appl. Pharmacol. 23:351-364.

Wisconsin Department of Natural Resources Groundwater Retrieval Network, 1997.

CARBARYL (Revision)

Carbaryl is an N-methyl carbamate (NMC) pesticide, which was first registered in 1959 for use on cotton. In 2001, the Agency identified the NMC pesticides as a group which shares a common mechanism of toxicity. Therefore, the Agency was required to consider the cumulative effects on human health resulting from exposure to this group of chemicals when considering whether to establish, modify, or revoke a tolerance for pesticide residues in food, in accordance with the Food Quality Protection Act of 1996 (FQPA).

The insecticide carbaryl is used in agriculture to control pests on terrestrial food crops including fruit and nut trees, many types of fruit and vegetables, and grain crops; cut flowers; nursery and ornamentals; turf, including production facilities; greenhouses; golf courses; and in oyster beds. Carbaryl is also registered for use on residential sites (e.g., annuals, perennials, shrubs) by professional pest control operators and by homeowners on gardens, ornamentals and turfgrass.

Technical carbaryl is a white crystalline solid which melts at about 142^{o}C and has no appreciable odor. Carbaryl is soluble in most polar organic solvents such as acetone and mixed cresols and is only slightly soluble in water (40 ppm at 30^{o}C) and hydrolyses rapidly in alkaline solutions. It is stable to light, heat and acid with a melting point of 142^{o}C, a low vapor pressure (0.005 mm Hg at 26^{o}C) and no fumigant action.

CAS No.	63-25-2
Molecular Weight	201.23
Physical State	Odorless crystalline solid that varies from colorless to white or gray, depending on purity.
Water solubility	40 mg/L @ 30 C
Synonyms	Carbamine, Cekubaryl, Denapon, Devicarb, Dicarbam, Hexavin, Karbaspray, Nac, Rayvon, Septene, Sevin, Tercyl, Tricarnam, and Union Carbide-7744

Occurrence

The Wisconsin Department of Natural Resources reports that from 7/1/83 to 12/31/86 carbaryl was found in five well water samples. The highest detected level was 45 ug/L.

Monitoring of humans for carbaryl exposure is performed by analyzing urine for 1-naphthol. Preliminary results of a monitoring program indicate that 1-naphthol was detected at levels above 10 ppb in 19% of 265 samples from the general population with a maximum concentration of 0.24 ppm.

Toxicity

The acute toxicity of carbaryl varies by species and route of administration. Rats are more sensitive than dogs or monkeys. In humans, carbaryl is very highly toxic following absorption through the skin, highly toxic if ingested but only slightly toxic if inhaled. Depending on the route and degree of exposure, symptoms can include redness of the skin, convulsions, dizziness, labored breathing, nausea. unconsciousness, abdominal pain, vomiting, pupillary constriction, muscle cramps and excessive salivation.

Carbaryl is rapidly metabolized to several compounds which can build up in the liver and kidneys. Hydrolysis of carbaryl to the major urinary metabolites 1-napthyl glucuronide and 1-napthyl sulfate appears to be the primary metabolic pathway of carbaryl in man. Carbaryl has been shown to cross the placenta and accumulate in fetal brain, liver and ocular tissues.

In a subchronic neurotoxicity study (MRID 44122601), 12 Crl:CD(SD)BR rats/sex/group were administered technical carbaryl at doses of 0, 1, 10 or 30 mg/kg/day for 13 weeks. Cholinesterase (RBC, whole blood, plasma and brain) determinations were done on an additional three groups of five rats/sex/group at weeks 4, 8 and 13. Neurobehavioral screening, was performed prior to treatment and during Weeks 4, 8 and 13. There were no deaths during the study. There was an increased incidence of clinical signs of toxicity, including slight and moderate salivation and tremors, in the 30 mg/kg/day males and females. Multiple effects were seen in the 10 and 30 mg/kg/day males and females, including slight tremors, gait alterations, pinpoint pupils, increased salivation, reduced extensor thrust, decreased pinna reflex, reduced number of rearings, decreased vocalizations, decreased body temperature and decreased forelimb grip. Motor activity was significantly decreased in the 30 mg/kg/day males at Week 4 and the 30 mg/kg/day females at Weeks 4 and 8. The LOAEL for neurotoxicity was 10.0 mg/kg/day based on an increased incidence of FOB changes; the NOAEL was 1.0 mg/kg/day. The LOAEL for cholinesterase inhibition was 10.0 mg/kg/day based on statistically significant decreases in RBC, whole blood, plasma and brain cholinesterase; the NOAEL was 1.0 mg/kg/day.

Developmental

In a developmental neurotoxicity study the maternal toxicity LOAEL was 10 mg/kg/day based on decreased body weight gain, alterations in FOB measurements and RBC, plasma, whole blood and brain cholinesterase inhibition. The maternal NOAEL was 1.0 mg/kg/day. The developmental neurotoxicity LOAEL was 10 mg/kg/day based on a bilateral decrease in the size of the forebrain (Line A) in adult males (7.7-9.8%); a bilateral decrease in the length of the cerebella (Line F) in female pups (15-22%); and a bilateral increase in the length of the cerebella (Line F) in female adults (7.4-15%). The developmental NOAEL was 1 mg/kg/day (US EPA, 2002).

Carbaryl was found to be teratogenic to pups of pregnant beagle dogs fed 3.125, 6.25, 12.5, 25, and 50 mg/kg bw/day of carbaryl throughout gestation. Teratogenic effects observed at all but the lowest dose ranged from abdominal-thoracic fissures with varying degrees of intestinal agenesis and displacement to superfluous phalanges. Teratogenic effects were dose-related with no abnormalities noted in control pups.

A Union Carbide sponsored study confirmed that carbaryl produces teratogenic malformations in beagle dogs. In this experiment, pregnant beagle dogs were fed 2.0, 5.0 and 12.5 mg/kg/day of carbaryl in the diet from day 1 until weaning at 6 weeks. Birth defects including umbilical hernia, cleft palate, fat-like mass in the heart, intussusception of ileum into colon, extravasation of blood into the myocardium and unilateral microphthalmia were reported at the 5.0 and 12.5 mg/kg feeding levels. No defects were seen in control animals or animals dosed at 2.0 mg/kg.

Mutagenicity

Carbaryl was not mutagenic in *S. typhimurium* strains TA 100, TA 98, TA 1535, and TA 1537 in the presence of an aroclor induced rat liver microsome preparation. Carbaryl was not mutagenic with or without activation to *S. typhimurium* strains 1535, 1536, 1537 and 1538. USEPA cites one study in which carbaryl was claimed to be mutagenic to *S. typhimurium* after activation and that the 1-napthol metabolite is mutagenic without activation.

Carcinogenicity

US EPA Cancer Classification: L, Likely human carcinogen

Carbaryl is classified as "likely to be carcinogenic to humans," based on an increased incidence of vascular tumors in mice. Cancer risks are calculated by multiplying dietary exposure by the Q1*, or unit risk, which is a quantitative dose response factor, by the lifetime average daily dose. The Q* for carbaryl is 8.75 x 10^{-4} per mg/kg/day (US EPA, 2002).

Environmental Fate

Terrestrial

Carbaryl degradation varies with soil types in the order of clay loam> sandy loam> clay> loam> loamy sand. Carbaryl is moderately mobile in soil with decreased mobility related to increased organic carbon content of soils. The major environmental degradation product is 1-napthol.

Carbaryl's leaching characteristics, degradation rates and pathways make it unlikely to contaminate groundwater. Surface water contamination is possible due to spray drift and forest applications.

Surface Water

Carbaryl degrades in natural and sterilized natural water in 4 weeks and in sterilized distilled water in 12 weeks. This data indicates that chemical processes are most important in carbaryl aquatic metabolism with biological degradation of secondary importance.

In Little Miami River water, carbaryl was 95% degraded in one week and undetectable the second. In pond water (pH 7.5-7.8), carbaryl's half-life was between 14 and 21 days, and in creek water (pH 7.0-7.1) at between 34 and 50 days. Carbaryl movement into sediments appears to reduce its persistence in water. One week after a creek was treated with 1 ppm carbaryl, 47% of applied material was found in the bottom sediment vs. 30.2% in the water. From day 8 onward, measurable levels of carbaryl declined faster in creek water than sediment. A similar residue decline pattern was reported for carbaryl in pond water plus bottom sediment.

Bioaccumulation potential in aquatic food chains has not been assessed. One ecosystem study showed bioaccumulation factors of 140, 260, 300, 3600 and 4000 respectively for catfish, crayfish, snails duckweed, and algae. Carbaryl is extremely toxic to invertebrates and certain marine/estuarine organisms, extremely toxic to bees, moderately toxic to warm and cold water fishes. It has low toxicity to birds.

Regulatory Summary

MCL	None
MCLG	None
NOAEL	1.0 mg/kg/day (OPP RfD Tracking Report, 1997)
LOAEL	10.0 mg/kg/day (OPP RfD Tracking Report, 1997)
DWEL	0.4
Uncertainty Factor	100 (to account for the inter- and intra-species differences)
RfD	0.01 mg/kg/day (US EPA/Office of Water, 2006)
Cancer Classification	Likely
Cancer slope factor	8.75 x 10E-4/mg/kg/day

State drinking water standards and advisories

New York	29 µg/L
Vermont	70 µg/L
Wisconsin	960 µg/L

Recommendations and Conclusions

The Department of Health Services recommends revision of the enforcement standard, which is currently set a 960 ug/L to a level that will limit cancer risk to the 1-in-a-million lifetime risk level. Since carbaryl has carcinogenic effects, a 10% preventive action limit is proposed.

$$\frac{1 \times 10\text{-}6 \text{ lifetime risk} \times 70\text{-kg} \times 100\% \text{ exposure}}{8.75 \times 10\text{-}4/\text{mg/kg/day} \times 2 \text{ liters/day}} = 0.04 \text{ mg/L or } 40 \text{ µg/L}$$

Recommended Enforcement Standard:	40 µg/L
Recommended Preventive Action Limit:	4 µg/L

References

USEPA. IRIS, Carbaryl accessed July 2008.

USEPA Office of Water. Drinking Water Standards and Health Advisories, 2006.

USEPA Office of Pesticide Programs. Pesticide Tracking Report, 2/19/1997.

US EPA, HED. 2002. Carbaryl: Updated Toxicology Disciplinary Chapter for the Reregistration Eligibility Decision Document, completed: May 24, 2002.

WDNR. February 19, 1988. Groundwater Contaminant Occurrence Data. Memo from Bruce J. Baker, WDNR to Dr. Henry Anderson, DHSS.

CHLOROMETHANE (Revision)

Chloromethane is a gas which has been used as a refrigerant and propellant. Currently it is used as a chemical intermediate, principally in the production of silicones and tetramethyl lead. It is moderately toxic when inhaled causing central nervous system depression.

CAS No.	74-87-3
Chemical formula	CH_3Cl
Molecular weight	50.48
Physical state	Colorless, odorless gas
Density	0.9159
Water solubility	7,400 mg/L at 25 ^{o} C
Synonyms	Methyl chloride

Occurrence

Chloromethane is produced naturally in seawater by the reaction of methyl iodide with chloride ions. It is also released from brush and forest fires and is a volatile compound released from cedar and cypress trees. These natural sources are believed to be responsible for most of the chloromethane found in the global atmosphere. Agricultural slash burning is believed to be the source of high levels of methyl chloride in the Amazon and this, in addition to coal combustion, is thought to contribute to high levels in parts of China. It is formed in the chlorination of drinking water and sewage effluent and is found in the effluent of some publically owned treatment works.

Chloromethane may be emitted as fugitive emissions and in wastewater during its production and use in the manufacture of silicones, agrichemicals, methyl cellulose, quarternary amines, butyl rubber, and tetraethyl lead. It is released in tobacco smoke which contains up to 1200 ppm chloromethane and turbine exhaust as well as in its use as a solvent, propellant, and in the manufacture of fumigants. Just as forest fires contribute to natural sources of methyl chloride, so does wood burning, field burning, and backyard burning contribute to atmospheric burdens.

Most human exposure probably results from inhalation of chloromethane in the workplace where it is used in the manufacture of various synthetic materials, principally silicone. NIOSH has statistically estimated that 40,545 workers are exposed to methyl chloride in the USA. NIOSH (NOES Survey 1981-1983) has estimated that 4,534 workers are exposed to methyl chloride in the USA.

Evidence of human exposure has been documented. Mother's milk from 4 urban areas of the US - 2 of 8 samples positive detected not quantified. Methyl chloride was detected in expired air from a sample of 62 nonsmoking individuals.

Toxicity

Chloromethane is a relatively potent narcotic in humans. Inhalation exposures are associated with headaches, nervousness, sleepiness, unconsciousness, and in severe cases death. These symptoms may be delayed in onset and may increase in severity for up to 48 hours after the exposure has ended.

A 3 hour exposure to 200 ppm chloromethane resulted in a slight impairment of hand-eye coordination in male and female college students whose average age was 22 years.

Repko studied the effect of occupational exposure to chloromethane in 122 workers. The control group consisted of 49 unexposed workers in the same industry. The concentration of chloromethane in the ambient air of the exposed workers ranged from 7.4 to 70 ppm, with amean concentration of 34 ppm (70 mg/m^3). A battery of behavioral, psychological and neurological tests, and an electroencephalogram (EEG) was done on each worker. An increase in ambient air concentration and an increase in urine acidity were correlated with a poorer performance on the behavioral tasks. There was no relationship between exposure and psychological or personality effects. Likewise, there was no effect on neurological tests or EEG records. However, chloromethane exposure was correlated with an adverse effect on the performance of cognitive time-sharing tasks and a significant increase in the magnitude of finger tremors.

Carcinogenicity

US EPA Classification: Not Classified

US EPA has determined that there is inadequate information on which to base a classification for carcinogenic effects. In their IRIS document for Chloromethane, EPA states the following, "The few studies that have examined methyl chloride's potential carcinogenicity in humans have failed to convincingly demonstrate any association, and in one instance even indicated a lower cancer incidence than expected in workers chronically exposed to methyl chloride in a butyl rubber manufacturing plant. In animals, the only evidence of carcinogenicity comes from a single 2-year bioassay, which found a statistically significant increased incidence of renal benign and malignant tumors only in male B6C3F1 mice at the high concentration (1,000 ppm), although two renal adenomas occurring in 225-ppm males may also be treatment-related. Neoplasia were not found at lower concentrations or at any other site in the male mouse, nor at any site or concentration in female mice or F-344 rats of either sex. Renal cortical tubuloepithelial hyperplasia and karyomegaly were also confined to 1,000-ppm male mice (IRIS Document accessed January 29, 2009).

Mutagenicity

Chloromethane was mutagenic to TK6 human lymphoid cells in vitro and caused an increased incidence of sister chromatid exchange and breakage of DNA strands. Chloromethane was mutagenic to *Salmonella typhimurium* with and without metabolic activation (US EPA, IRIS).

Reproductive Effects

Hamm et al reported a decrease in male fertility in F344 rats exposed to chloromethane. There was a significant decrease in the number of fertile matings in the males exposed to 475 ppm. Males exposed to 1,500 ppm were sterile. There was no effect on female reproductive ability.

Environmental Fate

Atmospheric

The dominant loss mechanism for chloromethane in the troposphere is upward diffusion although washout by rain may also be important. From the tropopause to about 30 km, both upward diffusion and reaction with hydroxyl radicals will be of approximately equal importance, and above 30 km in the stratosphere diffusion, reaction with hydroxyl radicals, and photo dissociation will have approximately equal weight. The surface half-life resulting from upward diffusion is 80 days (HSDB, 2000).

Aquatic

If chloromethane is released into water, it will be lost primarily by volatilization (half-life 2.1 hr in a typical river (HSDB, 2000).

Terrestrial

Land disposal will result in rapid volatilization to the atmosphere with small amounts leaching to groundwater. Landfill disposal may result in contamination of the groundwater where it may biodegrade very slowly (HSDS, 2000).

Regulatory Summary

MCL/MCLG	None
Lifetime health advisory	30 µg/l (US EPA, 2006)
Reference dose	0.004 mg/kg/day (US EPA, 2006)
Cancer classification	Not classifiable (US EPA, IRIS, 7/17/2001)

State Drinking Water Standards and Advisories

Connecticut	55 µg/L
Arizona	0.19 µg/L
Florida	2.7 µg/L
Maine	3 µg/L
Washington	1.3 µg/L
Wisconsin	3 µg/L

Recommendations and Conclusions

The Department of Health Services recommends revision of the groundwater enforcement standard from 3 to 30 ug/L. This change reflects modification of the US EPA's cancer risk assessment and lifetime health advisory chloromethane. Since chloromethane appears to have weak carcinogenic and mutagenic effects, we recommend that the preventive action limit continue to be set at the 10% level.

Recommended enforcement standard	30 µg/l
Recommended preventive action limit	3 µg/l

References

ATSDR. Toxicological Profile for Methyl Chloride. Atlanta, GA.

HSDB. Methyl Chloride, accessed January 29, 2009.

Repko J.D., et al. 1991. Behavioral and neurological effects of methyl chloride: behavioral and neurological evaluation of workers expsed to industrial solvents: methyl chloride. DHEW (NIOSH) Publ. No. 77-125, p. 66; as cited in US Environmental Protection Agency. Drinking Water Health Advisories:Volatile Organic Compounds. Lewis Publishers, Chelsea, MI, 1991.

US EPA. IRIS Document for Methyl Chloride, Accessed January 29, 2009.

Hamm TE, Raynor TH and Phelps MC, et al. 1985. Reproduction in Fischer-344 rats exposed to methyl chloride by inhalation for two generation. Fund Appl Toxicol. 5(3):568-577.

DIBUTYL PHTHALATE (Revision)

Dibutyl phthalate (DBP) is used primarily as a plasticizer for polyvinyl acetate emulsions. Other uses include use as a plasticizer for other specialized vinyl formulations, varnishes and carpet backing and as an insect repellant for impregnation of clothing. Phthalates are used in a variety of personal care products. DBP was used in some nail polishes; all major producers began eliminating this chemical from nail polishes in the fall of 2006.

CAS No.	84-74-2
Chemical Formula	$C_{16}H_{22}O_4$
Molecular Weight	278.34
Density	1.0459 at 20°C
Solubility in Water	13 mg/L at 25°C
Odor	Slight characteristic ester odor
Odor/Taste Threshold in Water	No data
Synonyms	Di-n-butyl phthalate, phthalate acid dibutyl ester

Occurrence

Dibutyl phthalate has been found in the drinking water of six U.S. cities at concentrations ranging from 0.01-5.0 ppb. Concentrations of 0.1-1 ppb have been detected in surface water samples from 14 industrialized U.S. river basins and in urban runoff from U.S. cities at concentrations of 0.5-11 ppb.

Air concentrations in the U.S. range from 0 to 20 ng/m^3. Dibutyl phthalate is used as a plasticizer in food wrappings and food containers and it can migrate from the plastic packaging into foods. It has been estimated that 150 mg of dibutyl phthalate will migrate into 1 kg cheese with 15% fat content.

Daily air and water intake are estimated at 0-400 ng and 20 ng-10,000 ng, respectively. Data on food intake is insufficient, but exposure via this route may be orders of magnitude greater than air or water intake.

Toxicity

LD_{50} (rat, intramuscular injection): 8 g/kg
LD_{50} (mouse, oral): 9 g/kg

The No Observable Adverse Effect Level (NOAEL) used by the U.S. Environmental Protection Agency to develop a reference dose was derived from a 1953 study in which male Sprague-Dawley rats in groups of 10 were fed diets containing 0, 0.01, 0.05, 0.25, and 1.25% dibutyl phthalate for a period of 1 year. One-half of all rats receiving the highest dibutyl phthalate concentration died during the first week of exposure. The remaining animals survived the study with no apparent ill effects. There was no effect of treatment on gross pathology or hematology. While it was stated that several organs were sectioned and stained, no histopathologic evaluation was reported. In this study, a NOAEL of 0.25% dibutyl phthalate, converted to 125 mg/kg/day, was identified. EPA's IRIS data base indicates that newer studies are available and that the reference dose for dibutyl phthalate, which was developed in 1986, is currently under review.

A number of other studies have been performed since that time in which experimental animals were administered higher doses for shorter periods of time. Effects were noted in animal mortality, liver enzyme activity, red blood cell count, and other nonspecific toxic endpoints.

Carcinogenicity

USEPA Cancer Classification: Group D, Not classifiable

No adequate long-term toxicity or carcinogenicity studies in animals or man are available. Phthalate esters are known to induce peroxisomal proliferation in the liver of mice and rats. In general the longer chain and branched chain dialkylphthalates are more potent for the induction of peroxisomal proliferation than others. Many peroxisome proliferators have been shown to induce hepatocellular tumors when administered at high dose-levels for long periods to mice and rats despite being non-genotoxic. The mechanisms of induction of carcinogenicity by peroxisome proliferators may be complex but are considered to have a threshold. A variety of independent studies have shown that there are marked species differences in the sensitivity to chemicals that cause peroxisome proliferation. Rats and mice are extremely sensitive, hamsters show a less marked response while guinea-pigs, primates and man are less sensitive (EU Report, 2004).

Mutagenicity

Dibutyl phthalate did not induce mutations in a modified reverse mutation plate incorporation assay in *Salmonella* strains TA100 and TA98 at concentrations up to 1000 ug/plate in the presence or the absence of S9 hepatic homogenate. It was a weak direct-acting mutagen in a forward mutation assay in *Salmonella typhimurium*. Dibutyl phthalate was mutagenic in the mouse lymphoma forward mutation assay only in the presence of metabolic activation. In addition, dibutyl phthalate showed some evidence of clastogenic activity in Chinese hamster fibroblasts but was negative in human leukocytes.

Reproductive/Developmental Effects

DBP was added to the California Proposition 65 (1986) List of suspected teratogens in November 2006. It is a suspected endocrine disruptor.

In utero exposure to di(n-butyl) phthalate (DBP) leads to a variety of male reproductive abnormalities similar to those caused by androgen receptor antagonists. DBP demonstrates no affinity for the androgen receptor, but rather leads to diminished testosterone production by the fetal testis. A study by Thompson, et al. examined the onset and reversibility of DBP effects on the fetal testis and identify points in the cholesterol transport and steroidogenesis pathways affected by DBP. These investigators concluded that high-dose DBP exposure leads to rapid and reversible diminution of the expression of several proteins required for cholesterol transport and steroidogenesis in the fetal testis, resulting in decreased testosterone synthesis and abnormal male reproductive development (Thompson et al, 2004).

Interactive Effects

No information on the effects of simultaneous administration of dibutyl phthalate with another chemical were located.

Environmental Fate

Di-n-butyl phthalate is a ubiquitous pollutant due to its widespread use primarily as a plasticizer in plastics which are used throughout our society. It may be released into the environment as emissions and in wastewater during its production and use, incineration of plastics and migration of the plasticizer from materials containing it.

If released into water it will adsorb moderately to sediment and particulates in the water column. The compound will disappear in 3-5 days in moderately polluted waters and generally within 3 weeks in cleaner bodies of water. It will not bioconcentrate in fish since it is readily metabolized.

If spilled on land it will adsorb moderately to soil and slowly biodegrade (66 and 98% degradation in 26 weeks from two soils). Dibutyl phthalate is found in groundwater under rapid infiltration sites and elsewhere. It has been suggested that its tendency to form complexes with water-soluble fulvic acids, a component of soils, may aid its transport into groundwater. Although it degrades under anaerobic conditions, its fate in groundwater is unknown.

Regulatory Summary

NOAEL	125 mg/kg/day
LOAEL	600 mg/kg/day (increased mortality)
Uncertainty Factor	1,000
Reference dose	0.1 mg/kg/day (1986)
MCL	None
MCLG	None
DWEL	4.0 mg/L
Cancer classification	D, not classifiable

State Drinking Water Standards and Advisories

Minnesota	700 µg/L
New Jersey	700 µg/L
New York	50 µg/L
Wisconsin	100 µg/L

Recommendations and Conclusions

The Department of Health Services recommends revision of the groundwater standard from 100 µg/L to 1,000 µg/L. This revision is based on the current EPA reference dose for this substance. Since dibutylphthalate has shown some evidence of mutagenicity in in vitro assays a 10% preventive action limit is proposed.

$$\frac{0.1 \text{ mg/kg/day} \times 10 \text{ kg} \times 100\%}{1 \text{ liter/day}} = 1{,}000 \text{ µg/L}$$

Recommended Enforcement Standard	1,000 µg/L
Recommended Preventive Action Limit	100 µg/L

References

Hazardous Substances Data Bank. Di-n-butyl phthalate. Washington, DC: National Library of Medicine, 1995.

USEPA (1995). IRIS Document for Di-n-butyl phthalate. Jan. 1, 1995.

Thompson CJ, Ross SM, Gaido KW. 2004. Di(n-butyl) phthalate impairs cholesterol transport and steroidogenesis in the fetal rat testis through a rapid and reversible mechanism. Endocrinology 145(3):1227-37.

European Union. 2004. Risk Assessment Report: Dibutyl Phthalate, Addendum to the Environmental Section.

ETHYLENE GLYCOL (Revision)

Ethylene glycol is a colorless, viscous liquid widely used as an antifreeze/coolant for automobiles and as a chemical intermediate in the production of synthetic fibers and plastics. The compound is also used in inks and skin moisturizing creams. U.S. production and imports of ethylene glycol was 2.2 x 10^9 kg in 1988 (HSDB, 1991).

CAS No.	107-21-1
Molecular Formula	$C_2H_6O_2$
Molecular Weight	62.07
Physical State	Liquid at room temperature
Water Solubility	Absorbs twice its weight in water
Odor/Taste Threshold	No odor, sweet taste (no data on threshold)
Specific Gravity	1.114
Synonyms	1,2-ethanediol, glycol, glycol alcohol

Occurrence

Ethylene glycol can enter the environment when released in waste water or from disposal on land. It is rapidly degraded in soils and surface waters (see **Environmental Fate** below). No information concerning ethylene glycol concentrations in environmental media was located.

The primary mode of human ethylene glycol exposure is thought to be contact with skin and eyes resulting from industrial handling. The chemical is not volatile at room temperature, however, inhalation may be a problem if material is handled hot or if a mist is generated by violent agitation (Clayton and Clayton, 1981). Exposure to ethylene glycol can occur from dermal contact with antifreeze and coolants containing ethylene glycol.

Elimination of administered ethylene glycol occurs in two phases. The half-life of the first phase is about 3-5 hr and of the second phase is about 12 hr (Marshall, 1982). Administered ethylene glycol is primarily excreted as oxalate, hippurate and unchanged ethylene glycol in the urine (Riley, 1982).

Toxicity

LD_{50} (rat, oral):	8.54 g/kg
LD_{50} (mouse, oral):	13.7 g/kg

A number of incidents have been reported in which humans have accidentally ingested large quantities of ethylene glycol. The lethal dose for an adult is estimated to be about 1.4 g/kg or about 100 ml (Kirk-Othmer, 1980). The underlying basis for the toxicity of ethylene glycol can be divided into two major categories: one is tissue destruction due to deposition of calcium oxalate crystals and the second is the production of severe acidosis due to aldehyde, glycolate, and lactate production (Haddad and Winchester, 1983). At lower doses, ingestion of ethylene glycol can result in intoxication resembling that due to alcohol with ataxia, drowsiness, and slurred speech, possibly stupor, coma, and convulsions (Parry and Wallach, 1974).

In one study (DePass et al, 1986) investigators conducted 2-year studies using groups of approximately 30 rats/sex and 20 mice/sex fed diets providing ethylene glycol dosages of 0, 40, 200, or 1000 mg/kg/day. High-dose rats had increased mortality, neutrophil count, water intake, kidney hemoglobin and hematocrit, and chronic nephritis. Female rats exposed to 1000 mg/kg/day had mild fatty changes in the

liver. No adverse effects occurred at other doses in rats or at any dose in mice. Based upon this study, the USEPA determined a NOAEL of 200 mg/kg/day (US EPA, 1991).

In another study (Blood, 1965), groups of Sprague-Dawley rats (16/sex/group) were fed diets containing 0, 0.1, 0.2, 0.5, 1.0, or 4.0% ethylene glycol for 2 years. Male rats at 1.0 and 4.0% and females at 4.0% had increased mortality, decreased growth, increased water consumption, proteinurea, and renal calculi. There was an increased incidence of cytoplasmic crystal deposition in renal tubular epithelium at 0.5 and 1.0%. There were no effects on organ weights or hematologic parameters. The authors concluded that 0.2% (2000 ppm) was a NOEL for rats; the LOAEL was 0.5% (5000 ppm). Assuming that a rat consumes food equivalent to 5% of its body weight/day, the NOEL and the LOAEL in this study are equivalent to 100 mg/kg/day and 250 mg/kg/day, respectively. The EPA chose the former study to determine the NOAEL because of the greater number of animals and overall quality of the data.

Carcinogenicity

EPA classification: D, Not Classified (inadequate human and animal evidence of carcinogenicity).

Two two-year rat studies did not result in increased incidence of tumors in any treated group of animals.

Mutagenicity

No significant mutagenic activity was observed using in *Salmonella typhimurium* with or without microsomal activation (Clark, 1979).

Reproductive Effects

In a study by Maronpot et al., (1983), investigators found increased preimplantation loss and increased incidence of poorly ossified vertebral centra in offspring of rats treated at 1000 mg/kg in the diet on days 6-15 of gestation. No effects occurred at 40 or 200 mg/kg. In another, investigators reported that exposure of male and female mice to 1.0% ethylene glycol in drinking water for 14 weeks resulted in significantly fewer litters, decreased mean live pup weight, and decreased number of live pups/litter (Lamb et al, 1985).

In a 3-generation study in which rats were treated with 0, 40, 200, or 1000 mg/kg/day in the diet (De Pall et al., 1986), no treatment-related effects were observed. Finally, investigators treated rats with gavage doses of 0, 1250, 2500, or 5000 mg/kg/day and mice with 0, 750, 1500, or 3000 mg/kg/day on days 6-15 of gestation (Price et al., 1985). The percentage of litters with malformed fetuses increased in a dose-related manner in both species at all doses. There was a dose-related increase in post-implantation losses per litter in both species, but it was significant only in high-dose rats. Maternal body weight gain was decreased at all doses in rats and at the two higher doses in mice.

Interactive Effects

Magnesium and ethanol have been found to inhibit ethylene glycol metabolism, thus protecting against the compounds toxic effects (HSDB, 1991).

Environmental Fate

Atmospheric
If ethylene glycol volatilizes, it will react in the atmosphere with hydroxyl radical with a half-life of about 1 day (HSDB, 1991).

Aquatic
Ethylene glycol will readily biodegrade in surface water with a half-life of approximately 3 days. Although no data are available on ethylene glycol persistence in groundwater, should the compound leach into the groundwater, biodegradation may occur (HSDB, 1991).

Terrestrial
No data are available that report the fate of ethylene glycol in soils; however, by analogy to its fate in water, biodegradation is probably fast and the dominate removal mechanism (HSDB, 1991).

Regulatory Summary

NOAEL	200 mg/kg/day
UF	100 (10 for animal/human extrapolation, 10 to account for sensitive humans)
RfD	2 mg/kg/day
DWEL	7,000 µg/L
Lifetime HA	14,000 µg/L
MCL	None
MCLG	None
Cancer Class	D, not classifiable

State Drinking Water Standards and Advisories

Arizona	5,500 µg/L
California	14,000 µg/L
Florida	14,000 µg/L
Massachusetts	14,000 µg/L
Minnesota	10,000 µg/L
New Hampshire	7,000 µg/L
New Jersey	300 µg/L
Vermont	7,000 µg/L
Wisconsin	7,000 µg/L

Recommendations and Conclusions

The Wisconsin Department of Health Services recommends revision of the groundwater enforcement standard from 7,000 µg/L to 14,000 µg/L. This change is needed to reflect the most current federal risk assessment for this substance. Because ethylene glycol is not known to have carcinogenic or mutagenic effects, a 20% preventive action limit is proposed.

Recommended Enforcement Standard: 14,000 µg/L
Recommended Preventive Action Limit: 2,800 µg/L

References

Blood, FR. 1965. Chronic toxicity of ethylene glycol in the rat. Food Cosmet Toxicol 3, 229-234.

Clark CR. 1979. Toxicol Appl Pharmacol 51, 529-35.

Clayton, GD and FE Clayton (eds.). 1981. Patty's Industrial Hygiene and Toxicology, Volume 2: Toxicology. 3rd ed. New York: John Wiley Sons, 3818.

DePass, LR, MD Woodside, RR Maronpot and CS Weil. 1986. Three-generation reproduction and dominant lethal mutagenesis studies of ethylene glycol in the rat. Fund Appl Toxicol 7, 566-572.

DePass, LR, RH Garman, MD Woodsidem et al. 1986. Chronic toxicity and oncogenicity studies of ethylene glycol in rats and mice. Fund Appl Toxicol 7, 547-565.

Haddad, LM and JF Winchester. 1983. Clinical Management of Poisoning and Drug Overdosage. Philadelphia, PA: W.B. Saunders Co., 402.

Hazardous Substances Data Base. 1991. Ethylene Glycol.

Kirk-Othmer Encyclopedia of Chemical Technology. 1980. 3rd ed., Volume 3. New York, NY: John Wiley and Sons, 94.

Lamb, JC, RR Maronpot, DK Gulati, VS Russell, L Hommel-Barnes and PS Sabharwal. 1985. Reproductive and development toxicity of ethylene glycol in the mouse. Toxicol Appl Pharmacol 81, 100-112.

Maronpot, RR, JP Zelenak, EV Weaver and NJ Smith. 1983. Teratogenicity study of ethylene glycol in rats. Drug Chem Toxicol 6, 579-594.

Marshall TC. 1982. J Toxicol Environ Health 10, 397-409.

Parry MF and R Wallach. 1974. Am J Med Sci 57, 143-50.

Price, CJ, CA Kimmel, RW Tyl and MC Marr. 1985. The developmental toxicity of ethylene glycol in rats and mice. Toxicol Appl Pharmacol 81, 113-127.

Riley JH. 1982. Vet Hum Toxicol 24, 331-4.

U.S. Environmental Protection Agency. 1991. Integrated Risk Information System. Ethylene Glycol. Rev. 4/1/91.

METHYL ETHYL KETONE (Revision)

Methyl ethyl ketone is a common industrial solvent and fabric coating. It is also used as a flavoring and fragrance agent in candy and perfume. Total U.S. production in 1999 was reported to be 260,000 metric tons.

Large quantities of methyl ethyl ketone are used as a solvent especially in the coating industry. MEK is discharged into the atmosphere from this and other industrial uses. It is also discharged in waste water. High atmospheric levels are associated with photochemical smog episodes although it is generally absent from ambient air. It is formed as a result of the natural photooxidation of olefinic hydrocarbons emitted by automobiles, etc.

CAS no.	78-93-3
Chemical Name	2-Butanone
Molecular Formula	$CH_3COCH_2CH_3$
Molecular Weight	72.1
Physical State	Colorless, flammable liquid with fragrant mint-like odor
Water Solubility	353 g/L at 10^{o}C
Specific Gravity	0.805 at 20^{o}C
Synonyms	2-Butanone, Ethyl Methyl Ketone, MEK, Methyl Acetone

Occurrence

Methyl ethyl ketone is an infrequent contaminant in drinking water supplies. In a federal survey of groundwater supplies, less than 5% contained detectable levels (Dyksen, 1982). In Wisconsin, MEK has been found in 18 of 4,893 wells tested in Wisconsin. The highest level detected (5,100 ug/L) was in a sample collected from a monitoring well at a county landfill (WDNR, 1990).

MEK may be found in soil and water in the vicinity of hazardous waste sites. It has also been detected as a natural component of tobacco smoke and in numerous foods, including: raw chicken breast, milk, nuts (roasted filberts), cheese (Beaufort, Gruyere, and cheddar), bread dough and nectarines at concentrations ranging from 0.3 to 19 ppm (ATSDR, 1992; HSDB, 1999; WHO, 1992). WHO (1992) estimated levels of daily MEK intake from different sources as follows: foodstuffs – 1,590 µg/day; drinking water – 3.2 µg/day; rural outdoor air – 36 µg/day; urban outdoor air - 760 µg/day; and tobacco smoke - 1,620 µg/day. NIOSH has estimated worker exposure at 3,031,000 (NIOSH,). People are primarily exposed to methyl ethyl ketone in occupational atmospheres, especially related to coatings, since it is a common solvent; and in polluted atmospheres, particularly during photochemical smog episodes. It is a component of many foods. Non-alcoholic beverages, ice cream, candy and baked goods can contain as much as 70, 270, 100 and 100 ppm MEK, respectively (Furia, 1975).

Toxicity

MEK is similar to, but more irritating than, acetone. Concentrations above 200 ppm are irritating to mucous membranes and eyes.

Evidence that MEK may induce solvent-like effects such as peripheral or central nervous system changes in humans is restricted to a small number of case reports and occupational studies. Three case studies demonstrated adverse effects among men who had repeated, high level exposures to MEK. In 1992, Seaton et al. reported that a maintenance fitter was exposed to MEK for 2–3 hours/day for 12 years.

Exposure was via both dermal and inhalation routes. The worker developed slurred speech, cerebral ataxia, and sensory loss in his arms and on the left side of his face. Nuclear magnetic resonance imaging showed severe cerebellar and brainstem atrophy; however, nerve conduction studies were normal. A survey of his work area revealed peak MEK concentrations in excess of 5,000 mg/m³ during some operations and 10-minute average concentrations of approximately 900 mg/m³.

In 1995, Callender reported that a 31-year-old male engineer developed severe chronic headache, dizziness, loss of balance, memory loss, fatigue, tremors, muscle twitches, visual disturbances, throat irritation, and tachycardia after working for 7 months in a quality assurance laboratory where he was exposed daily to MEK and fumes from burning fiberglass material. Personal protection equipment and formal safety training were not provided. Based on a physical examination, neuropsychological tests (Poet Test Battery and WHO Neurobehavioral Core Test Battery), electroencephalographic tests, evoked brain potential tests, nerve conduction velocity tests, rotational and visual reflex testing, vestibular function testing, and SPECT and MRI scans of the brain, the patient was diagnosed with chronic toxic encephalopathy, peripheral neuropathy, vestibular dysfunction, and sinusitis. Information concerning the exposure levels and subsequent possible progression or regression of these conditions was not provided.

In a third case, a 27-year-old man developed multifocal myoclonus, ataxia, and postural tremor after occupational exposure (through dermal and inhalation pathways) over a 2-year period to solvents containing 100% MEK (Orti-Pareja et al., 1996). The actual exposure levels are unknown. The patient reported symptoms of dizziness, anorexia, and involuntary muscle movement, beginning about one month prior to admission. Neurological examination confirmed multifocal myoclonus, ataxia, and tremor. Symptoms of solvent toxicity disappeared after cessation of exposure and treatment with clonazepam and propranolol. Symptoms did not recur after withdrawal of the drugs.

Prolonged exposure may produce CNS depression, however, no adverse health effects have been related to chronic exposure to low atmospheric concentrations in the workplace. Workers exposed by inhalation (300-600 ppm) and by skin contact developed dermatitis and a numbness in the extremities. Headache, mild vertigo, and diminished vision were noted (Clayton, 1981).

Three cases of polyneuropathy occurred in shoe factory workers exposed to combined methyl ethyl ketone and acetone or toluene vapors concentrations below 200 ppm. Skin absorption also occurred. Although not highly neurotoxic itself, MEK may potentiate substances known to cause neuropathy (Dyro, 1978).

In the 1955 study used by the USEPA for deriving an oral reference dose, LaBelle and Brieger (1955) exposed 25 rats to air containing 235 ppm of methyl ethyl ketone for 7 hours/day, 5 days/week for 12 weeks. No effects were observed, but only a few parameters were measured.

Carcinogenicity

USEPA Classification: D, Not classifiable as to human carcinogenicity

According to EPA's draft revised cancer guidelines (U.S. EPA, 1999), the hazard descriptor "*data are inadequate for an assessment of human carcinogenic potential*" is appropriate for MEK because cancer studies of humans chronically exposed to MEK are inconclusive, MEK has not been tested for carcinogenicity in animals by the oral or inhalation routes, and the majority of short-term genotoxicity testing of MEK has demonstrated no activity (EPA, IRIS, updated 2003).

Mutagenicity

The ability of methyl ethyl ketone to produce mutations has been studied in cultured mouse lymphoma cells (Microbiological Assoc, 1984), *Salmonella* and *Escherichia col*i bacteria, *Saccharomyces cerevisiae* tester strain JD1 and in cultured rat liver cells (Shell Sittingbourne Research Center, 1982). All studies done to date have failed to demonstrate a mutagenic effect.

Reproductive/Developmental Effects

Cox et al. (1975) conducted a multigeneration reproductive and developmental toxicity study of 2-butanol in which weanling FDRL-Wistar stock rats (30/sex/group) were given 2-butanol in drinking water at 0, 0.3, 1, or 3% solutions and a standard laboratory ration *ad libitum*. Weekly food consumption, fluid intakes, and body weights were measured to determine the efficiency of food utilization and to calculate the average daily intake of 2-butanol. The average daily intake of 2-butanol as reported by the authors for the initial 8 weeks of the study (intake was not reported for subsequent weeks) was 0, 538, 1,644, and 5,089 mg/kg-day (males) and 0, 594, 1,771, and 4,571 mg/kg-day (females) for the 0, 0.3, 1, and 3% solutions, respectively. Decreased F0 parental weight gain prior to mating, decreased F1A pup survival, and decreased F1A pup weights among survivors at postnatal days 4 and 21 were observed in the groups exposed to 3% 2-butanol in the drinking water. At the 2% level, decreased maternal body weight gain during the second pregnancy of the F0 dams, decreased F1B fetal weights when pregnancy was terminated at gestation day 20, and decreased F2 pup weights at postnatal days 4 and 21 were observed. At the next lower dose level (1%), reduced F1A pup weight was observed, but the reduction was not seen in subsequent generations at the same exposure level. Developmental endpoints were not affected at the 0.3% exposure levels in any of the generations. 2-Butanol increased the incidence of kidney lesions in F1A generation rats that were exposed from gestation continuing through 12 weeks after birth, mating, and gestation and lactation of the F2 generation. No other treatment-related histopathology was observed.

Environmental Fate

Aquatic
When released into water, methyl ethyl ketone will evaporate into the atmosphere with expected half-lives of 3 and 12 days in rivers and lakes, respectively. It will also biodegrade slowly in both fresh and salt water. No information is available concerning its fate in groundwater but biodegradability studies in anaerobic systems suggest that it may degrade slowly after a long acclimation period. Adsorption to sediment will not be a significant loss process (HSDB, 1988).

Atmospheric
When released into the atmosphere, MEK will degrade principally by reaction with photochemically produced hydroxyl radicals. Under photochemical smog situations, degradation may be slightly faster (HSDB, 1988).

Terrestrial
When spilled on land, methyl ethyl ketone will partially evaporate into the atmosphere and partially leach into the ground. Its degradation in soil is unknown (HSDB, 1988).

Bioconcentration
No information concerning the bioconcentration of methyl ethyl ketone was found in the literature. However, it has a very low octanol water partition function which indicates that bioconcentration will not be a significant transport process.

Regulatory Summary

Reference Dose: 0.6 mg/kg/day

Point of Departure:	639 mg/kg/day(EPA 635/R-03/009 Toxicological Review of Methyl Ethyl
UF	1000 (10 each for intra- and interspecies variability, 10 for use of data subchronic study)
MCL/MCLG	None
LHA	4 mg/L
Cancer classification	D, not classifiable

In 2003, the US EPA selected the reproductive and developmental drinking water study of 2-butanol in rats (Cox et al., 1975) as the principal study for deriving an RfD for MEK. This study also served as the principal study for the RfD of 0.6 mg/kg-day that was previously entered in the IRIS database in 1993. Benchmark dose modeling of F1A pup body weight data at postnatal day 21 was used to develop a point of departure of 657 mg/kg/day for 2-butanol (i.e., the lower 95% confidence limit on a dose producing a mean 5% decrease in body weight compared with control). Adjustment to account for differences in the molecular weights of 2-butanol and MEK yielded a point of departure of 639 mg/kg-day. The agency applied a combined uncertainty factor of 1,000 to derive the chronic RfD. This RfD is the same as the RfD from the previous 1993 IRIS assessment. EPA's confidence in the principal study is listed in the IRIS database as medium to low.

State Drinking Water Standards and Advisories

Arizona	170 µg/L
Florida	4,200 µg/L
Connecticut	1,000 µg/L
Massachusetts	4,000 µg/L
Maine	1,440 µg/L
Minnesota	4,000 µg/L
New Hampshire	170 µg/L
New Jersey	270 µg/L
Vermont	4,200 µg/L
Wisconsin	460 µg/L

Recommendations and Conclusions

Following a review of current toxicological information and federal guidelines, the Department of Health Services recommends adoption of the federal lifetime health advisory for methyl ethyl ketone. This action will raise the groundwater enforcement standard from 460 to 4,000 µg/L. A 20% preventive action limit factor is appropriate because MEK has been not shown to have carcinogenic or mutagenic effects.

$$\frac{0.6 \text{ mg/kg/day} \times 10\text{-kg} \times 100\%}{10 \times 1 \text{ liter/day}} = 0.6 \text{ mg/liter}$$

Recommended Groundwater Enforcement Standard	4,000 µg/L
Recommended Preventive Action Limit	800 µg/L

References

Altenkirch H., Mager J., Stoltenburg G., Helmbrecht J. 1977. Toxic polyneuropathies after sniffing a glue thinner. J Neurol. 214:137-152.

Clayton G.D. and Clayton F.E. 1981. Patty's Industrial Hygiene and Toxicology, 3rd ed., Vol 2C:4728-4733. John Wiley & Sons, New York.

Cox, GE; Bailey, DE; Morgareidge, K. (1975) Toxicity studies in rats with 2-butanol including growth, reproduction and teratologic observations. Food and Drug Research Laboratories, Inc.

Waverly, NY. Report No. 91MR R 1673.

Dyksen J.E. and Hess A.F. III. 1982. J Amer Water Works Assoc 74:394-403.

Dyro F.M. 1978. Methyl ethyl ketone polyneuropathy in shoe factory workers. Clin Toxicol 13:371-376.

Furia T.E. and Bellanca N., editors and translators. 1975. Fenaroli's Handbook of flavor Ingredients. Volume 2, 2nd ed. Cleveland, OH, The Chemical Rubber Co.

Goldstein M.N. 1981. Effect of methyl-n-butyl ketone and other ketone homologs on mammalian cells in culture. NIOSH-210-75-0073.

Gosselin R.E., Smith R.P. and H.C. Hodge. 1984. Clinical Toxicology of Commercial Products, 5th ed. Baltimore, Williams and Wilkins.

LaBelle W. and Brieger H. 1955. The vapor toxicity of a composite solvent and its principal components. Am. Med. Assoc. Arch. Ind. Health. 12:623-627.

Microbiological Associates Inc. 1984. Activity of methyl ethyl ketone in the morphological transformation assay using BALB/3T3 mouse embryo cells, Final report. EPA Document Mo. 40-8444072, EPA Fiche No. OTS0507470.

National Library of Medicine. 1988. Hazardous Substances Data Bank: Methyl ethyl ketone.

Orti-Pareja, M; Jimenez-Jimenez, FJ; Miquel, J; et al. (1996) Reversible myoclonus, tremor, andataxia in a patient exposed to methyl ethyl ketone. Neurol 46(1):272.

Sax, N. Irving. Dangerous Properties of Industrial Materials, 6th Edition, 1984, Van Nostrand Reinhold, N.Y.

Schmidt R. 1984. Ultrastructural alteration of intrapulmonary nerves after exposure to organic solvents. A contribution of 'sniffers disease'. Respiration 46(4):362-9.

Seaton, A; Jellinek, EH; Kennedy, P. (1992) Major neurological disease and occupational exposure to organic solvents. Quart J Med 84(305):707-12.

Shell Sittingbourne Research Centre. 1982. Toxicity studies with chemical solvents: Short-term in vitro tests for genotoxic activity with methyl ethyl ketone. EPA Document No. 878210125, Fiche No. OTS0206206.

Sittig M. 1985. Handbook of toxic and hazardous chemicals and carcinogens, 2nd ed. Park Ridge, NJ. Noyes Data Corp.

Traiger G.J., Plaa G.L., Hanasono G.K. and Witshci H. 1973. The participation of 2-butanone in 2-butanol induced potentiation of carbon tetrachloride hepatotoxicity. J. Pharmacol. Exp. Ther. 196:493-500.

US EPA. IRIS Document for Methyl Ethyl Ketone, 2003.

Wisconsin Department of Natural Resources (DNR). 1990. Summary of Groundwater Monitoring.

METOLACHLOR (Revision)

Metolachlor is a selective herbicide which can be used as either a pre-plant incorporated or pre-emergence surface-applied treatment to control annual grasses, certain broadleaf weeds in field corn (except fresh and popcorn), soybeans, peanuts and grain sorghum. Metolachlor is marketed in two emulsifiable concentrate products (one contains 68.5 percent a.i. and 31.5 percent inerts vs. 86.4 percent a.i. and 13.6 percent inerts for the second product) and in combination with atrazine or propachlor to provide a broader spectrum of weed control. In the US, the Ciba-Geigy Corporation is the sole registrant and manufacturer of metolachlor.

CAS No.	51218-45-2
Molecular Weight	283.8
Physical State	Clear liquid
Water Solubility	530 mg/L
Synonyms	DUAL, BICEP, MILOCEP

Occurrence

In its summary of groundwater pesticide monitoring data from July 1, 1983, through April 30, 1986, the Wisconsin Department of Natural Resources reported 27 detects from 141 private wells sampled for metolachlor and 1 detect from 11 wells tested at public facilities. The highest reported level of metolachlor was 230 ug/l in private facilities and 55 ug/l in public facilities.

Most exposure occur among workers involved in the storage, handling, or shipment of the herbicide. Spray droplets produced during application of the herbicide in the field could result in dermal or inhalation exposures. The general population is not expected to be subject to dermal or inhalation exposure whereas these routes of exposure would be of importance to pesticide production plant workers and agricultural workers.

Toxicity

Technical metolachlor has low mammalian toxicity, but is very toxic to fish.

Acute Oral LD50 Rat: 2,780 mg/kg
Rainbow Trout 96 hour LC50: 2 ppm
Bluegill Sunfish 96 hour LC50: 15 ppm
Channel Catfish 96 hour LC50: 4.9 ppm

Albino CD rats were divided into four groups and fed diets containing 0, 1.5, 15, and 150 mg/kg/day of technical metolachlor for 2 years (Ciba-Geigy, 1983). The NOEL for this study is 15 mg/kg/day, based on decreased body weight gain in rats fed the highest dose tested.

Metolachlor technical was fed diets containing 0, 1.5, 15, and 50 mg/kg/day to Charles River CD strain albino rats (15 males and 30 females/group) beginning at 32 days (Ciba-Geigy, 1981). Animals were mated after either 14 weeks (F0) or 17 weeks (F1) on test. Mating occurred once per generation. The F1 parental animals were randomly selected from the F1a litter after weaning of F1a. F0 males were sacrificed after 135 days on test and F0 females were sacrificed after 164 days on test. No compound related effect on parental body weight was observed. Food consumption was not effected by treatment in

the F0 generation, but was significantly reduced among treated females. Pup body weights of the 50 mg/kg/day dose group were significantly reduced for F1a litters on days 14 and 21 and on days 4, 7, 14, and 21 for the F2a litters. Pup body weights of the 1.5 and 15 mg/kg/day dose groups did not appear to be effected in a compound-related manner. Liver-to-body weight ratios were significantly increased for both F1 parental males and females at 50 mg/kg/day. The thyroid-to-body weight ratio and thyroid-to-brain weight ratio of high dose F1 males were significantly increased. Body weights of the weanling high dose F1a females and F2a males were reduced, though not significantly, and body weights of F2a weanling females were significantly reduced. The NOEL and LOL for reproductive toxicity were 15 and 50 mg/kg/day, respectively, based on reduced pup weights and reduced parental food consumption (EPA, 1994).

Carcinogenicity

US EPA Classification — C; possible human carcinogen.

Metolachlor has been evaluated for carcinogenic activity in both rats and mice. No treatment-related carcinogenic effects were observed in two acceptable chronic studies in mice.

Both Charles River CD-1 mouse studies were two years in duration. One utilized dietary concentrations of 0, 30, 1000, or 3000 ppm and the other used 0, 300, 1000, or 3000 ppm (450 mg/kg/day) (Guideline 83-1, 83-2; 248722; MRID 000015634, 00042725, and 00084003, 00117597).

Metolachlor was fed to CD-Crl:CD (SD) BR albino rats from Charles River for 2 years at 0, 1.5, 13.5 or 150 mg/kg/day as part of a combined chronic toxicity and carcinogenity study. The NOEL was 15 mg/kg/day for systemic toxicity. The LOEL was 150 mg/kg/day based on decreased body weight gain and increased liver weights in high dose males. A significant increase in liver neoplastic nodules was observed in females at the highest dose level. This study satisfies the requirement for a chronic toxicity study in rats. Increases of neoplastic modules and hepatocellular carcinomas were found in high dose females.

The 1991 HED Peer Review Committee recommended that metolachlor be classified as a Group C carcinogen with a Q* of 9.2 x 10 per mg/kg/day. The classification of Group C was based on increases in liver tumors in the female rat, by both pair-wise and trend analysis and the replication of the finding of tumors in the female rat in a second study.

Mutagenicity

Metolachlor was not found to be mutagenic in several tests (US EPA, 1995). The tests for gene mutation were the *Salmonella* assay and an L5178/TK+/- mouse lymphoma test. The tests for structural chromosome aberration were an *in vivo* micronucleus assay in Chinese hamsters and a dominant lethal assay in mice. Tests for other genotoxic activity included DNA damage/repair assays in rat hepatocytes and in human fibroblasts and an *in vivo/in vitro* unscheduled DNA synthesis assay. However, metolachlor was positive in a test for induction of cell proliferation for hepatocytes from male rats.

Environmental Fate

Atmospheric

Metolachlor's use as an herbicide is expected to result in its direct release to the environment. If released to air, a vapor pressure of 3.14 x 10-5 mm Hg at 25 deg C indicates metolachlor will exist in both the vapor and particulate phases in the ambient atmosphere. Vapor-phase metolachlor will be degraded in the

atmosphere by reaction with photochemically- produced hydroxyl radicals; the half-life for this reaction in air is estimated to be 7 hrs. Particulate-phase metolachlor will be removed from the atmosphere by wet and dry deposition. Metolachlor absorbs light in the environmental UV spectrum and has the potential for direct photolysis in the atmosphere with reported half-lives of 8-22 days.

Aquatic
The aquatic biodegradation half-lives for metolachlor under aerobic and anaerobic conditions are 47 and 78 days, respectively. Photolysis is expected to be important in sunlit surface water. The surface photolysis half-life of metolachlor was 11 and 77 days in lake water under summer and winter illumination conditions, respectively. Volatilization from water surfaces is not expected to be an important fate process. Hydrolysis is expected to occur slowly in water based on an estimated hydrolysis half-life of 210 days. Fish are unlikely to accumulate metolachlor because of rapid elimination and low bioconcentration potential of metolachlor.

Terrestrial
If released to soil, metolachlor is expected to be moderately mobile. Volatilization is not expected to be an important fate process, but has been shown to occur in experiments. Cumulative volatilization loss of 22% and 6% applied using broadcast treatment and banded treatment, respectively, was noted during a 10 day field study. Metolachlor degrades with half-lives of 67 and 81 days in a sandy loam soil under aerobic and anaerobic conditions, respectively. If released into water, metolachlor is expected to adsorb to suspended solids and sediment based upon the measured Kocs.

Regulatory Summary (US EPA, 1995)

NOEL	9.7 mg/kg/day
RfD	0.1 mg/kg/day
MCL	None
MCLG	None
Cancer class	C, possible human carcinogen
Cancer slope	9.2 x 10 per mg/kg/day

The RfD for metolachlor was determined to be 0.10 mg/kg/day based on the one-year toxicity study in dogs. The NOEL was 9.7 mg/kg/day, based on decreased body weight gain at 33 mg/kg/day. An uncertainty factor of 100 was used to derive the RfD for metolachlor (US EPA, 1995).

State Drinking Water Standards and Advisories

Florida	100 µg/L
Massachusetts	100 µg/L
Maine	100 µg/L
Minnesota	100 µg/L
New York	10 µg/L
Vermont	70 µg/L
Wisconsin	15 µg/L

Recommendations and Conclusions

The Department of Health Services recommends revision of the enforcement standard for metolachlor from 15 ug/L to 100 ug/L. The revision is based on EPA's current risk assessment for this substance. Because metolachlor is classified as a possible human carcinogen, an uncertainty factor of 10 was applied to the reference dose and a 10% preventive action limit is proposed.

$$\frac{0.1 \text{ mg/kg/day} \times 10 \text{ kg} \times 100\%}{10 \times 1 \text{ liter/day}} = 100 \text{ µg/L}$$

Recommended Enforcement Standard	100 µg/L
Recommended Preventive Action Limit	10 µg/L

References

US EPA. 1995. Reregistration Eligibility Decision for Metolachlor.

Hazardous Substances Data Bank: Metolachlor, accessed January 21, 2009.

US EPA. IRIS Database: Metolachlor, accessed January 21, 2009

METRIBUZIN (Revision)

Metribuzin is a triazine herbicide that selectively controls certain broadleaf and grassy weeds on field and vegetable crops, bermuda grass, and noncrop areas. It is used in Wisconsin as a pre- and post-emergence herbicide on corn, soybeans, potatoes and other crops.

Metribuzin works as a systemic herbicide which is absorbed by the root system and then translocated throughout the plant causing chlorosis, growth inhibition, and necrosis. Metribuzin, a photosynthetic inhibitor, was first registered for use in 1973 and is currently produced by Mobay Chemical Corporation. US Production volume in 1987 was 4.8 million pounds (HSDB: Metribuzin).

CAS no.	21087-64-9
Molecular weight	214.3
Physical state	White crystalline solid
Water solubility	very slightly soluble in water (1200 ppm)
Synonyms	Lexone, Sencor, Sencorex

Occurrence

Metribuzin has been detected in ground water in Connecticut, Iowa, Illinois, Kansas, Maine, Minnesota, Missouri, New Jersey, Ohio, South Dakota, Virginia, and Wisconsin because of probable nonpoint source use (US EPA, 1998). Concentrations in ground water range up to 25.1 ppb. Monitoring for metribuzin in 11 other states did not yield any detections. Recent evidence suggests that metribuzin is likely to be detected in ground waters in areas where it is used.

Metribuzin and two of its degradates were detected in groundwater in a small retrospective study conducted in Portage County, Wisconsin. Concentrations ranged up to 2.3 ug/L parent metribuzin and 7.6 ug/L total residues. Residues were still detected in groundwater more than two years after the final application was made. New monitoring information in Wisconsin indicates that metribuzin can leach to groundwater at concentrations as high as 54 ug/L (US EPA, 1998).

Toxicity

In a chronic feeding/carcinogenicity study, metribuzin was fed to Fischer 344 rats at doses of 0, 30, 300, or 900 ppm (0, 1.3, 13.8, or 42.2 mg/kg/day in males; 0, 1.6, 17.7, or 53.6 mg/kg/day in females) for either 52 or 104 weeks. Toxicity was noted at 300 ppm and above based on decreased body weight gain in females; increased thyroid weight and thyroid/body weight ratio in males, increased liver weight and liver/body weight ratio in males and females. At the lowest dose, there were statistically significant changes in thyroxine (T4) and triiodothyronine (T3) levels, but no other systemic effects were observed. The OPP/HED RfD Committee determined that the 1.3 mg/kg/day dose level (males) should be considered as the NOEL since the effects at the 1.3 mg/kg/day dose were considered to be of marginal biological significance. This conclusion was based primarily on the knowledge that metribuzin is a liver enzyme inducer and that the rat has no other compensatory mechanism to re-establish normal levels of thyroid hormones other than to increase thyroid production of these hormones, the effect observed at the lowest dose was considered a compensatory homeostatic response and not a toxic effect. There was no evidence of carcinogenicity and there was no increase in tumor incidence. For chronic toxicity, the NOEL is 30 ppm (1.3 mg/kg/day in males and 1.6 mg/kg/day in females) and the LOEL is 300 ppm (13.8 mg/kg/day in males and 17.7 mg/kg/day in females) based on decreased body weight gains in females, increased thyroid weights in males, and increased liver weights in males and females (US EPA, 1998).

In a carcinogenicity study, dietary doses of 0, 200, 800, or 3200 ppm (0, 25, 111, or 438 mg/kg/day for males; 0, 35, 139, or 567 mg/kg/day for females) metribuzin (92.9% a.i.) were given to CD1 mice for two years. Systemic toxicity was noted at the high dose as increased liver weights along with decreased hemoglobin and hematocrit values. Under these test conditions metribuzin did not increase the incidence of tumors in mice. For chronic toxicity, the NOEL is 800 ppm (111 mg/kg/day in males, 139 mg/kg/day in females) and the LOEL is 3,200 ppm (438 mg/kg/day for males, 567 mg/kg/day for females) based on increased liver weights and decreased hematological parameters (US EPA, 1998).

Developmental Toxicity

Metribuzin was administered in doses of 0, 25, 70, or 200 mg/kg/day by gavage on gestation days 6-18 to pregnant Charles River Crl:CD BR rats. Maternal toxicity was shown at all dose levels as reduced body weight gain, reduced mean gravid uterine weights, and decreased food consumption. The mid (70 mg/kg/day) and high (200 mg/kg/day) doses showed an effect on the thyroid gland as demonstrated by reduced T4 levels. At the high dose there was also increased thyroid weight. The maternal toxicity NOEL is less than 25 mg/kg/day and the maternal toxicity LOEL is equal to or less than 25 mg/kg/day. For developmental toxicity, the NOEL is 70 mg/kg/day and the LOEL is 200 mg/kg/day based on decreased fetal body weight and reduced ossification or unossified skull bones, ribs, vertebrae, sternebrae, pelvic bones, and appendages (US EPA, 1998).

Mutagenicity

The available data indicate that metribuzin is unlikely to be mutagenic.

Carcinogenicity

US EPA Cancer classification: D, Not classified

Studies conducted in experimental animals provide conflicting results and are inadequate to assess the carcinogenic potential of metribuzin. While studies in mice have been negative, one chronic exposure study in rats revealed an increased incidence of liver bile duct and pituitary gland tumors in females. It is not currently clear whether these tumors were compound-related.

Environmental Fate

Terrestrial
Little leaching occurs from soils with high organic content, but metribuzin is readily leached in sandy soils. Adsorption decreases as soil pH increases. Loss from soil surfaces via volatilization is not an important fate process.

Aquatic
Metribuzin has a half-life of about 4 hours in surface water. It is not expected to evaporate, but is degraded by photodecomposition and possibly also be microbial degradation. The potential for metribuzin to bioconcentrate in aquatic organisms is low.

Atmospheric
Metribuzin will exist in both the vapor and particulate phases in the ambient atmosphere. Vapor-phase is degraded by reaction with hydroxyl radicals. The half-life for this reaction in air is estimated to be 21 hrs(SRC), calculated from its rate constant of 1.8X10-11 cu cm/molecule-sec at 25 deg C determined using a structure estimation method. Particulate-phase metribuzin may be removed from the air by wet and dry deposition(SRC). In freshwater lakes and rivers, metribuzin has a half-life of a few 3 days.

Regulatory Summary

The OPP/HED RfD Committee recommended that an RfD be established on the basis of a two-year feeding study in rats (MRID 42672501). Increased absolute and relative weight of thyroid, decreased lung weight in females, statistically significant increases in blood levels of thyroxine (T4) and statistically significant decreases in blood levels of triiodothyronine (T3) were observed at 30 ppm (1.3 mg/kg/day for males and 1.6 mg/kg/day in females). However, as previously stated, the effects observed at the lowest dose tested were considered to be of marginal biological significance. Therefore, the RfD Committee determined that the dose of 30 ppm (1.3 in males) should be considered as a NOEL. An uncertainty factor (UF) of 100 was applied to account for the inter-species extrapolation and intra-species variability. On this basis, the RfD was calculated to be 0.013 mg/kg/day. It was also recommended to use the reproductive toxicity study with a NOEL of 1.5 mg/kg/day as a co-critical study.

Reference Dose	0.01 mg/kg/day (1998)
MCL	None
MCLG	None
Lifetime HA	70 µg/L
Cancer Classification	D, not classifiable

State Drinking Water Standards and Advisories

Florida	180	µg/L
Minnesota	200	µg/L
New York	50	µg/L
Vermont	32.5	µg/L
Wisconsin	250	µg/L

Recommendations and Conclusions

The Department of Health Services recommends adoption of the US EPA Lifetime Health Advisory as the enforcement standard for metribuzin. The recommendation, which reduces the enforcement standard from 250 to 70 µg/L, is based on our review of the most current toxicity database and federal risk assessment for this chemical. Because metribuzin is not known to have carcinogenic or mutagenic effects a 20% preventive action limit is proposed.

Recommended Enforcement Standard:	70 µg/L
Recommended Preventive Action Limit Factor:	20%
Recommended Preventive Action Limit:	14 µg/L

References

US EPA. 1998. Reregistration Eligibility Decision: Metribuzin.

US EPA Office of Water. Drinking Water Standards and Health Advisories, Summer 2006.

US EPA. IRIS Document for Metribuzin, accessed December 2008.

HSDB. Metribuzin, accessed February 27, 2009.

PHENOL (Revision)

Phenol has a wide variety of industrial uses. The major use is in phenolic resins, which are used as glues and plywood adhesives in the construction, automotive and appliance industries. It is also used as an intermediate of many other materials including textiles, paints, dyes, pharmaceuticals, disinfectants and herbicides (ATSDR, 1989). "Phenol" is not the same as "Total Phenolics," which refers to the entire class of compounds containing one or more hydroxylated aromatic rings. In its pure form, phenol is a waxy white solid. However, for most uses, it is either melted or saturated with water such that it remains liquid. Although it has a somewhat low vapor pressure at room temperature (0.41 mm Hg), it can be readily smelled if present. Phenol is very soluble in water.

CAS no.	108-95-2
Chemical Formula	C_6H_6O
Molecular Weight	94.14
Specific Gravity	1.07
Solubility in Water	87 g/L
Odor/Taste Threshold	7.9 mg/L
Physical State	Waxy, white solid with characteristic odor
Synonyms	Hydroxybenzene, phenyl hydroxide, phenic alcohol

Occurrence

Major environmental sources of phenol are emissions from automobiles and woodburning and in wastewater from industries which use phenol as a solvent (plastics, paper pulp mills and wood treatment facilities, disinfectants and pharmaceuticals). Two natural phenol sources are animal wastes and decomposition of organic wastes.

Since phenol is a petroleum derived product, production decreased somewhat during the 1979 oil crisis but has since increased to pre-crisis levels. Production in 1978 and 1983 exceeded 1 billion kg^2. There are no manufacturers of phenol in Wisconsin (HSDB, 1989).

Phenol has been found in 630 of 3443 groundwater samples taken across the U.S. at a mean level of 1.5 µg/L and in drinking water from 5 of 14 U.S. treatment plants (ATSDR, 1989). In a recent survey by the Wisconsin Department of Natural Resources phenol was detected in 86 of 137 wells with a maximum concentration of 520 µg/L.

Phenol is absorbed readily upon inhalation, ingestion or skin contact. Human exposure occurs primarily through inhalation of cigarette and other smoke, ingestion of contaminated drinking water, and use of phenol-containing consumer products such as mouthwashes, gargles, throat lozenges and ointments. No data exist on the relative contribution of these routes to total phenol exposure.

Toxicity

Argus Research Laboratories. (1997) Oral (gavage) developmental toxicity study of phenol in rats. Horsham, PA. Protocol number: 916-011.

The US EPA used data from a developmental toxicity study conducted by Argus Research Laboratories (1997) to develop a reference dose for phenol. In this study pregnant Sprague-Dawley rats received phenol by oral gavage on gestation days (GDs) 6 through 15. The maternal NOAEL was 60 mg/kg-day, based on small decreases in maternal body weight gain at 120 mg/kg-day, and the developmental NOAEL was 120 mg/kg-day, based on decreased fetal body weight and delayed ossification at 360 mg/kg-day. Benchmark dose (BMD) modeling was also conducted for the decreased maternal weight. Defining the benchmark response as a one-standard-deviation decrease in maternal body weight gain, the 95% lower confidence limit on the BMD (i.e., the BMDL) was 93 mg/kg-day. This BMDL was calculated using the polynomial model, which gave slightly better fit than the power and Hill models, using BMDS Version 1.3 (US EPA, IRIS).

In addition to the Argus Laboratory study described above, the oral toxicity database for phenol includes a 2-year drinking water studies have been conducted in rats and mice (NCI, 1980), a two-generation drinking water study was conducted in rats (Ryan et al., 2001; available in unpublished form as IIT Research Institute, 1999), and gavage developmental toxicity studies in rats (NTP, 1983a; Narotsky and Kavlock, 1995) and mice (NTP, 1983b).

Carcinogenicity

The EPA has classified phenol as Class D, Not Classified

Chronic rat feeding studies have not demonstrated a carcinogenic effect of orally-administered phenol (US EPA, IRIS).

Mutagenicity

Phenol is clastogenic in some mammalian cell culture assays including human lymphocytes but not mutagenic in *Salmonella* assays (Tennant, et al. 1987).

Reproductive Effects

Growth was stunted in rat pups given over 625 mg/kg/day of phenol in drinking water, and tremors, ataxia, lethargy and irritability were noted in pregnant rats given over 140 mg/kg/day phenol in drinking water on days 6 through 15 of gestation (Heller, et al. 1938).

Phenol administered by gavage to pregnant rats on days 6 through 15 of gestation (30, 60 and 120 mg/kg/day) decreased body weights at doses above 60 mg/kg/day; the EPA used this NOAEL in its determination of the RfD (Jones-Price et al, 1983).

Environmental Fate

Atmospheric

Phenol does not remain in air for long periods of time. Its half life in the presence of sunlight was estimated to be 0.61 days. This degradation is likely due to reaction with hydroxyl radicals (ATSDR, 1989).

Aquatic

In surface water, phenol appears to biodegrade readily; complete removal of phenol in river water has been reported after 2 days at 20deg C and 4 days at 4 deg C. However, levels monitored in surface water and at sewage treatment plants indicate that this process is not as efficient as predicted. The degradation rate of phenol in groundwater has not been reported, although the compound was detected in groundwater for at least 1.5 years after a spill in Wisconsin (Delfino, 1976).

Terrestrial

Phenol biodegrades in soil under both aerobic and anaerobic conditions although it may persist in soil for much longer periods at locations such as waste sites where phenol is repeatedly released (Baker, 1980). In one study, soil degradation was completed in 2-5 days (ATSDR, VIEW, 1988).

Regulatory Summary

RfD	0.3 mg/kg/day
DWEL	11 mg/L
Lifetime HA	2 mg/L
MCL/MCLG	None
Cancer Classification	D, not classifiable

State Drinking Water Standards and Advisories

California	4,200 µg/L
Florida	10 µg/L
Maine	4,000 µg/L
Minnesota	4,000 µg/L
New Hampshire	4,200 µg/L
New Jersey	2,000 µg/L
Vermont	2,100 µg/L
Wisconsin	6,000 µg/L

Recommendations and Conclusions

The Department of Health Services recommends lowering the groundwater enforcement standard from 6,000 µg/L to 2,000 µg/L, which is the level of the EPA Lifetime Health Advisory for phenol. Because phenol is not known to have carcinogenic or mutagenic effects, a 20% preventive action limit is proposed.

Recommended Ground Water Enforcement Standard:	2,000 µg/L
Recommended Preventive Action Limit:	400 µg/L

References

ATSDR. 1988. VIEW database. Atlanta, GA: Office of External Affairs, Exposure and Disease Registry Branch.

ATSDR. 1989. Toxicological Profile for Phenol. Oak Ridge, TN, Oak Ridge National Laboratory.

Baker, M.D. and C.I. Mayfield. 1980. Microbial and nonbiological decomposition of chlorophenols and phenol in soil. Water Air Soil Pollut 13: 411-424.

Delfino, J.J. and D.J. Dube. 1976. Persistent contamination of ground water by phenol J Environ Sci Health A11: 345-355.

Heller, B.G. and L. Pursell. 1938. Phenol-contaminated waters and their physiological action. J Pharmacol Exp Ther 63: 99-107.

HSDB. 1989. Phenol. National Library of Medicine.

Jones-Price, C.N., T.A. Ledoux, J.R. Reel et al. 1983. Teratological evaluation of phenol in CD rats. Research Triangle Park, NC: National Toxicology Program. Research Triangle Institute project nos. 31U-1287 and 31U-2312.

Narotsky, MG; Kavlock, RJ. (1995). A multidisciplinary approach to toxicological screening: II.

Developmental toxicity. J Toxicol Environ Health 45(2):145-71.

NTP (National Toxicology Program). (1983a). Teratologic evaluation of phenol in CD rats. Prepared by Research Triangle Institute, Research Triangle Park, NC. NTIS PB83-247726.

NTP. (1983b). Teratologic evaluation of phenol in CD-1 mice. Prepared by Research Triangle Institute, Research Triangle Park, NC. NTIS PB85104461.

Ryan, BM; Selby, R; Gingell, R; et al. (2001). Two-generation reproduction study and immunotoxicity screen in rats dosed with phenol via the drinking water. Inter J Toxicol 20:121-142.

Seaton, MJ; Schlosser, P; Medinsky, MA. (1995). In vitro conjugation of benzene metabolites by human liver: potential influence of interindividual variability on benzene toxicity. Carcinogenesis 16(7):1519-27.

Tennant, R.W., B.H. Margolin and M.D. Shelby et al. 1987. Prediction of chemical carcinogenicity in rodents from in vitro genetic toxicity assays. Science 236: 933-941.

U.S. EPA. 1989. Draft Drinking Water Health Advisory for Phenol. Office of Water.

PROMETON (Revision)

Prometon is a nonselective triazine herbicide used for control of most annual and perennial broad-leaved, grass and brush weeds on non-crop areas at 10-20 kg active ingredient per hectare. Prometon is not used on cropland, but is used around buildings, on roadsides, and on areas prior to installation of asphalt. Information on use of prometon in residential settings is not available.

Prometon is a photosynthesis inhibitor, disrupting carbon dioxide fixation and production of the intermediary energy components. Prometon affects photosystem II, competing with plastoquinone and modifying electron transport processes. Prometon is registered for weed control for use as a spot treatment around the home, driveways, patios, buildings, storage areas, fences, pumps, machinery, fuel tanks, recreational areas, roadways, guard rails, airports, military installations, highway medians, pipelines, railroads, lumberyards, rights-of-way, and industrial sites (US EPA, 2008).

CAS No.	1610-18-0
Chemical Formula	$C_{10}H_{19}N_5O$
Molecular Weight	225.34
Density	1.088
Solubility in Water	750 mg/L
Physical state (25^{o}C)	White crystals
Odor/TasteThreshold	No data
Synonyms	Gesafram, Ontrack, Pramitol, Prometone

Occurrence

The Wisconsin Department of Natural Resources had tested 45 private wells for prometon in a nonrandom survey. Detects were noted in 31 wells, with the highest concentration at 93 ppb (WDNR, 1995).

Most exposure to prometon is occupational. Workers can be exposed during the mixing and application of the herbicide. People may also be exposed via dermal contact or inhalation when they enter recently treated fields. In rats, 50% of an orally administered dose of prometon was excreted within 12-26 hr. The primary route of excretion is via the urine.

Toxicity

Prometon technical was fed to Sprague-Dawley rats at doses equivalent to 0, 0.89, 23.3 and 73.3 mg/kg/day for 104 weeks. None of these doses increased the incidence of neoplastic lesions or survival. The U.S. EPA's Office of Pesticides and Toxic Substances determined that the systemic LOEL was 23.3 mg/kg/day and the NOEL was 0.89 mg/kg/day based on body weight depression (US EPA, 1992).

Technical grade prometon was fed to dogs (breed unspecified) at doses of 0, 5, 20 and 50 mg/kg/day for a period of one year. Statistically significant effects on body weight gain were noted at the 20 mg/kg/day level in females and at the 50 mg/kg/day level in both sexes. Based on this effect, the NOEL for this study was 5 mg/kg/day. Preliminary and monthly examinations indicated that the dogs were healthy throughout the study. Therefore, episodes of diarrhea and emesis, and reduced weight gain were judged to be compound-related (US EPA, 1993).

Carcinogenicity

U.S. EPA Cancer Classification for Prometon: Not likely to be Carcinogenic to Humans" based on the absence of significant tumor increases in two adequate rodent carcinogenicity studies (US EPA, 2008).

Carcinogenicity studies have been conducted in rats and mice. None of these studies have shown a statistically significant increase in tumor incidence among treated versus control animals.

Mutagenicity

No information on the mutagenicity of prometon was located.

Reproductive Effects

In a two-generation reproductive toxicity study, Sprague-Dawley rats were fed diets containing prometon technical at 0, 20, 500, or 1500 ppm. Reproductive toxicity observed at 1500 ppm in both generations, and at 500 ppm in the second generation, was evident as decreased pup body weight during the entire lactation period. Therefore, the NOEL and LOEL for reproductive toxicity were 20 and 500 ppm, respectively. These feeding levels correspond with daily doses of 1.45 and 35.08 mg/kg/day in males, and 1.59 and 39.17 mg/kg/day in females (USEPA, 1992).

Environmental Fate

Terrestrial
When prometon is applied to land it will adsorb moderately to the soil. It is moderately persistent in soil with an estimated half-life between 1.5 and 6 months. It is not known whether it degrades by chemical or microbial processes. An important mechanism by which prometon is lost from soil is by volatilization. Prometon rises to the soil surface with evaporating water and as the concentration of the herbicide at the soil-air interface increases, the amount of prometon volatilizing increases (Spencer, 1988).

Aquatic
If released into water, prometon will partially adsorb to sediment and particulate matter in the water column. Degradation should be slow. Bioconcentration in fish should not be significant. Volatilization should not be an important fate process (HSDB, accessed Feb 2, 2009).

Atmospheric
In the atmosphere prometon would be expected to degrade by reaction with photochemically produced hydroxyl radical. Its estimated half-life is approximately two hours (Atkinson, 1987).

Regulatory Summary

No federal drinking water standards for prometon have been proposed or adopted. However, USEPA has published the following guidelines:

NOAEL	5 mg/kg/day (1 yr dog study)
LOAEL	20 mg/kg/day
Uncertainty Factor	100 (10 each for inter- and intraspecies differences)
RfD	0.05 mg/kg/day (US EPA, 2008)
Longer-term adult health advisory	500 ug/L

Longer-term child health advisory	200 ug/L
Lifetime health advisory	100 ug/L
MCL/MCLG	None/none
Cancer classification	Not Likely

State Drinking Water Standards and Advisories

Minnesota	100 µg/L
New York	50 µg/L
Prometon	100 µg/L
Vermont	100 µg/L

Recommendations and Conclusions

The Department of Health Services recommends adoption of EPA's lifetime health advisory as a groundwater enforcement standard for Prometon. This revision increases the enforcement standard from 90 to 100 ug/L. Because Prometon is not known to be carcinogenic or mutagenic, a 20% preventive action limit is proposed.

Recommended Enforcement Standard	100 µg/L
Recommended Preventive Action Limit:	20 µg/L

References

Atkinson R; Int J Chem Kinet 19: 799-828, 1987.

Spencer WF et al; J Environ Qual 17: 504-9, 1988.

US EPA. 2008. Reregistration Decision for Prometon. Washington, DC.

USEPA Memorandum from Sheryl K. Reilly to Kathryn Davis/Thomas Luminello, Apr 28, 1993.

USEPA Memorandum from Vivian A. Williams to Thomas Luminello, Aug 18, 1992.

Wisconsin Department of Natural Resources. Groundwater Retrieval Network, 1995.

TOLUENE (Revision)

Toluene is a clear, colorless liquid with many industrial uses. Approximately 92% of the toluene produced in the US is used as a component of gasoline. The remainder is used in manufacture of paints, lacquers, adhesives, rubber and in some printing and leather tanning processes. US production is estimated at around 6.5 billion pounds per year.

A Wisconsin Groundwater Enforcement Standard of 343 µg/L was adopted in 1985 and was later revised to 1 mg/L.

CAS No.	108-88-3
Molecular Formula	C_7H_8
Molecular Weight	92.15
Physical State	Liquid at room temperature
Water Solubility	515 mg/L at 25° C
Odor/Taste Threshold in Water	0.04 mg/L
Specific Gravity	0.8669
Synonyms	Methylbenzene, Toluol

Occurrence

Toluene is found relatively infrequently in municipal water systems. A 1981 survey found the compound in 11
of 929 groundwater systerms and 20 of 99 surface water systems. In private wells, toluene is often found associated with chemicals waste sites or leaking underground fuel storage tanks. In Wisconsin, toluene was detected in 179 of 4633 wells sampled. Toluene concentrations exceeded the enforcement standard in 27 of these (WDNR, 1991).

Toxicity

In humans and animals, the most profound effect of acute toluene overexposure via inhalation is central nervous system depression and narcosis which may lead to death. No other effects have been noted. No studies of acute oral toluene exposures have been performed.

In a two year subchronic gavage study conducted by the National Toxicology Program (NTP, 1990), prostration, hypoactivity, ataxia, lacrimation, excessive salivation and tremors were noted in rats given doses greater than 2500 mg/kg. The same effects were noted in rats that inhaled 300-1250 ppm for up to two years and in humans who intentionally inhaled toluene-containing solvent vapors. In the NTP study, absolute and relative kidney and liver weights were increased in rats treated with doses greater than or equal to 625 mg/kg/day for 5 days/week but not at 312 mg/kg. Benchmark analysis was performed for absolute kidney weight changes in male rats (NTP, 1990). Male rat kidney data were chosen for BMD modeling as these data exhibited a greater response than that seen in female rats. A BMDL of 238 mg/kg-day was derived and used as the point of departure for EPA's reference dose for toluene (EPA, IRIS).

Carcinogenicity

EPA classification: I, Inadequate human and animal evidence of carcinogenicity).

No studies have shown increased cancer incidence among animals inhaling toluene. No carcinogenic response was noted among animals inhaling up to 300 ppm for 6 h/day, 5 d/week, for two years or in rats

inhaling up to 1200 ppm for two years. No ingestion studies investigating carcinogenicity have been performed.

Mutagenicity

Toluene has been found to be non-mutagenic in most *in vitro* microbial and eukaryotic cell assays. Only one study reported potentially positive result in a mouse lymphoma cell line but these results were considered to be equivocal.

Reproductive/Developmental Effects

Epidemiologic studies of women exposed either occupationally or as a result of substance abuse to a number of solvents including toluene during pregnancy have been performed. The investigators in these studies found an increased incidence of central nervous system anomalies, growth retardation and developmental delays in children of exposed women. Exposure to toluene in all of the developmental studies performed in animals was by inhalation. These studies, performed in rats, rabbits, and mice, have shown increased incidences of skeletal anomalies in exposed whose mothers were exposed during gestation. The LOAEL determined in these studies was approximately 780 mg/kg/day.

Environmental Fate

Atmospheric
Toluene is released into the atmosphere principally from the volatilization of petroleum fuels, solvents and thinners, and from motor vehicle exhaust. Its production and use as an intermediate in the production of benzoic acid, benzaldehyde, benzene, explosives, dyes and many other organic compounds may also result in its release to the environment through various waste streams. Toluene has also been detected in emissions from volcanos, forest fires and crude oil. If released to air, a vapor pressure of 28.4 mm Hg at 25 deg C indicates toluene will exist solely as a vapor in the ambient atmosphere. Vapor-phase toluene will be degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals; the half-life for this reaction in air is estimated to be 3 days. Toluene may also be degraded in the atmosphere by reaction with nitrate radicals and ozone molecules, but these reactions are too slow to be environmentally important (HSDB, 2009).

Terrestrial
If released to soil, toluene is expected to have high to moderate mobility based upon Koc values in the range of 37-178. Volatilization from moist soil surfaces is expected to be an important fate process based upon a Henry's Law constant of 6.64X10-3 atm-cu m/mole. Toluene may volatilize from dry soil surfaces based upon its vapor pressure. Biodegradation is expected to occur rapidly in soil surfaces, with half-lives in the range of several hours to 71 days.

Aquatic
If released into water, toluene is not expected to adsorb to suspended solids and sediment based upon a Koc of 166 measured in lake sediment. Biodegradation is expected to occur rapidly in water, with reported half-lives of 4 and 56 days in aerobic and anaerobic water, respectively. Volatilization from water surfaces is expected to be an important fate process based upon this compound's Henry's Law constant. Estimated volatilization half-lives for a model river and model lake are 1 hour and 4 days, respectively. Measured BCF values of 13 and 90 in fish suggest bioconcentration in aquatic organisms is low to moderate. Hydrolysis is not expected to be an important environmental fate process for toluene due to lack of hydrolyzable functional groups (HSDB, 2009).

Regulatory Summary (EPA, IRIS)

BMDL	238 mg/kg/day
UF	3000
RfD	0.08 mg/kg/day [NOAEL/UF]
DWEL	3 mg/L
Lifetime HA	1 mg/L
MCL	1 mg/L
MCLG	1 mg/L
Cancer class	I, Inadequate information to classify

*The MCL was determined by multiplying the DWEL by 20%. This procedure assumes 20% of the total toluene intake comes from drinking water.

State Drinking Water Standards and Advisories

Minnesota	1,000 µg/L
New Jersey	600 µg/L
Wisconsin	1,000 µg/L
WHO	700 µg/L

Recommendations and Conclusions

Wisconsin Department of Health Services recommends revision of the groundwater enforcement standard from toluene from 1,000 to 800 ug/L. This revision reflects EPA's most current risk assessment for toluene which resulted in a lower reference dose of 0.08 mg/kg/day. Because toluene is not known to have carcinogenic or mutagenic effects, a 20% preventive action limit is proposed.

$$\frac{0.08 \text{ mg/kg/day} \times 10 \text{ kg} \times 100\%}{1 \text{ liter/day}} = 800 \text{ µg/L}$$

Recommended Enforcement Standard:	800 µg/L
Recommended Prev. Action Limit:	160 µg/L

References

Agency for Toxic Substances and Disease Registry. 1989. Toxicological Profile for Toluene. Atlanta, GA.

HSDB Document for Toluene, accessed February 11, 2009.

Maltoni C, Ciliberti A, Pinto C, et al. (1997) Results of long-term experimental carcinogenicity studies of the effects of gasoline, correlated fuels, and major gasoline aromatics on rats. Ann NY Acad Sci 837:15-52.

NTP (National Toxicology Program). (1990) Toxicology and carcinogenesis studies of toluene (CAS No. 108-88-3) in F344/N rats and B5C3F1 mice (inhalation studies). Public Health Service, U.S. Department of Health and Human Services; NTP TR 371. Available from: National Institute of Environmental Health Sciences, Research Triangle Park, NC.

U.S. Environmental Protection Agency. 1991. IRIS document for toluene, access February 4, 2009.

US EPA. 2005. Toxicological Review Of Toluene (CAS No. 108-88-3) In Support of Summary Information on the Integrated Risk Information System (IRIS) September 2005.

WDRN Groundwater Retrieval Information Network. Accessed February, 2009.

WHO. 2004. Toluene in Drinking Water, Geneva, Switzerland.

XYLENE (Revision)

Xylene is a clear, colorless liquid with many industrial uses. The term "xylene" usually refers to a mixture of three isomers, ortho-, meta- and para-xylene (o-, m- and p-xylene, respectively). The mixture is sometimes referred to as "total xylenes." The term "xylene" when used in this document refers to the mixture of isomers.

Xylene occurs in petroleum and coal tar and is a component of refined fuels and gasoline. Approximately 70% of the xylene produced in the US (not including that found in refined fuels) is used in the production of ethylbenzene, another gasoline component, and the remainder is used in the chemical, plastic, synthetic fiber and paper industries (ATSDR, 1990). In 1987, U.S. petroleum refiners produced over two billion kg of mixed xylenes and over 400 million kg of o-xylene (US ITC, 1988).

CAS no.	1330-20-7
Molecular Formula	C_8H_{10}
Molecular Weight	106.16
Physical State	Liquid at room temperature
Water Solubility	130 mg/L at 25° C
Odor/Taste Threshold	0.5-1.5 mg/L
Specific Gravity	0.86
Synonyms	Dimethylbenzene, xylol

Occurrence

Xylene is a common air contaminant in outdoor, industrial and home settings. The compound is present in automobile emissions, as a chemical intermediate in many manufacturing processes and in many consumer products such as gasoline, aerosols and paints, varnishes, shellac and rust preventatives. Median concentrations of 12 μg/m^3 have been reported in urban areas^3 and approximately 20 μg/m^3 indoors (Siefert and Abraham, 1982).

Xylene is found relatively infrequently in municipal water systems utilizing either groundwater or surface water; a 1981 survey found the compound in less than 6% of public water systems (US EPA, 1985). In private wells, however, xylene is often found associated with chemical waste sites or leaking underground storage tanks. In Wisconsin, o and p-xylene was detected in 315 of 5709 wells sampled; of those, 55 were at a concentration above the current Enforcement Standard (WDNR, 1991).

In non-occupationally exposed populations, inhalation of xylene is likely to be the major source of exposure, providing an average of approximately 3 μg/day (ATSDR, 1990). Cigarettes can contain up to 30 μg/cigarette (Higgins, et al, 1983).

In humans, approximately 64% of inhaled xylene is absorbed (Sedivec and Flek, 1976). In animals, oral exposure of a single xylene dose results in 90% absorption. In humans, approximately 5-10% of the absorbed xylene dose accumulates in the fat and is taken up in lipid-rich tissues such as brain and blood . The compound is metabolized in the liver to glucuronides and hippuric acid derivatives which are excreted in the urine. The majority of absorbed xylenes are excreted in a matter of hours (ATSDR, 1990).

The odor threshold for p-xylene is 500 μg/L. P-xylene concentrations above the taste and odor threshold may be objectionable to some individuals.

Toxicity

No pathological examinations have been performed in animals given a single lethal dose of xylenes. Impairment of visual function, as evidenced by significant decreases in flash-evoked potentials, was noted in rats treated one time at doses of 250 mg/kg p-xylene and higher.

In a National Toxicology Program (1986) study, mice and rats were treated with 0-1000 mg/kg/day xylenes for up to two years. In this study, increased mortality was noted at 250 mg/kg/day, but this increase was not statistically significant. Based on this study, the EPA uses a NOAEL of 178 mg/kg/day (rats were exposed for 5 days/wk so the NOAEL=250 x 5/7). Also, in this study, mice were hyperactive 5-30 minutes after administration of 1000 mg/kg/day. Although pathological examination of the liver in the NTP study did not reveal any treatment-related effects, other studies found increased liver weight, increased cytochrome P450 content and increased liver enzyme activities in rats given 1060 mg/kg/day for one week (Pykko, 1980). No renal, respiratory, cardiovascular, gastrointestinal, hematological or musculoskeletal effects were noted in the NTP study.

Carcinogenicity

EPA classification: I (inadequate human and animal evidence of carcinogenicity).

A 1986 NTP study reported "no evidence of carcinogenicity" for orally administered mixed xylene in rats or mice of either sex at any dosage tested. No inhalation carcinogenicity studies have been performed. No epidemiologic studies addressing xylene carcinogenicity have been performed.

Mutagenicity

Technical xylene mixtures or individual isomers are not mutagenic in *Salmonella* or *E. Coli* (US EPA, 1987). Chromosomal aberrations were not increased in bone marrow cells of rats exposed to xylenes by inhalation (Donner et al, 1980).

Reproductive/Developmental Effects

In the NTP study, no effects on reproductive organs resulting from oral xylene exposure were noted. However, oral exposure to 2,060 mg/kg/day mixed xylenes was associated with cleft palate and decreased fetal weight in mice (Marks et al, 1982). No human studies addressing reproductive or developmental effects of xylenes have been performed.

Environmental Fate

Atmospheric
Most xylene entering the environment is released directly to the air (approx. 3×10^9 kg), with the bulk of these releases from refinery losses, other solvent losses and automobile exhaust (Merian and Alexander, 1982). Once in the air, the predominant method of degradation is photooxidation. The half-life of xylene in the atmosphere is estimated to be 24.1 hr (Jori, 1986).

Aquatic
The predominant method of xylene transformation in surface water is evaporation. Hydrolysis or biotransformation are not expected to be significant (ATSDR, 1990). In groundwater, xylene is moderately biodegraded with an expected half life of 10 days (Merian and Zander, 1982).

Terrestrial

Xylene does not bind tightly to soil particles. However, precise estimates of leachability from different soil types are not available. Anaerobic biodegradation appears to be the predominant transformation process in soils, with an estimated half life of 24 hr (Merian and Zander, 1982).

Regulatory Summary

NOAEL	179 mg/kg/day (250 x 5/7)
Uncertainty factor	1000 (revised 2/21/2003)*
Reference dose	0.2 mg/kg/day (revised 2/21/2003)
DWEL	7 mg/L
Lifetime Health advisory	10 mg/L
MCL	10 mg/L [DWEL x 20%*]
MCLG	10 mg/L
Cancer Classification	I, inadequate

*In its 2003 reassessment of the reference dose for xylene, EPA added an additional UF of 10 to account for database uncertainty stating:

"The available oral database for xylenes includes chronic and subchronic gavage toxicity studies in mice and rats and a developmental toxicity study. None of these studies indicate that additional data would result in a lower RfD. However, the database lacks adequate studies of the oral neurotoxicity of xylenes as well as multigenerational reproductive toxicity and developmental neurotoxicity studies. Given the identification of neurological impairment as a critical health hazard from inhalation exposure to xylenes, the lack of comprehensive neurotoxicity testing following chronic oral exposure is of particular concern. It should be noted that transient neurotoxic effects (e.g., lethargy, tremors and unsteadiness) were reported in mice following oral exposure to xylenes for 13 weeks (NTP, 1986). There are no toxicokinetic data identifying oral dose levels at which first-pass hepatic metabolism of xylenes becomes saturated in animals or humans; such data could decrease uncertainty regarding whether neurological impairment may occur at dose levels below those causing body weight decreases and mortality in rats. It is uncertain whether the availability of comprehensive oral neurotoxicity data would result in a lower RfD."

State Drinking Water Standards and Advisories

New Jersey	1,000 µg/L
Minnesota	10,000 µg/L
Vermont	10,000 µg/L
Wisconsin	10,000 µg/L

On November 1, 1985, Wisconsin adopted an enforcement standard and preventive action limit for xylenes of 620 and 124 µg/L, respectively. The enforcement standard was later revised to 10,000 mg/L to bring it into line with the federal drinking water standard.

Recommendations and Conclusions

The Department of Health Services recommends revision of the groundwater enforcement standard for xylene from 10,000 ug/L to 2,000 ug/L. This action reflects revision of the EPA reference dose for this substance which was finalized in 2003. Since xylene is not known to have carcinogenic or mutagenic effects, a 20% preventive action limit is proposed.

Recommended Enforcement Standard	2,000 µg/L
Recommended Prev. Action Limit:	400 µg/L

References

Agency for Toxic Substances and Disease Registry. 1990. Toxicological Profile for Total Xylenes. Atlanta, GA.

Donner, MJ, H Maki-Paakanen, H Norppa, M Sorsa and H Vainio. 1980. Genetic toxicology of xylenes. Mutat Res 74:171-172.

Higgins E, WH Griest and G Olerich. 1983. Applications of Tenzx trapping to analysis of gas phase organic compounds. J Assoc Off Anal Chem 66:1074-1083.

Jenkins, LJ, RA Jones and J Siegel. 1970. Long-term inhalation studies on benzene, toluene, o-xylene and cumene on experimental animals. Toxicol Appl Pharmacol 16: 818-829.

Jori A, D Calamari and A Di Domenico. 1986. Ecotoxicological profile of xylenes: working party on ecotoxicological profiles of chemicals. Ecotoxicol Environ Safety 11:44-80.

Marks TA, TA Ledoux and JA Moore. 1982. Teratogenicity of a commercial xylene mixture in the mouse. J Toxicol Environ Health 9:97-105.

Merian, E and M Zander. 1982. Volatile aromatics. In: Hutzinger G, ed. Handbook of environmental chemistry. Vol. 3 (Pt B), Berlin:Springer, 117-161.

National Toxicology Program. 1986. NTP technical report on the toxicology and carcinogenesis studies of xylenes (mixed) (60% m-xylene, 14% p-xylene, 9% o-xylene and 17% ethylbenzene) (CAS no. 1330-20-7) in F344/N rats and B6C3Fq mice (gavage studies).

Pykko, K. 1980. Effects of methylbenzenes on microsomal enzymes in rat liver, kidney and lung. Biochim Biophys Acta 633:1-9.

Sedivec V and J Flek. 1976. The absorption, metabolism and excretion of xylenes in man. Int Arch Occup Environ Health 37:205-217.

Siefert B and H-J Abraham. 1982. Indoor air concentrations of benzene and some other aromatic hydrocarbons. Ecotoxicol Environ Safety 6:190-192.

U.S. Environmental Protection Agency. 1987. IRIS document for xylenes. Rev. 9/30/87.

U.S. Environmental Protection Agency. 1991. 40 CFR Parts 141, 142 and 143: National Primary Drinking Water Regulations: Final Rule. Fed Reg 56: 3526-3598.

US ITC. 1988. Synthetic organic chemicals: United States production and sales, 1987. Washington, DC: USITC. Publication 2118.

Wisconsin Department of Natural Resources. 1991. Summary of groundwater monitoring.

1,4-DIOXANE

1,4-Dioxane is a colorless, flammable liquid with a mild odor. It is miscible with water, most organic solvents, aromatic hydrocarbons, and oils and is available in reagent, technical, spectrophotometric, and scintillation grades (HSDB 2001). 1,4-Dioxane is used as a stabilizer in chlorinated solvents and as a solvent for lacquers, paints, dyes, resins, oils, fats, waxes, and greases. It may also have been used in adhesives, cosmetics, and pharmaceuticals (HSDB 2001).

CAS no.	123-91-1
Chemical Formula	C4H8O2
Molecular Weight	88.1
Physical State	Colorless liquid
Water Solubility	Miscible
Density at 20 deg C	1032.9 g/liter at 20 °C
Synonyms	*p*-Dioxane

Occurrence

1,4-Dioxane has been commercially produced in the United States for more than 50 years. It is currently listed with the US EPA as a high production volume chemical indicating that annual production or importation exceeds 1 million pounds. In 1982, nearly 15 million lb of 1,4-dioxane were produced in the United States (USITC 1983).

According to the Wisconsin Department of Natural Resources GRIN database, 29 wells that have been tested for 1,4-Dioxane. 1,4-Dioxane concentrations ranged from below detection to 1100 ug/L and exceeded 3 µg/L in 25 of these water supplies.

Exposure of the general population to 1,4-dioxane could occur from contact with products containing residues of the compound. According to the Consumer Product Safety Commission (CPSC), consumers may possibly be exposed to residual levels of 1,4-dioxane formed during the manufacture of detergents, shampoos, surfactants, and certain pharmaceuticals. CPSC reported that the presence of 1,4-dioxane, even as a trace contaminant, is cause for concern and the Commission continues to monitor its use in consumer products. Residues may also be present in food packaging and on food crops treated with 1,4-dioxane-containing pesticides. Occupational exposures can occur during its manufacture and use as a solvent.

1,4-Dioxane has a high potential for entering the environment due to its volatility and solubility in water. Emissions to the atmosphere can occur at the sites of manufacture and use. EPA's Toxic Chemical Release Inventory (TRI) estimated that 977,447 lb of 1,4-dioxane were released to the environment (on- and off-site releases) from 64 facilities that produced, processed, or used the chemical in the United States in 1996.

1,4-dioxane is rapidly absorbed following ingestion or inhalation. It is metabolized in the liver and does not accumulate in the body. The principal metabolite in humans and mammals is beta-hydroxyethoxyacetic acid (HEAA). Other metabolites determined in animal studies include 1,4-dioxan-2-one, β-hydroxyethoxyacetaldehyde, diethylene glycol, oxalic acids and carbon dioxide. Unchanged 1,4-dioxane is excreted in the urine and expired air (DeRosa et al., 1996).

Two occupational fatalities involving exposure to 1,4-dioxane have been described (DeRosa et al., 1996). Haemorrhagic nephritis, centrilobular liver necrosis, severe epigastric pain, convulsion and coma were found as the major effects. In volunteer short-term exposure studies (720 or 1080 mg/m3 for 15 min; 5760 mg/m3 for 10 min; 19 800 mg/m3 for 1 min), mucous irritation in eyes, nose and throat was noted as a clinical sign (DeRosa et al., 1996). After exposure to 1,4-dioxane at 180 mg/m3 for 6 h, only mild eye irritation was noted, with no other clinical signs, as demonstrated by chest X-ray, electrocardiograms, respiratory function tests, blood determinations and urinalysis (Young et al., 1977).

Toxicity

Oral LD50 values are in the range of 5400–7300 mg/kg of body weight in rats, 5900 mg/kg of body weight in mice, 3300–4000 mg/kg of body weight in guinea-pigs and 2000 mg/kg of body weight in rabbits (DeRosa et al., 1996). LC50 values following inhalation for 2 hours were found to be 46 g/m3 in rats and 37 g/m3 in mice (RTECS, 2000). The dermal LD50 in rabbits was 7600 mg/kg of body weight, although there were no equivalent toxicological effects in Wistar rats treated with 8,300 mg/kg of body weight (DeRosa et al., 1996). The main acute effects at near-lethal doses in experimental animals (rats, mice, guinea-pigs, rabbits or dogs) are central nervous system depression (e.g., narcosis) and severe gastric, pulmonary, hepatic and renal lesions (DeRosa et al., 1996).

Male SD rats administered 0, 10 or 1000 mg of 1,4-dioxane per kg of body weight per day in drinking-water for 11 weeks demonstrated increased relative liver weight and a minimal degree of liver lesion at 1000 mg/kg of body weight per day, but not at 10 mg/kg of body weight per day (Stott et al., 1981).

Sherman rats of both sexes were administered 100, 1,000 or 10,000 mg of 1,4-dioxane per liter in their drinking-water for 2 years. The 10,000 mg/liter group exhibited decreased body weight gain, survival rate and water consumption. Other histopathological findings at the 1,000 or 10,000 mg/liter doses included renal tubular and hepatocellular degeneration and necrosis. The NOAEL was determined to be 9.6 mg/kg/day in males and 19 mg/kg/day in females) (Kociba et al., 1974). In F344/DuCrj rats receiving 200, 1000 or 5000 mg/liter in drinking-water for 2 years liver changes were detected at doses equivalent to 16–21 mg/kg/ day in males (Yamazaki et al., 1994).

Reproductive and Developmental Toxicity

SD rats were given 1,4-dioxane at 258, 516 or 1033 mg/kg/day by gavage on days 5–14 of pregnancy (sperm = day 0). Reduced food consumption, decreased fetal weight and delayed ossification were observed at 1.0 ml/kg of body weight per day. These findings support a NOAEL for developmental toxicity of 516 mg/kg of body weight per day (Giavini et al., 1985).

Mutagenicity

1,4-Dioxane has been tested with and without activation in several *in vivo* and *in vitro* systems. The weight of evidence indicates that 1,4-dioxane is probably not mutagenic or genotoxic.

Carcinogenicity

US EPA Cancer Classification: B2, probable human carcinogen

Although there is inadequate evidence for the carcinogenicity of 1,4-dioxane in humans the US EPA and International Agency for Research on Carcinogens have determined that 1,4-Dioxane is likely to be a human carcinogen based on sufficient evidence of carcinogenicity in experimental animals (EPA, 2008; IARC 1999). When administered in drinking water, 1,4-dioxane increased the incidences of squamous

cell carcinomas of the nasal turbinates as well as hepatocellular adenomas in rats. Drinking water exposure also induced hepatomas and carcinomas of the gallbladder in male guinea pigs and hepatocellular carcinomas in mice of both sexes. As a promoter in a two-stage skin carcinogenesis study, the compound increased the incidence of skin tumors in mice of both sexes. Intraperitoneal injections increased the incidence of lung tumors in male mice.

A Danish mortality study was conducted with 19 000 cases in the cancer registry (Hansen, 1993). Liver cancer death rates were significantly increased among men who worked with 1,4-dioxane. The authors noted that while alcohol consumption did not explain this increase, co-exposure to chemicals other than 1,4-dioxane, exposure time period, and exposure dose were not controlled for.

Regulatory Summary

MCL	None
MCLG	None
RfD	None
10-Day Health Advisory	0.4 mg/L
Lifetime Health Advisory	None
Cancer Classification	B2, Likely to be carcinogenic to humans
Cancer Slope Factor	1.1E-2 per mg/kg/day
10^{-6} Cancer Risk Level in Water	3 µg/L

State Drinking Water Standards and Advisories

California	3 ug/L*
Florida	5 ug/L*
Maine	32 ug/L
Massachusetts	50 ug/L*
Vermont	20 ug/L

Recommendations and Conclusions

The Department of Health Services recommends use of the US EPA's cancer slope factor to develop a groundwater enforcement standard (GWES) for 1,4-dioxane that equates with a one-in-a million lifetime cancer risk. Because this substance has carcinogenic effects, a 10% preventive action limit (PAL) is proposed.

$$\frac{1 \times 10^{-6} \text{ lifetime risk} \times 70\text{-kg} \times 100\% \text{ exposure} \times 1000\ \mu g/mg}{0.011 \text{ per mg/kg/day} \times 2 \text{ liters/day}} = 3\ \mu g/L$$

Recommended GWES	3 µg/L
Recommended PAL	0.3 µg/L

References

ATSDR. 2001. Toxicological Profile for 1,4-Dioxane, US Dept of Health and Human Services, Atlanta, GA.

DeRosa CT et al. 1996. Health evaluation of 1,4-dioxane. Toxicology and Industrial Health, 12:1–43.

Giavini E, Vismara C, Broccia ML. 1985. Teratogenesis study of dioxane in rats. Toxicology Letters, 26:85–88.

Hansen J. 1993. The industrial use of selected chemicals and risk of cancer 1970–1984. Copenhagen, National Institute of Occupational Health as cited in Drinking-water background document for development of WHO Guidelines for Drinking-water Quality, 2005.

Hazardous Substances Data Bank. 2001. Summary for 1,4-Dioxane.

IARC. 1987. 1,4-Dioxane. Lyon, International Agency for Research on Cancer, pp. 272–274 (IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Suppl. 7).

IARC (1999) Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide. Lyon, International Agency for Research on Cancer, pp. 589–602 (IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, Vol. 71).

Kociba RJ et al. 1974. 1,4-Dioxane. I. Results of a 2-year ingestion study in rats. Toxicology and Applied Pharmacology, 30:275–286.

NTP. 1978. Report on carcinogens, 11th Edition.

Stott WT, Quast JF, Watanabe PG (1981) Differentiation of the mechanisms of oncogenicity of 1,4-dioxane and 1,3-hexachlorobutadiene in the rat. Toxicology and Applied Pharmacology, 60:287–300.

US International Trade Commission Report, 1983.

World Health Organization. 2005. 1,4-Dioxane in Drinking-water Background document for development of WHO Guidelines for Drinking-water Quality.

Yamazaki K et al. 1994. Two-year toxicological and carcinogenesis studies of 1,4-dioxane in F344 rats and BDF1 mice. In: Proceedings of the Second Asia-Pacific Symposium on Environmental and Occupational Health. Kobe, Japan, Kobe University, pp. 193–198.

Young JD et al. 1977. Pharmacokinetics of 1,4-dioxane in humans. Journal of Toxicology and Environmental Health, 3:507–520.

ACETOCHLOR

Acetochlor is a chloroacetanilide herbicide used for pre-emergence control of weeds in corn. Acetochlor is available as an emulsifiable or soluble concentrate, microencapsulated or granular formulation that can be applied as pre-plant, pre-emergence, or early post-emergence weed control treatment.

CAS no.	34256-82-1
Chemical Formula	$C_{14}H_{20}ClNO_2$
Molecular Weight	269.77
Physical State	Amber, oily liquid
Water Solubility	223 mg/L
Density at 20 deg C	1.123 g/ml
Synonyms	None

Occurrence

Acetochlor was given conditional registration by the U.S. Environmental Protection Agency in March 1994 which provided an opportunity to investigate the occurrence of a pesticide during its first season of use. Water samples collected and analyzed by the U.S. Geological Survey during this time documented the distribution of acetochlor in the hydrologic system. It was detected in 29% of the rain samples from four sites in Iowa, 17% of the stream samples from 51 sites across nine states, and 0% of the groundwater samples from 38 wells across eight states. Acetochlor exhibited concentration increases in rain and streams following its application to corn in the midwestern United States, with 75% of the rainwater and 35% of the stream samples having acetochlor detected during this time period. Concentrations in rain decreased as the growing season progressed.

More than 70 wells, including 27 monitoring wells, 22 private drinking water wells, and 23 municipal wells in Wisconsin were sampled for alachlor, metolachlor, acetochlor, and their ethane sulfonic acid (ESA) and oxanillic acid (OA) metabolites. Wells were selected based on previous detections of pesticides or proximity to agricultural fields to increase the likelihood of exposure to the compounds of interest. Alachlor, metolachlor, and acetochlor are chloroacetanilide herbicides that are commonly used on corn and other crops in Wisconsin. Sample results showed over 80 percent of the monitoring wells and drinking water wells contained the ESA and OA metabolites of alachlor and metolachlor. The metabolites of acetochlor, which has only been used since 1994, showed a lower frequency of detection. Concentrations of the metabolites in groundwater ranged from near the level of detection to 42 µg/l. The monitoring wells and private drinking water wells showed higher detection frequencies and concentrations than the deeper municipal wells, but the municipal wells did show significant impacts. Fifty-two percent of the municipal wells had a detection of at least one of the compounds of interest. However, none of the municipal wells contained pesticide levels that exceeded an enforcement standard (WDATCP, 2000).

Toxicity

Acetochlor has low acute toxicity by the oral, dermal and inhalation routes and is mildly irritating to the eyes. Acetochlor has shown mild skin irritation in one study, however in another study it was a strong skin irritant. Acetochlor is also a strong dermal sensitizer.

Acetochlor is well absorbed by the oral route, undergoes extensive metabolism to produce reactive species that are responsible for its carcinogenicity in nasal tissue. The major target organs affected in rats, dogs and mice exposed to acetochlor appear to be the liver, thyroid, nervous system, kidney, testes, and erythrocytes. Species specific target organs include the nasal olfactory epithelium in rats and the

lungs in mice. Dogs are more sensitive to chronic exposure than rats. Chronic toxicity in the dog appeared in the form of testicular, hepatic, and renal histopathology, and at high doses, brain histopathology. Evidence of neurotoxicity has been observed in several studies.

Groups of 20-week old purebred beagles (5/sex/dose) were administered acetochlor by gelatin capsule for 52 weeks at dose levels of 0, 2, 10, or 50 mg/kg/day. Control animals received empty capsules. Systemic toxicity was evident at 10 and 50 mg/kg-day in both male and female dogs. Symptoms included excessive salivation and abnormal shaking of the head. Significant neurological effects were observed at 50 mg/kg/day and consisted of abnormal head movements; stiffness and rigidity of the hindlimbs; ataxia; tremor; depressed righting, hopping, and flexor reflexes; and exaggerated tonic neck reflex. Three animals in the high dose group were euthanized between weeks 39-51 due to severe neurological effects. Based upon the findings from this study, the LOEL for systemic toxicity is 10 mg/kg-day based on salivation, increased alanine aminotransferase and ornithine carbamyl transferase accompanied by significant increases in triglyceride levels, and decreased blood glucose levels, and histopathological changes in the kidney and testes of males. The NOEL for systemic toxicity in this study was 2 mg/kg/day (EPA, 2006). The US EPA used this study as the basis for its oral reference dose. The agency applied an uncertainty factor (UF) of 100 to account for intra and inter species variability. EPA noted that principal study is of good quality and is given a high confidence rating. Additional studies are of adequate quality and supportive of the critical study. Therefore, the database is given a high confidence rating. High confidence in the RfD follows.

Carcinogenicity

EPA Cancer Classification: Likely to be carcinogenic to Humans (US EPA, 2006).

Cancer slope factor: 0.0327 (EPA, 2006)

The carcinogenicity of acetochlor was evaluated by the US EPA Health Effects Division's Carcinogenicity Assessment Review Committee and the Mechanism of Toxicity Assessment Review Committee in a joint meeting held April 21-22, 2004. Three studies in the rat and two in the mouse were submitted for acetochlor. In addition, numerous mechanistic studies were submitted to evaluate the mechanism of nasal, thyroid and liver tumorigenesis. Acetochlor's classification was based on treatment-related increases in lung tumors in male and female mice, histiocytic sarcoma in female mice and nasal epithelial and thyroid follicular cell tumors in male and female rats. A non-mutagenic mechanism of carcinogenicity has been hypothesized for the rat nasal and thyroid tumors. Calculation of a Q_1* was based on lung tumor incidence in male mice (EPA, 2006).

Mutagenicity

In vitro studies do not indicate that acetochlor has high genotoxic potential *in vivo*. Weak positive findings in some studies have been attributed to cytotoxicity secondary to glutathione depletion (EPA, 2006).

Reproductive and Developmental Effects

There is no evidence that acetochlor is teratogenic or that offspring are more susceptible than adults, but acetochlor does cause developmental toxicity in rats at maternally toxic doses.

Environmental Fate

Soil and Groundwater

Acetochlor is adsorbed by soil colloids and leaches very little. Low soil moisture has little influence on efficiency. Laboratory studies indicate that acetochlor does not degrade by hydrolysis or photolysis. The primary method of degradation is microbial breakdown. Acetochlor's average persistence in surface soils at recommended application rates is 8 to 12 weeks, but this rate will vary depending on soil type, temperature and soil organic and moisture content (EPA, 2006). The principal environmental breakdown products are ethane sulfonic acid (ESA) and oxanilic acid (OA) metabolites which are more mobile in soils and more persistent in the environment compared to the parent herbicide (EPA, 2006). These metabolites leach readily and have been detected in a high percentage of groundwater and surface waters in the Midwestern US (Kolpin et al. 2000).

Surface Water

No information was found on degradation in surface waters.

Vegetation

Acetochlor is absorbed by germinating plant shoots and roots and can be translocated throughout the plant, with higher concentrations in vegetative parts rather than in reproductive parts. Acetochlor inhibits protein synthesis in susceptible plants.

Analytical Methods

Acetochlor can be analyzed in water samples using EPA method 525.2. Method 525.2 is used to determine semi-volatile organics in drinking water and drinking water sources. The analytes are extracted from the water using a 47 mm C18 disk. The disk is extracted with ethyl acetate and methylene chloride, the extract dried with sodium sulfate, and reduced in volume to 1.0 mL. Final analysis is by GC/MS.

Regulatory Summary

MCL	None
MCLG	None
LOAEL	10 mg/kg/day
NOAEL	2 mg/kg/day
Uncertainty Factor	100
RfD	0.02 mg/kg/day
Cancer Classification	Likely to be carcinogenic to humans
Cancer Slope Factor	0.032

State Drinking Water/Groundwater Standards

None found

Recommendations and Conclusions

The Department of Health Services recommends use of the cancer slope factor to develop a groundwater enforcement standard (GWES) for acetochlor. Because acetochlor has carcinogenic effects, a 10% preventive action limit (PAL) is proposed.

$$\frac{1 \times 10^{-6} \text{ LCR} \times 70\text{-kg} \times 100\% \text{ exposure}}{0.032 \text{ LCR/mg/kg/day} \times 2 \text{ liters/day}} = 1.0 \ \mu g/L$$

Recommended enforcement standard	1.0 µg/L
Recommended preventive action limit	0.1 µg/L

References

Kolpin D. W., Nations b. K., Goolsby D. A.; Thurman E. M. (1996) Acetochlor in the hydrologic system in the midwestern united states, 1994. ES&T 30(5): 1459-1464.

US EPA. 2006. Acetochlor. Revised HED Chapter of the Tolerance Reassessment Eligibility Decision (TRED) Document. PC Code:121601, DP Barcode: D292336.

USEPA. UCMR Contaminants and Corresponding Analytical Methods. accessed at http://www.epa.gov/OGWDW/ucmr/ucmr2/methods.html on October 1, 2008.

WDATCP. 2000. Chloroacetanilide herbicide metabolites in Wisconsin groundwater: Final Report.

ACETOCHLOR ETHANE SULFONIC AND OXANILIC ACID METABOLITES

(Combined Standard)

Acetochlor ethane sulfonic acid (ESA) and acetochlor oxanilic acid (OXA) are environmental degradates of acetochlor which is a chloroacetanilide herbicide used for pre-emergence control of weeds in corn.

	Acetochlor OXA	Acetochlor ESA
CAS no.	184992-44-4	187022-11-3
Molecular Weight	267.77	315.80
Physical State	Liquid	Liquid
Water Solubility	Freely soluble	Freely soluble
Density at 20 deg C	Not available	Not available
Synonyms	Acetochlor OXA, MON 52755	Acetochlor ESA, MON 52754

Occurrence

The herbicide acetochlor was given conditional registration by the U.S. Environmental Protection Agency in March 1994 which provided an opportunity to study the environmental distribution and fate of a pesticide during its first season of use. Water samples collected and analyzed by the U.S. Geological Survey during this time documented the distribution of acetochlor in the hydrologic system. It was detected in 29% of the rain samples from four sites in Iowa, 17% of the stream samples from 51 sites across nine states, and 0% of the groundwater samples from 38 wells across eight states. Acetochlor exhibited concentration increases in rain and streams following its application to corn in the midwestern United States, with 75% of the rainwater and 35% of the stream samples having acetochlor detected during this time period. Concentrations in rain decreased as the growing season progressed.

More than 70 wells, including 27 monitoring wells, 22 private drinking water wells, and 23 municipal wells in Wisconsin have been sampled for alachlor, metolachlor, acetochlor, and their ethane sulfonic acid (ESA) and oxanilic acid (OA) metabolites. Wells were selected based on previous detections of pesticides or proximity to agricultural fields to increase the likelihood of exposure to the compounds of interest. Alachlor, metolachlor, and acetochlor are chloroacetanilide herbicides that are commonly used on corn and other crops in Wisconsin. Sample results showed over 80 percent of the monitoring wells and drinking water wells contained the ESA and OXA metabolites of alachlor and metolachlor. Acetochlor metabolites were detected less frequently. Analytical results for acetochlor OXA ranged from below the level of detection to 1.9 µg/L with detects in 19% of the monitoring wells and 9% of the private drinking water supplies. Analytical results for acetochlor ESA ranged from below the level of detection to 6.4 µg/L with detects in 33% of the monitoring wells and 14% of the private drinking water supplies. None of the public water supplies had detectable levels of these degradates, however (WDATCP, 2000).

Toxicity

The metabolism of acetochlor and the toxicity of its metabolites are summarized in a March 1, 2006 US EPA document titled Acetochlor: Revised HED Chapter of the Tolerance Reassessment Eligibility Decision Document. The following is a summary of information provided by the EPA document.

Following oral dosing of rats, 34 to 39% of acetochlor OXA was absorbed and approximately 85% was excreted untransformed. In a 4-week range finding study conducted in rats, NOAELs of 372.6/367.2 and 370.3/374.6 mg/kg/day (M/F) were established for acetochlor OXA and acetochlor ESA, respectively, based on changes in thyroid hormone levels. A 90-day feeding study in rats yielded a NOAELs of 230.2 and 225.4 mg/kg/day for the

OXA and ESA metabolites, respectively, based on reduced body weights, lower weight gains and decreased food intake in males. In comparison, the 90-day NOAEL for acetochlor was 40 mg/kg/day. These findings indicate that the ESA and OXA metabolites of acetochlor are significantly less toxic than the parent herbicide.

Carcinogenicity

Acetochlor ESA and OXA have not been tested for carcinogenicity.

Mutagenicity

In vitro studies using bacterial assays and mammalian cells indicate that acetochlor ESA and OXA are not mutagenic (EPA, 2006).

Reproductive and Developmental Effects

The maternal and developmental toxicity of acetochlor OXA has been studied in rats. The maternal NOAEL and LOAEL were 500 and 1000 mg/kg/day based on maternal mortality. The developmental NOAEL was greater than 1,000 mg/kg/day (EPA, 2006).

Environmental Fate

Soil and Groundwater: The principal environmental breakdown products of acetochlor include the ethane sulfonic acid (ESA) and oxanilic acid (OA) metabolites which are more mobile in soils and more persistent in the environment than to the parent herbicide (EPA, 2006). These metabolites leach readily and have been detected in a high percentage of groundwater and surface waters in the Midwestern US (Kolpin et al. 2000).

Surface Water: Acetochlor ESA and OXA have been detected in surface waters in areas of use. No information was found on its degradation in surface waters, however.

Regulatory Summary

	Acetochlor OXA	Acetochlor ESA
LOAEL	955.2 mg/kg/day	919.4 mg/kg/day
NOAEL	230.2 mg/kg/day	225.4 mg/kg/day
RfD	None	None
MCL	None	None
MCLG	None	None
DWEL	None	None
LHA	None	None
Cancer Classification	Not classified	Not classified

State Drinking Water/Groundwater Standards

None found

Recommendations and Conclusions

The Department of Health Services recommends that NOAELs from 90-day rat feeding studies for acetochlor ESA and OXA be averaged and used as the point of departure for a combined groundwater enforcement standard (GWES). A combined standard is justified because these metabolites frequently occur in aquifers together and are similar in molecular structure. Their toxicity profiles are virtually identical with both chemicals having effects on thyroid hormone levels and on body weight gain in rats. Because these substances are not known to have carcinogenic or mutagenic effects, a 20% preventive action limit (PAL) is appropriate. An uncertainty factor of 10,000 is recommended to account for the use of a subchronic study, for intra- and inter-species variability, and for data gaps. Data gaps for these substances include the lack of studies in a second species, as well as the lack chronic toxicity studies and carcinogenicity evaluations.

$$\frac{228 \text{ mg/kg/day} \times 10\text{-kg} \times 100\% \text{ exposure}}{10{,}000 \times 1 \text{ liter/day}} = 228 \text{ µg/L (rounded to 230)}$$

Recommended GWES	230 µg/L
Recommended PAL	46 µg/L

References

Kolpin DW, Nations BK, Goolsby DA; Thurman EM. (1996) Acetochlor in the hydrologic system in the midwestern united states, 1994. ES&T 30(5):1459-1464.

US EPA (2004) Method 535 -Analytical Method Development for Chloroacetanilide and Other Acetamide Degradation Products in Drinking Water - Research Summary J.A. Shoemaker and M.V. Bassett, National Exposure Research Laboratory, Office of Research and Development U. S. Environmental Protection Agency, Cincinnati, OH accessed at *http://www.regulations.gov/fdmspublic/component/main?main=DocketDetail&d=EPA-HQ-OW-2004-0001* on January 12, 2009.

US EPA (2006). Acetochlor. Revised HED Chapter of the Tolerance Reassessment Eligibility Decision (TRED) Document. PC Code:121601, DP Barcode: D292336.

USEPA. UCMR Contaminants and Corresponding Analytical Methods accessed at http://www.epa.gov/OGWDW/ucmr/ucmr2/methods.html on October 1, 2008.

WDATCP. 2000. Chloroacetanilide herbicide metabolites in Wisconsin groundwater: Final Report.

ALUMINUM

Aluminum is the third most prevalent element and the most abundant metal in the earth's crust. In nature, aluminum is bound to other elements such as oxygen, silicon, and fluorine. Metallic aluminum, which is used for a variety of industrial and household products, is obtained from these aluminum-containing minerals. Small amounts of aluminum can be found naturally in surface water. Aluminum metal is light in weight and silvery-white in appearance. It is used for beverage cans, cookware, airplanes, siding and roofing, and as aluminum foil. Aluminum is often mixed with other metals to form alloys, which are stronger and harder than pure aluminum.

Aluminum compounds are used as alums in water-treatment and alumina in abrasives and furnace linings. They are also found in consumer products such as antacids, astringents, buffered aspirin, food additives, and antiperspirants.

CAS no.	91728-14-2
Atomic Weight	26.9
Physical State	Shiny, soft metal
Water solubility	Insoluble in metallic form, salts are soluble
Density at 20 deg C	2.7
Synonyms	Aluminium, Bauxite

Occurrence

WDNR's GRIN database provides aluminum data for 399 water supply wells. Levels ranged from < 0.0005 to 39,200 ug/L and exceeded the current health advisory level of 31 wells. Levels were highest in Brown and Wood counties where aluminum levels averaged 4,752 and 1,698 ug/L, respectively. Data from private water supply wells tested through the local health departments suggests that elevated aluminum levels are rare with only 6 or 1,128 wells having an aluminum level above 180 ug/L (LIMS, accessed 12/04/08.

Toxicity

At least three studies have investigated the effect of aluminum-contaminated drinking water on the incidence of Alzheimer's Disease (AD) among elderly populations. Martyn et al. (1997) conducted a case-control study in eight regions of England and Wales and found no difference between current aluminum levels in water consumed by people with AD vs controls diagnosed with other forms of dementia, brain cancer or other diseases. Two prospective studies have found positive associations between aluminum levels in water and the development of AD, however. Researchers in Quebec reported that 'after adjustment for education level, presence of family cases, and ApoE ε4 allele, exposure to organic monomeric aluminum estimated at the onset of the disease was associated with AD (odds ratio 2.67)' (Gauthier et al, 2000) Rondeau et al. (2009) examined associations between exposure to aluminum or silica from drinking water and risk of AD among elderly subjects followed for 15 years. These researchers also found that the risk of dementia and AD were higher for subjects with high daily aluminum intake while silica content in water was protective against dementia.

Dietary aluminum is ubiquitous, but in such small quantities that it is not a significant source of concern in people with normal renal function. Urban water supplies may contain a greater concentration because alum is often used as a flocculant. No known physiologic need exists for aluminum. However, because of its atomic size and electric charge (0.051 nm and 3+, respectively), it is sometimes a competitive inhibitor of several essential elements such as magnesium, calcium, and iron. Approximately 95% of an aluminum load becomes bound to serum transferrin and albumin and is then eliminated by the kidneys. If exposure levels exceed the body's excretory capacity, the excess is deposited in various tissues including bone, brain, liver, heart, spleen, and muscle. This accumulation causes morbidity and mortality through various mechanisms.

Most cases of human aluminum toxicity have involved patients with impaired renal function or patients who were exposed to high levels of aluminum from contaminated water used in dialysate solutions or parenteral nutrition fluids. Acute intoxication is extremely rare. However, in persons with impaired kidney function, aluminum can accumulate in the body. In the brain, where aluminum has an estimated half life of 7 years, it induces oxidative stress and interferes with neurofilament axonal transport and neurofilament assembly. Some experts believe that exposure plays a role in the formation of the characteristic neurofibrillary tangles see in Alzheimer's Disease. Aluminum also has a direct effect on the formation of red blood cells inducing microcytic anemia similar to that seen in patients suffering from lead poisoning.

Flaten et al. (1996) described several reports of aluminum accumulation and toxicity in individuals without chronic renal failure, especially preterm infants (primarily fed intravenously), and stated that preterm infants are at risk for aluminum loading because of their immature kidney function. Term infants with normal renal function may also be at risk because of their rapid growth and immature blood-brain barrier. Until they are 1 to 2 years old, infants have lower glomerular filtration rates than adults which affect their ability to excrete aluminum. The US Food and Drug Administration is concerned that young children are at a higher risk resulting from exposure to aluminum. Accordingly, the agency requires warnings on all aluminum-containing antiperspirants to inform parents to keep these products away from children, and to seek professional assistance if accidental ingestion occurs.

Aluminum (Al) impairment of bone matrix formation and mineralization may be mediated by its direct effect on bone cells or indirectly by its effect on parathyroid hormone and calcium metabolism. The risk for Al toxicity is greatest in infants with chronic renal insufficiency, recipients of long term parenteral nutrition, and preterm infants with low Al binding capacity. The rapid growth during infancy would theoretically potentiate Al toxicity in all infants, although the critical level of Al loading causing bone disorders is not known. To minimize tissue burden, Al content of infant nutrients should be similar to "background" levels, i.e., similar to whole milk -less than 50 micrograms/L (Koo and Kaplan, 1988).

Aluminum, cadmium and lead concentrations in the sperm and seminal plasma of 27 employees of two industrial companies, a refinery and a polyolefin factory, and 45 consecutive sperm donor candidates at a sperm bank were studied using atomic absorption measurements. The relationship between metal concentration and parameters of semen analysis was studied. A high concentration of aluminum in sperm was correlated with decreased sperm motility. The concentrations of cadmium and lead were low and did not show any correlation with parameters of semen analysis. Hovatta et al. (1998) concluded that aluminum may be one of the environmental pollutants that causes impaired semen quality.

Animal studies

Animal studies in rats and recent case reports have implicated the use of oral aluminum-containing antacids during pregnancy as a possible cause for abnormal fetal neurologic development.

Animal reproductive and gestational studies may provide the most sensitive endpoints for selection of a point of departure for risk assessment. In open field tests of motor activity, significant delays in pivoting, longer latencies and more rearings were observed in the offspring of rats administered gavage doses of 73 mg Al per kg/day as aluminum chloride (Misawa and Shigeta, 1992 as cited by ATSDR).

An intermediate duration oral study in male rats found that sperm counts were decreased following exposure to 2.5 mg Al/kg/day as aluminum chloride for 6-12 months. A dose of 0.25 mg/kg was considered the threshold level for adverse effects while a dose of 0.025 mg/kg had no effect on sperm production, chromosomal changes or blood phosphatase levels (Krasovskii et al. 1979 as cited by ATSDR).

Yousef et al. (2005) described the protective effects of ascorbic acid against the toxicity of aluminum chloride (AlCl3) on reproductive performance, lipid peroxidation and enzyme activities in male New Zealand white rabbits. Six rabbits per group were assigned to one of four treatment groups: 0 mg AA and 0 mg AlCl3 /kg body weight (BW) (control); 40 mg AA/kg BW; 34 mg Al (as AlCl3) per kg BW; 34 mg Al plus 40 mg AA/kg BW. Rabbits were orally administered their respective doses every other day for 16 weeks. Results obtained showed that AlCl3 significantly ($P<0.05$) decreased libido (by increasing the reaction time), ejaculate volume, sperm concentration, total sperm output, sperm motility (%), total motile sperm per ejaculate (TMS), packed sperm volume (PSV), total functional sperm fraction (TFSF), normal and live sperm and semen initial fructose while pH and dead and abnormal sperm were increased ($P<0.05$). Live body weight (LBW), feed intake (FI) and relative weights of testes (RTW) and epididymis (REW) were significantly ($P<0.05$) decreased. The study suggested that ascorbic acid might be protective against aluminum-induced reproductive toxicity.

Guo et al demonstrated the effect of aluminum on testosterone levels in male mice. Intraperotineal injections of 35 mg Al/kg body weight /day, administered for 12 days, significantly increased nitric oxide production and decreased both testicular adenosine 3',5'-cyclic monoposphate and testosterone levels (Guo et al, 2005).

Azzaoui et al. investigated the effects of aluminum nitrate administered in drinking water during 90 days (sub-chronic toxicity), on body weight gain, motor activity, brain aluminum accumulation and recognition memory of young, female Wistar rats. Treated rats received 80 mg/L of aluminum nitrate diluted in drinking water, while control rats received drinking water only. Body weight, motor activity, object recognition memory (NOR) and brain aluminum concentration were evaluated. Body weights were taken weekly, whereas the memory abilities and the motor activity are measured once every fourteen days, by submitting rats to the open field test and to the novel object recognizing memory test. The results revealed a significant decrease in body weight ($p < 0.05$). Though, no significant change in motor activity was seen, a significant effect on recognition memory was observed ($p < 0.01$). Brain tissue aluminum levels were not significantly different between treated and control rats. (Azzaoui FZ et al., 2008).

Carcinogenicity

US EPA: Not classified

IARC: Group 1, carcinogenic to humans

Although the US EPA has not evaluated the carcinogenicity of aluminum, at least two studies have shown carcinogenic effects in animals. Schroeder and Mitchener (1975a) exposed Long-Evans weanling rats (52/sex) to drinking water containing 5 mg/L aluminum (as aluminum potassium sulfate) for life. Specific tumor types were not specified; the incidence of total tumors was 13/25 in treated males and 4/26 in control males. The incidence of malignant tumors was 6/25 in treated males and 2/26 in control males. In another study, groups of 54 Swiss mice/sex were given 5 mg aluminum/L (as aluminum potassium sulfate) in the drinking water for life (Schroeder and Mitchener, 1975b). The incidence of leukemia in treated females was 10/41, while the incidence in control females was 3/47.

IARC has classified aluminum production as a Group 1 human carcinogen citing excess cancers of the lung and bladder among workers in the Canadian Province of Quebec where five aluminum plants were operating using the Söderberg production process (IARC, 1987).

Regulatory Summary

The EPA has recommended a Secondary Maximum Contaminant Level (SMCL) of 0.05–0.2 milligrams per liter (mg/L) for aluminum in drinking water. The SMCL is based on taste, smell, and color and does not consider health impacts. The US EPA has established a criteria continuous concentration of 87 ug/L and a criteria maximum concentration of 750 ug/L for aluminum in fresh water.

NOAEL	None
LOAEL	None
MCL	None
SMCL	0.05-0.2 mg/L
MCLG	None
DWEL	None
LHA	None
Cancer Classification	D, not classified

The Food and Drug Administration (FDA) has set the allowable concentration of aluminum in bottled water at 0.2 mg/L.

Recommendations and Conclusions

The Department of Health Services' review of toxicity literature has determined that the study by Yousef et al. provides the most sensitive endpoint for aluminum toxicity that complies with current laboratory standards. In this study, a dose of 34 mg Al per kg body weight every other day for 16 weeks resulted in male reproductive changes. A modifying factor of 2 is recommended to convert this dosing regimen to a daily dose of 17 mg Al per kg body weight. Three uncertainty factors of 10 each were applied to convert a LOAEL to a NOAEL, and to account for intra- and inter- species variability. Because aluminum has

been shown to have carcinogenic properties in animals, a 10% PAL is recommended.

$$\frac{17 \text{ mg/kg/day} \times 10\text{-kg}}{1{,}000 \times 1 \text{ liter/day}} = 170 \text{ ug/L}$$

Recommended Enforcement Standard	170 ug/L
Recommended Preventive Action Limit	17 ug/L

References:

Azzaoui FZ, Ahami AO, Khadmaoui A. 2008. Impact of aluminum sub-chronic toxicity on body weight and recognition memory of Wistar rat. Pak J Biol Sci. 15;11(14):1830-4.

Flaten TP, Alfrey AC, Birchall JD, Savory J and RA Yokel. 1996. Status and future concerns of clinical and environmental aluminum toxicology. J Toxicol Environ Health. 30:527-41.

Gauthier E, Fortier I, Courchesne F, Pepin P, Mortimer J and Gauvreau D. 2000. Aluminum forms in drinking water and risk of Alzheimer's Disease. Env Research, 84: 234-246.

Guo CH, Lin CY, Yeh MS, Hsu GSW. Aluminum-induced suppression of testosterone through nitric oxide production in male mice. 2005. Environ Toxicol. Pharmacol. 19:33-40.

Hovatta O, Venäläinen ER, Kuusimäki L, Heikkilä J, Hirvi T, Reima I. 1998. Aluminium, lead and cadmium concentrations in seminal plasma and spermatozoa, and semen quality in Finnish men. Human. Reprod. 13(1):115-9.

IARC Monographs, Suppl. 7, 89, 1987.

Klein GL. 1989. Aluminum in parenteral products: medical perspective on large and small volume parenterals. J Parenter Sci Technol. 43(3):120-4.

Koo WW, Kaplan LA. 1988. Aluminum and bone disorders: with specific reference to aluminum contamination of infant nutrients. J Am Coll Nutr. 7(3):199-214.

Krasovskii GN, LY Vasukovich, OG Chariev. 1979. Experimental Study of Biological Effects of Lead and Aluminum Following Oral Administration. EHP, 30:47-51.

Martyn CN, Coggon DN, Inskip H, Lacey RF, Young WF. 1997. Aluminum concentrations in drinking water and risk of Alzheimer's Disease. Epidemiol Resources. 8: 281-286.

Rondeau V, Jacqmin-Gadda H, Commenges D, Helmer C, Dartigues JF. 2009. Aluminum and silica in drinking water and the risk of Alzheimer's Disease or cognitive decline: Findings from a 15-yr follow-up of the PAQUID cohort. Amer J Epidemiol. 169:489496.

Schoeder HA, Mitchener M. 1975a. Life-term studies in rats. Effects of aluminum, barium, beryllium and tungsten. J Nutr 105:421-427.

Schoeder HA, Mitchener M. 1975b. Life-term studies in rats. Effects of mercury, methylmercury and nine other trace metals on mice. J Nutr 105:452-458.

Yousef MI, El-Morsy AM, Hassan MS. 2005. Aluminium-induced deterioration in reproductive performance and seminal plasma biochemistry of male rabbits: protective role of ascorbic acid. Toxicology 5;215(1-2):97-107.

AMMONIA

Ammonia is a naturally-occurring inorganic chemical that is ubiquitous in nature. In aqueous solution, the ammonium ion (NH_4+) and unionized ammonia (NH_3) exist in a pH-dependent equilibrium. Alkaline conditions favor the unionized form, while the ionized form predominates at physiologic pHs. Ammonia is used in fertilizers, refrigeration systems, household cleaners, and manufacturing processes. It is also used in conjunction with chlorine to form chloramine which is used as a drinking water disinfectant.

CAS no.	1336-21-6
Molecular weight	17.03
Physical state	Colorless gas with a very pungent odor, liquid under pressure
Density	0.6818
Water solubility:	531 grams per liter
Taste threshold:	34 mg/L
Synonyms:	Ammonium hydroxide

Occurrence

Major natural sources of ammonia include animal excreta, decaying vegetation, human sewage, industrial wastewater, combustion of fossil and non-fossil fuels. The commercial synthesis of ammonia is a minor source thought to contribute no more than 5% of the total global ammonia budget. Due to its volatility and rapid conversion to nitrate, ammonia is not a major contaminant of groundwater or surface water. Background levels in these media range from 0 to ~1 mg/L.

Most human exposure to ammonia occurs as a result of inhalation of household cleaning products and through dermal contact. Occupational exposure usually involves inhalation of ammonia gas. Ammonia is produced in the human digestive tract during bacterial degradation of nitrogenous compounds from ingested food. Ammonia absorbed from the gastrointestinal tract is transported to the liver where it is converted to urea and glutamine. In healthy adults liver detoxification is rapid and very little ammonia reaches the systemic circulation.

Toxicity

An acute LD50 of 350 mg/kg was reported in rats administered ammonia (Smyth et al, 1941).

Most cases of acute ammonia exposure involve inhalation of concentrated forms of ammonia gas. Clinical effects range from a mild irritation to life-threatening cases of pulmonary edema depending on the concentration and length of exposure. Household ammonia solutions typically contain 5 to 10% ammonia in water. These concentrations rarely cause burns, but can irritate the eyes, nose, throat, and upper respiratory tract. Higher concentrations used in agricultural and industrial settings can cause irritation and severe burns of the eyes, lungs, upper airway, and skin. When heated to decomposition, ammonia emits toxic fumes of ammonia and nitrogen oxides.

Suicidal or accidental ingestion of household ammonia can cause esophageal burns with late resulting strictures. Gastric, duodenal, and jejunal lesions have also been reported. One teaspoonful of strong (28%) ammonia has been reported to be fatal but recoveries have followed ingestion of as much as one fluid ounce on several occasions (Gosselin et al. 1984).
Ammonium chloride has been used as a diuretic and urine-acidifying agent. Therapeutic dosage levels for adults range from 4 to 12 grams/day. Based on an average body weight of 70 kg, these are equivalent to 19 to 57 mg/kg/day as ammonium. The usual acidifying dose for children is 25 mg/kg/day as

ammonium (Reynolds and Prasad, 1982). The drug is given in four divided doses for three to four days, followed by a two-day rest period. If given continuously, particulary to patients with renal impairment, it may cause severe metabolic acidosis. Any use is contraindicated in patients with liver or renal disease since accumulation of ammonia in such patients may lead to central nervous system toxicity. Other adverse effects associated with the administration of ammonium chloride include: gastric irritation, anorexia, metabolic acidosis, and electrolyte disturbances (Amer Hosp Form Serv, 1988).

Chronic toxicity

Enlarged adrenal glands and increases in blood pressure were observed in rabbits that received 124 mg ammonium/kg/day as ammonium hydroxide by gavage for 17 months (Fazekas, 1939). Reduced food intake and decreased body weights were observed in rats fed 500 mg ammonium sulfamate per kg 6 days/week for 90 days. This dose is equivalent to 428 mg/kg/day as ammonium sulfamate, or 79 mg ammonium cation per day. The NOAEL for this study was 214 mg/kg/day (40 mg/kg/day as ammonium) (Gupta et al, 1979). Administration of 0.02 % ammonia (200 mg/L) as drinking water for 24 weeks caused glandular atrophy in the gastric mucosa of male Donryu rats. Treatment at this dose for 8 weeks delayed healing of acetic acid-induced gastric ulcers (Hata et al, 1994).

Absorption and metabolism

Ammonia is rapidly absorbed from the gastrointestinal tract. Absorbed ammonia is transported to the liver where it is converted to urea which is excreted by the kidneys and glutamine which is distributed to the tissues where it is used as a source of nitrogen for protein synthesis. Metabolism and excretion of ammonia is inefficient in persons suffering from certain inherited or acquired metabolic disorders, and in patients with liver or renal diseases (Smith, 1990). Ammonia is normally found in human blood at concentrations of 80 to 110 micrograms/deciliter (Braunwald et al, 1987).

Persons who have been suggested as being more sensitive to the toxic effects of ammonia include: 1) persons suffering from advanced liver or kidney disease; 2) persons with genetic defects in the urea cycle enzymes, or in ornithine transcarbamylase; 3) persons suffering from gout; and 4) women in the last trimester of pregnancy who are at risk for toxemia of pregnancy (Reprotext Database, 1996).

Ammonia accumulates in the blood, brain, and cerebral spinal fluid of patients suffering from acute liver failure causing a condition termed hepatic encephalopathy. High-protein diets, gastrointestinal hemorrhage, and constipation can exacerbate this condition by increasing colonic ammonia production (Kirk, 1986).

Reproductive/developmental effects

Decreased egg production has been demonstrated in birds and pullets. An elevated ammonia tissue concentration in cows has been found to decrease conception rates and increase the calving-to-conception intervals . No data were located regarding the teratogenic potential of ammonia.

Carcinogenicity assessment

EPA cancer classification: D, not classified

Animal studies conducted in Japan have found that the administration of 0.01% (100 mg/L) ammonia in drinking water for 24 weeks significantly increased the number of cancers in the glandular stomach of rats pretreated with the experimental carcinogen N-methyl-N'-nitro-N-nitrosoguanidine (MNNG). These

researchers concluded that ammonia appears to be an important promoter of gastric cancer in rats and possibly in *Helicobacter pylori*-associated gastric carcinogenesis in humans (Tsujii, 1995).

Genotoxicity

Mutations and chromosome aberrations have been reported following exposure of bacteria or cultured cells to lethal concentrations of ammonia gas. The relevance of these findings to sublethal exposure levels is controversial (ATSDR, 1990).

Environmental fate

Aquatic
In surface waters ammonium undergoes microbiological nitrification, which yields hydrogen and utilizes oxygen so that, in certain systems, acidification and oxygen depletion may result. In one study, one-third of the acidifying effect of precipitation was attributed to ammonium deposition. Ammonia may be assimilated by aquatic plants as a nitrogen source or transferred to sediments or volatilized. Concentrations of ammonia that are acutely toxic to fish can cause loss of equilibrium; hyperexcitability; increased breathing, cardiac output, oxygen uptake; and in extreme cases convulsions, coma, and death. 48 and 96-hr LC50s for freshwater fish range from 0.56 to 2.48 mg/L (WHO, 1986). Lower levels and caused reductions in fish egg hatching success, a reduction in growth rate and morphological development, and pathological changes in the tissues of the gills, liver and kidney (USEPA/OWRS, 1986).

Atmospheric
Ammonia that volatilizes into the atmosphere may undergo a variety of reactions with sulfur dioxide or ozone to produce aerosols or ammonium sulfate or ammonium nitrate. These products return to the earth's surface in wet or dry deposition.

Terrestrial
The application of certain synthetic fertilizers also contributes to soil ammonia levels. The ammonium cation is relatively immobile in soil, however, most ammonium is oxidized to nitrate which is highly mobile. Nitrate is removed by leaching, plant root uptake, or denitrification.

Regulatory Summary

NOEL/LOEL	None
RfD	None
MCL/DWEL	None
Lifetime Health Advisory	30 mg/L (taste threshold)
Cancer class	D, Not classified

Summary of toxicity information for ammonia

Species	Route	Exposure Duration	Dose* mg/kg/day	Effect	Form	Reference
Guinea Pig	Oral	1 day	303	Death	NH_4Cl	Koenig, 1941
Human	Oral	3-4 days	25	Gastric irritation, CNS toxicity	NH_4Cl	Reynolds, 1982
Dog	Oral	11 weeks	337	Bone deformity and softening	NH_4Cl	Bodansky, 1932
Rabbit	Oral	17 months	124	Increased blood pressure, Enlarged adrenal glands	NH_4OH	Fazekas, 1939
Rat	Oral	90 days	79	Decreased weight, No systemic effects	$NH_4NH_2SO_3$	Gupta, 1979

*All doses are expressed as ammonium cation

State Drinking Water Standards and Advisories

New Jersey 3 mg/L

Recommendations and conclusions

The U.S. Environmental Protection Agency has not established a health-based drinking water standard for ammonia. Our review of current literature indicates that the federal lifetime health advisory may not be adequate to protect sensitive subpopulations, such as persons suffering from kidney or liver disease, against the toxicity of ingested ammonia. Therefore, in accordance with the provisions of ss NR 160.13, the Department of Health Services recommends that a health-based groundwater enforcement standard be established based on the human toxicity of ammonium chloride which has been used as a therapeutic agent. Following ingestion, ammonium chloride dissociates to produce the chloride anion and the ammonium cation. The chloride anion exerts a diuretic effect, but has little overt toxicity. Chloride is currently regulated in public drinking water supplies and in groundwater as an indicator parameter. The gastric irritation and neurotoxicity that have been associated with the use of ammonium chloride have been attributed to the effect of ammonia on the upper digestive tract and to its systemic toxicity.

To develop a health-based groundwater standard that will be protective against the toxicity of ingested ammonia, application of an uncertainty factor of 20 to the therapeutic dosage level is recommended. This includes a factor of 10 to convert a human LOAEL to a NOAEL, and an additional factor of 2 to account for the use of information from a discontinuous exposure. Since ammonia has been shown to have mutagenic and carcinogenic effects, a 10% preventive action limit is proposed.

$\frac{25 \text{ mg/kg/day} \times 10 \text{ kg}}{}$ = 12.5 mg/L as ammonium (9.7 mg/L as ammonia-nitrogen)

20 x 1 liter/day

Recommended enforcement standard: 9.70 mg/L (as ammonia-nitrogen)
Recommended preventive action limit: 0.97 mg/L

References

American Hospital Formulary Service-Drug Information 88. Bethesda, MD: American Society of Hospital Pharmacists, 1988; as cited by the National Library of Medicine in the Hazardous Substances Data Bank.

ATSDR. Toxicological Profile for Ammonia. December 1990.

Braunwald E, Isselbacher KJ, Petersdorf RG et al: Principles of internal medicine, 11th ed. McGraw-Hill, New York 1987.

Fazekas IG. 1939. Experimental suprarenal hypertrophy induced by ammonium hydroxide. Endokrinologie 21:315-337; as cited in the Toxicological Profile for Ammonia, U.S. Dept of Health and Human Services, Agency for Toxic Substances and Disease Registry, 1990.

Federal Register. Jul 29, 1985; EPA Water Quality Criteria; p. 30785.

Gosselin RE, Smith RP, Hodge HC. Clinical Toxicology of Commercial Products, 5th ed. Williams and Wilkins, Baltimore, 1984.

Gupta BN, Khanna RN, Datta KK. 1979. Toxicological studies of ammonium sulfamate in rat after repeated oral administration. Toxicol 13:45-49.

Hata M, Yamazaki Y, Ueda T, Kato T, et al. 1994. Influence of ammonia solution of gastric mucosa and acetic induced ulcer in rats. Eur J Histochem; 38(1):41-52.

Janicki RH. 1970. Renal adaptation during chronic NH_4Cl acidosis in the rat: No role for hyperplasia. Am J Physiol 219:613-618.

Kirk RW (Ed): Current Veterinary Therapy IX. Saunders, Philadelphia, PA, 1986.

Reprotext Database: Ammonia, 1996.

Reynolds JEF, Prasad AB. Marindale-The Extra Pharmacopoeia. 28th ed. The Pharmaceutical Press, London, 1982.

Smith BP: Large Animal Internal Medicine. The CV Mosby Company, Philadelphia, PA, 1990.

Smyth HF, Seaton J, Fischer L. 1941. The single dose toxicity of some glycols and derivatives. J Ind Hyg Toxicol 23(6):259-268.

Tsujii M, Kawano S, Tsuji S, Takei Y, et al. 1995. Mechanism for ammonia-induced promotion of gastric cacinogenesis in rats. Carcinogenesis; 16(3):563-6.

USEPA/OWRS. Quality Criteria for Water: Ammonia; 1986, EPA440/5-86-001.

WHO Environmental Health Criteria (54); 1986, 210 p.

CHLORODIFLUOROMETHANE (FREON-22)

Chlorodifluoromethane is a hydrochlorofluorocarbon (HCFC) used in refrigeration and air conditioning. It is currently being used in "closed loop" geothermal heating/cooling systems and may pose a risk to groundwater.

CAS no.	75-45-6
Molecular Weight	86.5
Molecular Formula	CHClF2
Physical State	Ether-like, clear liquid under pressure; gas at room temperature
Water Solubility	3 to 4 grams/L
Synonyms	Freon 22, HCFC-22, CFC-22,Genetron 22

Occurrence

Although Freon 22 has never been detected in WI groundwater, very little testing has been conducted and the risk of contamination is considered to be high due to its use as a refrigerant fluid in "closed loop" geothermal heating/cooling systems.

Toxicity

Freon 22 has low acute toxicity. The 4 hr - inhalation LC50 in the rat is 220,000 ppm.

The compound is a skin irritant and a slight eye irritant, but is not a skin sensitizer in animals. Effects from single high exposures include central nervous system depression, anesthesia, rapid breathing, lung congestion and microscopic liver changes (Dupont, 1996).

Inhalation of high concentrations of vapor is harmful and may cause heart irregularities, unconsciousness or death. Higher exposures may lead to temporary alteration of the heart's electrical activity with irregular pulse, palpitations, or inadequate circulation. Fatality may occur from gross overexposure. Individuals with pre-existing diseases of the central nervous or cardiovascular system may have increased susceptibility to the toxicity of excessive exposures (Dupont, 1996).

After exposure to decomposed chlorodifluoromethane (Freon-22), a 65-year-old man developed respiratory symptoms such as cough, blood-stained sputum, and increasing dyspnea. Three weeks later, he was diagnosed with infectious bronchitis. He died 4 weeks after his exposure due to myocardial infarction. The authors hypothesized that his death resulted from an inflammatory process caused by the inhalation of decomposed freon (Sjogren et al. 2002).

Increased kidney, adrenal and pituitary weights... The female rats in the 50,000-ppm group exhibited a statistically significant increase in liver, kidney, adrenal gland, and pituitary weights. No non-neoplastic histopathological changes were observed. The liver weight effect was not considered adverse because it did not exceed a 10% weight change and there was no histopathology observed. Based on effects on the kidney, adrenal gland, and pituitary weight, a NOAEL of 10,000 ppm [NOAEL (HEC) = 5,260 mg/cu.m] and a LOAEL of 50,000 ppm [LOAEL (HEC) = 26,300 mg/cu.m] were estimated (US EPA IRIS document for Chlorodifluoromethane).

Carcinogenicity

US EPA: Not classified

There is *limited evidence* for the carcinogenicity of chlorodifluoromethane to experimental animals (IARC, 1986).

Chlorodifluoromethane was tested for carcinogenicity in one experiment in rats by oral administration by gavage and in experiments in rats and mice by inhalation exposure. No increase in tumor incidence was observed in rats after oral administration. The inhalation study in mice was inconclusive for males, and negative results were obtained for females. In the inhalation study in rats, males receiving the high dose had increased incidences of fibrosarcomas and zymbal-gland tumors. No increased cancers were seen in female rats (IARC, 1986).

Reproductive and Developmental Effects

Chlorodifluoromethane causes malformations of the eyes of fetal rats, but has no reproductive effect in male rats and does not cause prenatal toxicity in rabbits following exposure by inhalation.

Palmer et al. (1978a) conducted a large developmental study in an attempt to elucidate the role of CFC-22 exposure in the eye lesion seen in the previous studies. In this study, 34 control pregnant rats were used, and 22/group were exposed to 100, 1000, or 50,000 ppm of CFC-22 (354, 3,540, or 176,800 mg/cu.m, respectively) for 6 hours/day on gestation days 6-15. This protocol was repeated 19 times so that more than 6,000 control fetuses and 4,000 fetuses from each exposed group were thoroughly examined for the eye defect... The eye abnormalities (small or missing eye) were noted in all exposure groups, but statistical significance for these effects was achieved only in the 50,000-ppm group (US EPA IRIS Document for Chlorodifluoromethane).

Regulatory Summary

RfC	50 mg/cu.m
RfD	None
MCL	None
LHA	None
Cancer	Not classified

State Drinking Water Standards and Advisories

None found

Recommendations and Conclusions for Chlorodifluoromethane:

The Department of Health Services recommends use of the US EPA Reference Concentration as a point of departure for development of a groundwater standard. A relative source contribution factor of 50% is applied assuming that, in situations where household water is contaminated with freon, approximately half of the exposure comes from inhalation. This correction is needed because of the volatility of this chemical at room temperature. Conversion of the reference concentration to a reference dose was accomplished using the following formula:

$$RfD = \frac{RfC \times IR \times AR}{BW \times 100}$$

where:

RfC = Reference Concentration in Air (mg/m^3)
IR = Inhalation Rate (20 m^3/day)
AR = Absorption Rate (100% assumed unless otherwise specified)
BW = Adult Body Weight (70 kg)

$$\frac{50\ mg/cu.m \times 20\ cu.m/day \times 100\%}{70\ kg} = 14.3\ mg/kg/day$$

The department recommends application of an uncertainty factor of 10 to protect against developmental and carcinogenic effects. A 10% preventive action limit factor is proposed for this substance which has carcinogenic and mutagenic properties.

$$\frac{14.3\ mg/kg/day \times 10\text{-}kg \times 50\%\ RSC^*}{10 \times 1\ L/day} = 7\ mg/L$$

*50% relative source contribution assumes equal exposure from oral intake and inhalation. This factor is needed due to the volatility of freon at room temperature.

Recommended Enforcement Standard	7 mg/L
Recommended Preventive Action Limit	0.7 mg/L

References:

Dupont, 1996. Material Safety Data Sheet for Freon 22.

IARC. 1986. Summary of data reported and evaluation.

International Program on Chemical Safety (IPCS). 2002. accessed online at http://www.inchem.org/documents/icsc/icsc/eics0049.htm

Sjogren B, Gunnare S, Sandler H. 2002. Inhalation of decomposed chlorodifluoromethane (Freon-22) and myocardial infarction. Scand J Work Environ Health 28:205-7.

US EPA. IRIS Document for Chlorodifluoromethane accessed January 13, 2009.

CHLORPYRIFOS

Chlorpyrifos is a broad-spectrum organophosphate insecticide. While originally used primarily to kill mosquitoes, it is no longer registered for this use. Chlorpyrifos is effective in controlling cutworms, corn rootworms, cockroaches, grubs, flea beetles, flies, termites, fire ants, and lice. It is used as an insecticide on grain, cotton, field, fruit, nut and vegetable crops, and well as on lawns and ornamental plants. It is also registered for direct use on sheep and turkeys, for horse site treatment, dog kennels, domestic dwellings, farm buildings, storage bins, and commercial establishments. Chlorpyrifos acts on pests primarily as a contact poison, with some action as a stomach poison. It is available as granules, wettable powder, dustable powder and emulsifiable concentrate. Also known as Lorsban, chlorpyrifos is one of the most widely used insecticides in the U.S.

CAS No:	2921-88-2
Molecular weight	350.62
Physical State	Amber to white crystalline solid with a mild sulfur odor
Specific gravity:	1.162
Water solubility:	2 mg/L @ 25 C
Synonyms	Trade names include Brodan, Detmol UA, Dowco 179, Dursban, Empire, Eradex, Lorsban, Paqeant, Piridane, Scout, and Stipend.

Occurrence

Chlorpyrifos was the most frequently detected pesticide in well water samples located in an area of tobacco production in Brazil. The study investigators found that chlorpyrifos was persistent four months after the application is discontinued. This is due to the long period of application and possibly to the concentration of chlorpyrifos in the same area, as well to the continuous runoff process commonly found in the studied drainage basin (Bortoluzzi et al, 2007).

The US EPA examined data for more than 3,000 samples of filtered well monitoring samples from the NAWQA database, and in the agency's Pesticides in Ground Water Data Base (PGWDB). The NAWQA data showed that chlorpyrifos was detected in groundwater in fewer than 1% of the 3000 wells sampled, with the majority of concentrations reported at <0.01 ppb, and occasional detections at a maximum level of 0.026 ug/L. Although the available monitoring data represent a large part of the U.S., it is not clear that they represent the most vulnerable groundwater where chlorpyrifos is used most intensively. The PGWDB reports a maximum detected concentration of 0.65 ug/L. Chlorpyrifos use as a termiticide is significant, with a recent estimate of 7 million pounds applied annually, constituting about 30% of the total annual use. Chlorpyrifos groundwater exposure from termiticidal use occurs only in wells located within 100 feet of the treatment area and when the well casing is cracked. The maximum reported dissolved concentration following termiticide use is 2,090 ppb (US EPA, Jul 31, 2006).

Toxicity

Chlorpyrifos is readily absorbed following ingestion, inhalation or dermal contact and is eliminated rapidly by the kidneys. Chlorpyrifos does not bioaccumulate in tissues. It is an irreversible inhibitor of cholinesterase (ChE) including acetylcholine esterase (AChE), and inhibition of AChE in the central and peripheral nervous systems causes accumulation of acetylcholine, a neurotransmitter, which in turn results in neurotoxicity in animals and humans. Inhibition of ChE is believed to be the most sensitive response in all animal species evaluated and in humans, regardless of route or duration of exposure (U.S. EPA, 2001).

Chlorpyrifos is toxic to the central nervous system, the cardiovascular system, and the respiratory system and is irritating to the skin and eyes. Symptoms of exposure include numbness and tingling, headache, dizziness, tremor, nausea, abdominal cramps, sweating, blurred vision, breathing difficulties, problems with coordination and slow heartbeat. Very high doses may result in unconsciousness, convulsions and death. Delayed neuropathies can onset up to a month after exposure. Recovery may take several months and may be incomplete resulting in permanent disabilities. Workers who are repeatedly exposed can experience problems with memory and concentration, disorientation, depression, irritability, confusion, headache, speech difficulties, delayed reaction times, nightmares, sleepwalking, and drowsiness or insomnia. An influenza-like condition with headache, nausea, weakness, loss of appetite, and malaise has also been reported (Extoxnet, 1996).

EPA Reference Dose

On March 11, 1986, the US EPA has verified a reference dose of 0.003 mg/kg/day for chlorpyrifos (US EPA, IRIS Database, accessed Jan 2009). This guideline is based on a no effect level of 0.03 mg/kg/day from a study in which 16 male volunteers (4/dose) were treated with 0, 0.014, 0.03, or 0.10 mg/kg/day of chlorpyrifos by capsule for a total of 20 days at the low and mid dose, and for 9 days at the high dose. Treatment of the high-dose group (0.1 mg/kg/day) was discontinued after 9 days due to a runny nose and blurred vision in one individual. Mean plasma ChE in this group was inhibited by about 65% compared to the control average. No effect on RBC ChE activity was apparent at any dose. An uncertainty factor of 10 was applied to account for variations in sensitivity.

Carcinogenicity

US EPA Carcinogenicity Classification: Class D, Not classifiable.

A review of the literature found no evidence to support a carcinogenic effect of chlorpyrifos in animals or in humans.

Reproductive/Developmental Effects

Although some epidemiological studies have found associations between chlorpyrifos exposure and decreased fetal weights among women, animal studies have yielded conflicting findings. No effects were seen in a three-generation study with rats fed dietary doses as high as 1 mg/kg/day. In another study in which rats were fed 1.0 mg/kg/day for two generations, the only effect observed was a slight increase in the number of deaths of newborn offspring (Extoxnet, 1996).

Available evidence suggests that chorpyrifos is not teratogenic. No teratogenic effects in offspring were found when pregnant rats were fed doses as high as 15 mg/kg/day for 10 days. When pregnant mice were given doses of 25 mg/kg/day for 10 days, minor skeletal variations and a decrease in fetal length occurred. No birth defects were seen in the offspring of male and female rats fed 1.0 mg/kg/day during a three-generation reproduction and fertility study (Extoxnet, 1996).

Mutagenicity

There is no evidence that chlorpyrifos is mutagenic. No evidence of mutagenicity was found in any of four tests performed [Extoxnet, 1996].

Environmental Fate

Soil and groundwater: Chlorpyrifos is moderately persistent in soils with a half-life of 60 to 120 days. Chlorpyrifos is subject to degradation by UV light, chemical hydrolysis and by soil microbes. When applied to moist soils, the volatility half-life was 45 to 163 hours, with 62 to 89% of the applied chlorpyrifos remaining on the soil after 36 hours. Chlorpyrifos adsorbs strongly to soil particles and it is not readily soluble in water. It is therefore immobile in soils and unlikely to leach or to contaminate groundwater. TCP, the principal metabolite of chlorpyrifos, adsorbs weakly to soil particles and appears to be moderately mobile and persistent in soils (Extoxnet, 1996).

Breakdown in water: Volatilization is probably the primary route of loss of chlorpyrifos from water. Volatility half-lives of 3.5 and 20 days have been estimated for pond water. The photolysis half-life of chlorpyrifos is 3 to 4 weeks during midsummer in the U.S. Its change into other natural forms is slow. Research suggests that this insecticide is unstable in water, and the rate at which it is hydrolyzed increases with temperature, decreasing by 2.5- to 3-fold with each 10 C drop in temperature. The rate of hydrolysis is constant in acidic to neutral waters, but increases in alkaline waters. In water at pH 7.0 and 25 C, it had a half-life of 35 to 78 days (US EPA, 1989).

Regulatory Summary

Reference Dose	0.0003 mg/kg/day
MCL	None
MCLG	None
Lifetime Health Advisory	0.002 mg/L
Cancer Classification	Not classified

State Drinking Water Standards and Advisories

Florida	21 ug/L
New Jersey	20 ug/L
Vermont	20 ug/L

Recommendations and Conclusions

The Wisconsin Department of Health Services recommends adoption of the US EPA Lifetime Health Advisory as the groundwater enforcement standard for chlorpyrifos. Since this substance is not associated with carcinogenic, mutagenic or teratogenic effects, a 20% PAL is proposed. If chlorpyrifos is identified with other organophosphates, the effects should be considered additive and a hazard index approach should be used to assess the potability of the water supply.

Recommended Enforcement Standard	2.0 µg/L
Recommended Preventive Action Limit	0.2 µg/L

References

Bortoluzzi EC; Rheinheimer DS; Gonçalves CS; PellegriniII JBR; Maroneze AM; Kurz MHS; Bacar NM; Zanella R. 2007. Investigation of the occurrence of pesticide residues in rural wells and surface water following application to tobacco Quím. Nova 30:8.

Extoxnet, 1996. Chlorpyrifos. Accessed online January 27, 2009.

US Environmental Protection Agency. June, 1989. Registration Standard (Second Round Review) for the Reregistration of Pesticide Products Containing Chlorpyrifos. Office of Pesticide Programs, US EPA, Washington, DC.

US EPA. IRIS Document for Chlorpyrifos, accessed online January 27, 2009.

US EPA. 2001. Chlorpyrifos Interim Risk Management Decision.

DIMETHENAMID/S-DIMETHENAMID

Dimethenamid was originally registered as a mixture of R and S-isomers (50:50, S:R), and tolerances for the 50:50 mixture were established for dry beans, field corn, sweet corn, peanuts, sorghum, and soybean. Manufacture of the 50:50 mixture has ended and has been replaced by a mixture (Dimethenamid-P) that is enriched in the biologically active S-isomer (90:10, S:R). Registration of the original 50:50 mixture will be cancelled when existing stock is depleted. Currently, both Dimethenamid (50:50, S:R) and Dimethenamid-P, sold under the trade name Outlook (90:10, S:R) are used (Fed Reg, 2004).

Sold under the trade name Frontier, dimethenamid is a widely used amide herbicide. In 2001, about 7 million pounds of dimethenamid were used in the United States.

CAS #:	87674-68-8 (50:50 S:R); 163515-14-8 (90:10 S:R)
Molecular weight	275.8
Physical State	Liquid
Specific gravity:	1.105
Water solubility:	1,450 mg/L
Synonyms	Frontier, Outlook

Occurrence

Dimethenamid was detected in 2 of 428 (0.4%) wells tested by the Wisconsin Department of Agriculture, Trade and Consumer Protection. The highest detect level was 2.79 ug/L.

Acute Toxicity

Dimethenamid (50:50 SR) is less acutely toxic than Dimethenamid-P (90:10). In rats, the oral LD50 for the 50:50 mixture is approximately 2 g/kg body weight, while the LD50s for the 90:10 mixture were 429 mg/kg in males and 531 mg/kg in females. Both mixtures are much more toxic by inhalation with LD50s below 5 mg/kg.

Chronic Toxicity

A chronic toxicity/carcinogenicity study conducted in Sprague-Dawley rats fed a 50/50 mixture of the R and S isomers. This study provided NOAELs of 5.1 mg/kg/day and 6.8 mg/kg/day and LOAELs of 36 and 49 mg/kg/day in male and female rats, respectively, based on decreased weight gain and hepatic lesions in both sexes. A dose related increased incidence of liver tumors was observed in males.

A 13-week rat feeding study yielded a no-observed effect level (NOEL) of 33.5 mg/kg/day for males and 40.1 mg/kg/day for females.

Subchronic oral toxicity study of dimethenamid (50:50 S:R) conducted in dogs yielded NOAELs of 4.72 and 4.98 and LOAELs of 33.6 and 39.7 in males and females, respectively. The critical effects noted by investigators included decreased weight gain in females, increased relative liver weight in both sexes, increased periportal vacuolation in the liver in both sexes and dilation of liver sinusoids in females.

Carcinogenicity

US EPA Cancer classification: Class C, possible human carcinogen

A carcinogenicity study in mice with no carcinogenic effects observed at any dose level under the conditions of the study and a systemic NOEL of 40.8 mg/kg/day for males and 40.1 mg/kg/day for females, based on food consumption and a systemic lowest effect level 205 mg/kg/day for males and 200 mg/kg/day for females based on food consumption based on significantly elevated liver weights.

A rat chronic feeding/carcinogenicity study with a systemic NOEL of 5 mg/kg/day and an LEL of 35 mg/kg/day due to decreased food efficiency and histopathology findings. Under the conditions of the study limited evidence of carcinogenicity was observed based on a statistically significant increasing trend for benign liver cell tumors in male rats and a statistically significant increasing trend for ovarian tubular adenomas in female rats. A re-evaluation of the ovarian neoplasia data indicated that there was no statistically significant, dose-related, trend in the incidence of ovarian tumors in female rats.

The US EPA has classified the pesticide as a possible human carcinogen with limited evidence of carcinogenicity in animals. Based on a review by the Health Effects Division Peer Review Committee for carcinogenicity of the Office of Pesticide Programs, the Agency has determined that a quantitative risk assessment is not appropriate for the following reasons:

- The tumor response was primarily due to a significantly increasing trend for benign and/or malignant liver tumors in male rats and due to a significantly increasing trend for ovarian tubular adenomas in female rats. A re-evaluation of the ovarian neoplasia data indicated that there was not a statistically significant, dose-related, trend in the incidence of ovarian tumors in female rats.

- The chemical was not carcinogenic when administered to mice at dose levels ranging from 30 to 3,000 ppm. Based on this evidence, EPA concludes that dimethenamid poses a negligible cancer risk to humans and that for purposes of risk characterization the Reference Dose (RfD) approach should be used for quantification of human risk. Residues of dimethenamid will not concentrate in processed soybean commodities and a food or feed additive regulation is not required for dimethenamid. The standard risk assessment approach of using the RfD based on systemic toxicity was applied to dimethenamid.

Mutagenicity

An Ames mutagenicity assay negative with and without activation, an in vitro chromosomal aberration using CHO cells positive with and without activation, an unscheduled DNA synthesis in rat hepatocytes unequivocally positive in one in vitro assay and negative in another.

Reproductive Studies

A two generation reproduction study in rats with a parental and reproductive NOEL 36 mg/kg/day for males and 40 mg/kg/day for females and a parental and reproductive LEL 150 mg/kg/day for males and 160 mg/kg/day for females based on reduction of body weight and of food consumption, and increases in liver weights (parental toxicity), and significant reductions in pup weight during lactation.

A rabbit developmental study with a maternal NOEL of 37.5 mg/kg/day and a LEL of 75 mg/kg/day based on decreased body weight and food consumption, and with a developmental NOEL of 75 mg/kg/day and a LOEL of 150 mg/kg/day based on a low incidence of abortion/premature delivery and malformation of the upper mandible.

A rat developmental study with a maternal NOEL of 50 mg/kg/day and a LEL of 215 mg/kg/day based on excess salivation, increased liver weight and reduced body weight gain and food consumption, and with a developmental NOEL of 215 mg/kg/day and a LEL of 425 mg/kg/day based on increased resorptions.

Using an uncertainty factor of 100 and the NOEL of 5 mg/kg/day determined by the 2-year rat feeding study, EPA developed an RfD of 0.05 mg/kg/day.

US EPA Regulatory Position

MCL	None
MCLG	None
RfD	0.05 mg/kg/day
LHA	None
Cancer classification	Class C, Possible human carcinogen

State Drinking Water Standards and Advisories

None found

Recommendations and Conclusions for Dimethenamid

The Wisconsin Department of Health Services recommends use of the chronic reference dose to establish a groundwater enforcement standard for dimethenamid. Since dimethenamid is classified as a possible human carcinogen, an additional uncertainty factor of 10 was applied to the reference dose to protect against this effect and a 10% preventive action limit is proposed.

$$\frac{0.05 \text{ mg/kg/day} \times 10 \text{ kg}}{10 \times 1 \text{ liter/day}} = 0.05 \text{ mg/L (50 µg/L)}$$

Recommended Enforcement Standard	50 µg/L
Recommended Preventive Action Limit	5 µg/L

References

Federal Register: September 24, 2004, Vol 69, No 185. Dimethenamid; Pesticide Tolerance, Environmental Protection Agency, Final rule.

Federal Register, May 3, 2006 Vol 71, No 85. Dimethenamid-p; Pesticide Tolerances for Emergency Exemptions.

US EPA. 1992. Office of Pesticide Programs Reference Dose Tracking Report.

DINITROTOLUENES

Technical grade dinitrotoluene (TG DNT) is a mixture of chemicals. Analysis of TG DNT reveals the following composition: 76.49% 2,4-DNT, 18.83% 2.6-DNT, 0.65% 2,5-DNT, 2.43% 3,4-DNT, 1.54% 2,3-DNT, 0.05% trinitrotoluene (TNT), 0.005% cresols, 0.003% mononitrobenzene, and 0.003, 0.005, and 0.006% ortho-, meta-, and para- mononitrotoluenes, respectively. DNT can be released to the environment as a result of accidental releases and disposal. DNTs are used as gelatinizing and waterproofing agents in the manufacture of explosives, and in smokeless gunpowders. About 500 US workers are potentially exposed to DNT during the production of munitions and explosives. The main route of exposure at ammunition facilities is inhalation, but dermal contact and inadvertent ingestion can also be substantial. The primary route of exposure among the general population is likely the result of ingestion of contaminated food or water. Occupational studies indicate that after inhalation or dermal exposure, TG-DNT is absorbed and excreted in the urine. Oral absorption and excretion occur rapidly and are usually complete within 24 hours to 72 hours.

CAS No.	25321-14-6, See Table 1 for individual congeners
Molecular Weights	182.14
Physical State	Yellow-orange crystalline solid or oily liquid
Specific Gravity	1.32
Water Solubility	270 mg/L
Synonyms	DNT, Dinitrophenylmethane, Methyldinitrobenzene

Occurrence

Dinitrotoluenes have been detected in Wisconsin groundwater near the Badger ordinance facility in Sauk County. Under EPA's Unregulated Contaminant Monitoring Program, 2,4 and 2,6 DNT were analyzed in large community water systems and non-transient non-community water systems and in a statistically representative sample of qualifying small systems. Data for samples collected from 2001 through October 2004 indicate that only one water supply (0.04% of the systems) tested positive for 2,4 DNT and that 2,6-DNT was not detected in any of the samples.

Toxicity

Most toxicological and environmental studies have been conducted using either the technical grade mixture of these isomers, or purified 2,4- or 2,6-DNT. Only a few short-term or *in vitro* studies have been done on the minor isomers. These studies suggest that the minor isomers are toxicologically similar to 2,4- and 2,6-DNT. Effective doses or aquatic concentrations of the six DNT isomers are generally within an order of magnitude of each other.

All DNT isomers are capable of inducing cyanosis secondary to methemoglobin formation. At high doses, this is the critical effect that can lead to death. Target tissues include the hematopoetic system, the central nervous system and the male reproductive system. TG DNT, as well as 2,4- and 2,6-DNT are known to cause cancer in animals. Minor isomers have not been tested for this effect. All isomers have shown mutagenic effects in short-term studies. In order to protect against adverse health effects that can result from long-term exposure to DNT, a single health advisory for the summed concentration of all DNT isomers is proposed.

Microbial biodegradation of DNT in water can occur under both aerobic and anaerobic conditions. Biotransformation occurs mainly through the reduction of the nitrogroup. In surface waters, photolysis is probably the major route of degradation (ATSDR, 1998). The half-life of 2,6-DNT in river water exposed

to sunlight was 12 minutes and the degradation was determined to be from an indirect photoreaction. Once it reaches groundwater, DNT is much more persistent. However a half-life in groundwater was not found.

Dinitrotoluene can cause methemoglobinemia. Onset may be delayed as long as 4 hours after exposure. Chronic exposure to dinitrotoluene can cause anemia and jaundice. The effects of dinitrotoluene are exacerbated by alcohol consumption. In an occupational setting, DNT can be absorbed through the skin in toxic amounts. Human exposure has been linked to a variety of symptoms, including cyanosis, dizziness, headache, metallic taste, shortness of breath, weakness, loss of appetite, nausea, and vomiting. Other symptoms including pain or paresthesia in extremities, abdominal discomfort, tremors, paralysis, chest pain, and unconsciousness have also been reported. The primary targets of DNT toxicity are the blood cell formation, the cardiovascular system, the nervous system and the male reproductive system.

3,5-DNT is more toxic to male and female rats and mice than other isomers. Technical-grade DNT fed to rats for 24-months caused liver discoloration at a dose of 3.5 mg/kg/day and liver nodules and malignancies at a dose of 14 mg/kg/day. An NCI bioassay also showed that technical-grade DNT causes subcutaneous tissue fibromas in male rats and mammary gland fibroadenomas in female rate. DNT administered orally to dogs caused neurotoxic effects, with tremors, loss of coordination, and convulsions; neurotoxic effects are not seen in either rats or mice until much higher doses are given. Oral administration of DNT to rats, mice, and dogs causes reproductive effects, including testicular and ovarian atrophy, decreased fertility, and decreased sperm count.

Table 1. Screening Level Toxicity Information for DNT Isomers

	2,3-DNT	2,4-DNT	2,5-DNT	2,6-DNT	3,4-DNT	3,5-DNT
CAS No	602-01-7	121-14-2	619-15-8	606-20-2	610-39-9	618-85-19
% in Tech Grade	1.3%	78%	0.5%	18%%	2.4%	<0.1%
$LD50_{low}$ (rat)	911 mg/kg	270 mg/kg	517 mg/kg	177 mg/kg	177 mg/kg	216 mg/kg
Cancer Class	Not classified	B2	Not classified	B2	Not classified	Not classified
Mutagenicity	Positive	Positive	Positive	Positive	Positive	Positive
NOAEL Subchronic Chronic	None None	0.2 mg/kg/day None	None None	4 mg/kg/day 7 mg/kg/day	None None	None None
Aquatic toxicity*	1.8 mg/L	32.8 mg/L	1.3 mg/L	18.5 mg/L	1.5 mg/L	22.6 mg/L
USEPA RfD	None	0.002 mg/kg/day	None	0.001 mg/kg/day	None	None

USEPA MCL	None	None	None	None	None	None
WI GWES	None	0.05 µg/L	None	0.05 µg/L	None	None
ACGIH – TLV	1.5 mg/cu m	1.5 mg/cu m	1.5 mg/cu m	1.5 mg/cu m	1.5 mg/cu.m	1.5 mg/cu m

*96-hr static LC50 *Pimephales promelas* Liu, Bailey and Pearson, 1983

Carcinogenicity

U.S. EPA cancer classification for 2,4- and 2,6-DNT: B2, sufficient evidence of carcinogenicity in animals (USEPA, IRIS 1990)

In chronic studies, 2,4-DNT produced renal tumors in male mice and was moderately hepatocarcinogenic in rats. 2,6-DNT and technical grade DNT are potent hepatocarcinogens in rats. Increases in tumors were statistically significant and dose-related. One study of workers in a munitions plant found no significant increases in cancer mortality. However, this study was limited by small cohort size.

Mutagenicity

Both DNT isomers are positive in the *S. typhimurium* histidine reversion assay and the TM 677 forward-mutation assay both with and without metabolic activation but negative in numerous mammalian cell forward reversion assays.

Reproductive Effects

Male reproductive effects resulting from oral administration of 2,4-DNT include decreased spermatogenesis in rats and dogs at 20-25 mg/kg/day and testicular atrophy at 34 mg/kg/day. In a multigenerational rat study, decreased neonatal viability was noted at 40 mg/kg/day of 2,4-DNT.

A study of DNT's reproductive effects in workers showed decreased sperm counts, slight abnormalities in the sperm of workers, and a slight increase in the rate of spontaneous abortions in their wives. A retrospective cohort mortality study of DNT-exposed workers found a significant increase in mortality due to ischemic heart disease. The average DNT exposure of these workers was estimated to be 1 mg/kg/day or less from inhalation, ingestion, and dermal sources.

Interactive Effects

In a 1942 study, workers exposed to 2,4-DNT were found to be more sensitive to alcohol. Exposure of rats to 2,6-DNT both increased and decreased the rate of phenobarbital metabolism, dependent on the time of exposure.

Environmental Fate

Aquatic
The solubilities of 2,4- and 2,6-DNT in water are 270 and 180 mg/L, respectively. Major routes of DNT degradation in surface water are photo-oxidation and biodegradation. The half life of DNT is 3 to 10

hours in sunlit natural waters and 28 days in anaerobic sewage. No studies of DNT persistence in groundwater were found, but degradation under these conditions is likely negligible.

Atmospheric

The low vapor pressure of the DNTs (2,4-: 0.005 torr at 20□C; 2,6-: 0.018 Torr at 20°C) suggests that volatilization from contaminated surface water or soil are unlikely. In the atmosphere, DNT is degraded by photochemically produced OH radicals. The half-life is calculated to be approximately 84 days.

Terrestrial

DNTs are poorly adsorbed to soils. As a result, DNTs in buried munition wastes could potentially be released to groundwater or transported as contaminated soil and sediment. No studies have been performed on soil DNT biodegradation.

Regulatory Summary

RfD for 2,4-DNT (non-cancer effects):	0.002 mg/kg/day
RfD for 2,6-DNT (non-cancer effects):	0.001 mg/kg/day
MCL	None
Cancer classification	B2, possible human carcinogen
Cancer slope factor for 2,4-DNT and 2,6-DNT	0.68 per mg/kg/day
Drinking water conc at 1-in-a-million cancer risk	0.05 ug/L
Ambient Water Quality Criteria for Water & Fish	0.11 ug/L
Ambient Water Quality Criteria for Fish only	9.1 ug/L
ATSDR Minimal Risk Level	0.002 mg/kg/day

Recommendations and Conclusions

The Department of Health Services recommends that all isomeric forms of dinitrotoluene be regulated as a single entity and that the groundwater enforcement standard be set at a concentration that equates with a the lifetime cancer risk level of 1-in-a-million. This recommendation is based on the following findings:

1). A complete toxicological database is available for technical grade DNT, which is a mixture of all isomers, and for the two major isomers (2,4- and 2,6-DNT). Only limited testing has been conducted with the other 4 isomers making independent risk assessments for them impossible. In 2000, the Chemical Manufacturer's Association petitioned the US EPA to remove individual isomers of DNT from the High Production Challenge Program arguing that none of the minor isomers is produced separately in commerce. In a letter to Charles M. Auer, Director of the USEPA's Chemical Control Division, CMA stated, "Separately evaluating each isomer under the HPV program will not result in a better understanding of the adverse health or safety implications of dinitrotoluene." EPA's approval of this request alleviated a requirement for the manufacturers to provide screening level toxicity and environmental fate data for individual DNT isomers and allowed submission of data for technical grade DNT instead.

2). Published studies for the minor isomers indicate that their toxic effects are the same as that of technical grade DNT and that the minor isomers are as toxic or more toxic than 2,4- and 2,6-DNT.

3). All isomers of DNT have shown mutagenic activity in short-term studies.

4). Technical grade DNT, as well as the purified 2,4- and 2,6- isomers, are classified as known animal carcinogens. Minor isomers have not been tested for this effect, but are structurally and toxicologically similar suggesting that they may also contribute to cancer risks.

5) The six isomers of DNT are structurally and toxicologically similar, have a common commercial source and are frequently found together in the environment.

Because dinitrotoluenes have carcinogenic effects, a 10% preventive action limit is proposed.

Recommended enforcement standard: 0.05 µg/L
Recommended preventive action limit: 0.005 µg/L

References

2003 TLVs and BEIs. ACGIH, Cincinnati OH.

Letter to Charles M Auer dated March 21, 2000. Chemical Manufacturers Assoc.

NIOSH. Current Intelligence Bulletin: Dinitrotoluenes. July 1985.

SIDS Initial Assessment Report for SIAM 18. Dinitrotoluene. 2004. UNEP Publications, Paris France.

US EPA Drinking Water Health Advisories: Munitions. 1992. Lewis Publishers, CRC Press, Boca Raton FL.

US EPA Drinking Water Health Advisory for 2,4-Dinitrotoluene and 2,6-Dinitrotoluene, April 1992.

US EPA Drinking Water Health Advisory for 2,4-Dinitrotoluene and 2,6-Dinitrotoluene, Proposal Draft, Aug 2006.

US EPA IRIS: Dinitrotoluene; accessed June 2007.

ETHYL ETHER

Diethyl ether has limited solubility in water and is often used to extract organic substances from aqueous solutions. Diethyl ether is also used in reactions that involve organometallic reagents, in the production of cellulose plastics, and as a starting fluid for diesel and gasoline engines. Although it was popular clinical anesthetic during the late 1800s and early 1900s, this use of ether has been discontinued following the development of safer and more effective alternatives.

CAS No	60-29-7
Molecular Weight	74.12
Molecular Formula	C2H5OC2H5
Physical properties	Colorless liquid
Synonyms	Ethyl ether, ether 1,1'Oxybisethane;ethyl oxide; diethyl oxide;

Occurrence

Due to its volatility ether is an uncommon contaminant of Wisconsin groundwater. Ethyl ether has been detected in 44 Wisconsin wells. Levels ranged from 0.3 to 450 ug/L. All of the detections were in wells located in Sauk, Waukesha and Wood Counties.

Toxicity

Ethyl ether is a severe irritant of the eyes and mucous membrane. At high concentrations, it causes central nervous system depression. Exposure to a 6.4 percent concentration caused deep anesthesia in mice, and respiratory arrest occurred at 128,000 ppm ethyl ether. Rats exposed chronically over 30 weeks to 2,000 ppm ethyl ether did not experience adverse effects. However, their blood levels of liver enzymes were elevated.

Ether has been used as a surgical anesthetic at concentrations ranging between 50,000 and 150,000 ppm. It is a nasal irritant at concentrations above 200 ppm and causes dizziness at 2,000 ppm or higher [ACGIH 1991; Hathaway et al. 1991].

Symptoms of exposure vary by concentration and duration, but may include irritation of the nose and eyes, dizziness, excitement, drowsiness, vomiting, paleness, decreased pulse rate, decreased body temperature, irregular respiration, muscle relaxation, lung irritation with increased bronchial secretions, laryngospasm, loss of consciousness, and death [Clayton and Clayton 1982].

Four groups of male and female rats (30/sex/group) were gavaged daily with 0, 500, 2000, and 3500 mg/kg/day of ethyl ether for 13 weeks. Six weeks after the initiation of dosing, an interim sacrifice of 10 rats/sex was performed. The remaining animals continued in the experiment until the day of the final sacrifice. Data generated from this study included body weight changes; food consumption; ophthalmological examinations; clinical, biochemical, and gross morphological changes; and histopathology of target organs. An evaluation of data revealed marked toxicity of ethyl ether at the high dose (3500 mg/kg/day), including mortality, decreased food intake, and body weight loss. Body weight loss was observed in both sexes at the two highest doses; only females showed a significant reduction at the high dosage. Histopathological evaluations of tissues revealed no effects related to the administration of ethyl ether. Based on data available from this study, 500 mg/kg/day is considered a NOAEL and 2000 mg/kg/day a LOAEL (US EPA, 1986).

The US EPA applied an uncertainty factor of 3,000 including a factor of 10 to extrapolated from a subchronic study to chronic data, 10 for interspecies extrapolation, 10 to account for intra-species variability, and an additional factor of 3 for lack of toxicity data in a second species and reproductive/developmental studies to develop an oral reference dose of 0.2 mg/kg/day

Carcinogenicity

No information was found regarding the carcinogenic properties of diethyl ether. EPA has not classified the carcinogenicity of diethyl ether.

Mutagenicity

Ethyl ether is mutagenic in bacterial and mammalian test systems [NIOSH 1991].

Environmental Fate

Aquatic
When discharged to surface water, diethyl ether will evaporate with a half-life of less than 1 day. Very little breakdown is expected as a result of hydrolysis or photolysis. Ether is likely stable in groundwater. Because it is less dense than water, ether will tend to float on the top of the aquifer.

Ethyl ether has a log Kow of < 3.0 and is not expected to bioaccumulate. The LC50/96-hour values for fish are over 100 mg/l. This material is not expected to be toxic to aquatic life (Mallickrodt, 2007).

Atmospheric
When released into the air, this ether is expected to be degraded by reaction with photochemically produced hydroxyl radicals. Ether is not degraded by photolysis. Ether has an atmospheric half-life of 1 to 10 days (Mallinckrodt, 2007).

Terrestrial
When released to the surface soils, ether will tend to is expected to evaporate. However, some ether may also leach into groundwater contaminating underground aquifers. Ether is not expected to biodegrade (Mallinckrodt, 2007).

Regulatory Summary

MCL	None
Lifetime Health Advisory	None
RfD	0.2 mg/kg/day
Cancer classification	Not classified

State Drinking Water Standards and Advisories

Florida	750 µg/L
New Hampshire	1,400 µg/L
New Jersey	1,000 µg/L
Minnesota	1,000 µg/L

Recommendations and Conclusions

Following a review of the literature for ethyl ether, the Wisconsin Department of Health Services recommends the use of the EPA Reference Dose for calculation of a groundwater enforcement standard. A relative source contribution of 50% was applied assuming that in situations where household water is contaminated with diethyl ether, approximately half of the exposure comes from inhalation. This adjustment is needed because diethyl ether is volatile at room temperature. Since diethyl ether has been found to have mutagenic activity, a 10% preventive action limit factor is appropriate.

$$\frac{0.2 \text{ mg/kg/day} \times 10 \text{ kg} \times 50\%}{1 \text{ liter/day}} = 200 \text{ µg/L}$$

Recommended Groundwater Enforcement Standard	1,000 µg/L
Recommended Preventive Action Limit	100 µg/L

References

ACGIH [1991]. Documentation of the threshold limit values and biological exposure indices. 6th ed. Cincinnati, OH: American Conference of Governmental Industrial Hygienists.

Clayton G, Clayton F [1981-1982]. Patty's Industrial Hygiene and Toxicology. 3rd rev. ed. New York, NY: John Wiley & Sons.

Hathaway GJ, Proctor NH, Hughes JP, and Fischman ML [1991]. Proctor and Hughes' chemical hazards of the workplace. 3rd ed. New York, NY: Van Nostrand Reinhold.

Mallinckrodt Chemicals, MSDS Sheet for Ethyl Ether, Phillipsburg, NJ. May 11, 2007.

NIOSH, 1991. Criteria Document for Diethyl Ether, accessed online January 7, 2009.

U.S. EPA. 1986. Rat oral subchronic study with ethyl ether. Prepared by American Biogenics Corporation for the Office of Solid Waste, Washington, DC.

US EPA IRIS Document for Ethyl Ether, accessed January 7, 2009.

MANGANESE

Manganese is a naturally-occurring element that can be found in the air, soil, and water. It is also an essential trace nutrient for humans and animals. Adverse health effects can be caused by inadequate intake or by over exposure. Manganese deficiency in humans is thought to be rare because manganese is present in red meat and in green vegetables.

CAS no.	7439-96-5
Atomic symbol	Mn
Atomic Weight	54.94
Physical state	Hard, brittle, silvery metal
Density	7.4
Water solubility	Metallic form is practically insoluble, however salts dissolve freely in water

The greatest exposure to manganese is usually from food. Adults consume between 0.7 and 10.9 mg/day in the diet, with even higher intakes being associated with vegetarian diets (IOM, 2002). Intake from drinking water is normally a minor source of exposure. At the median drinking-water level of 10 µg/L the intake of manganese from drinking water would be 20 µg/day for an adult, assuming a daily water intake of 2 L. Inhalation is not a significant source of exposure in non-occupational settings. The Institute of Medicine (IOM, 2002) has set a tolerable upper intake level of 11 mg/day for adults.

Chronic exposure to high doses of manganese can be harmful. While the health effects depend on the route of exposure, the chemical form, and individual susceptibility, the nervous system is the target organ. Many of the reports of adverse effects from manganese exposures in humans are from inhalation exposures in occupational settings. Although there are substantial data supporting the neurological effects of inhaled manganese in humans and animals, there are few data for the association between oral exposure to manganese and toxic effects. Several epidemiological studies associate adverse neurological effects with exposure to manganese from drinking water. However, due to a lack of qualitative and quantitative details of the exposure scenario, these studies cannot be used for quantitative assessment.

As an element, manganese cannot undergo metabolic transformation, but it can exist in many oxidative states and can be converted from one oxidative state to another within the body. Manganese is almost entirely excreted in the feces. Fecal manganese is comprised of unabsorbed dietary manganese and manganese excreted in bile. Groups possibly sensitive to manganese would be those who absorb greater amounts of manganese or those who excrete less. These would include infants, the elderly, and patients with liver disease.

Manganese can exist in several oxidative states; the most environmentally and biologically important manganese compounds are those that contain Mn^{2+}, Mn^{4+}, and Mn^{7+}. At concentrations exceeding 0.1 milligrams per liter (mg/L), the manganese ion imparts an undesirable taste to beverages and stains plumbing fixtures and laundry. When manganese (II) compounds in solution undergo oxidation, manganese precipitates, resulting in encrustation problems. At concentrations as low as 0.02 mg/L, manganese can form coatings on water pipes that may later slough off as a black precipitate. The U. S. and a number of other countries have set secondary standards of 0.05 mg/L for manganese for aesthetic properties.

As a metallic element, manganese does not undergo metabolic conversion to other products. However, manganese has the potential to exist in several oxidation states in biological systems. Circumstantial evidence from the study of manganese-containing enzymes and from electron spin trapping experiments

suggests that manganese undergoes conversion from Mn(II) to Mn(III) within the body (ATSDR, 2000). The conversion from Mn(II) to Mn(III) appears to be catalyzed by ceruloplasmin (Andersen et al., 1999). Manganese plays a catalytic or regulatory role in enzymatic reactions involving select hydrolases, dehydrogenases, kinases, decarboxylases and transferases.

Manganese is almost entirely eliminated in the feces, with only a small proportion (0.1-2%) being excreted in the urine. Fecal manganese is comprised of unabsorbed dietary manganese plus manganese excreted in bile. In humans, elimination is biphasic, with half-lives of 13 and 37 days. Sweat, hair and the milk of lactating mothers also contribute to excretion (EPA, 2004).

Toxicity

Symptoms resembling Parkinson's disease were seen in an individual who ingested 1.8 mg/kg-day potassium permanganate for 4 weeks (Bleich et al., 1999; Holzgraefe et al., 1986). The symptoms onset 9 months after the exposure.

The neurological effects of inhaled manganese have been well documented in humans (ATSDR, 2000). The syndrome known as "manganism" is caused by exposure to very high levels of manganese dusts or fumes and is characterized by a "Parkinsonlike syndrome" including weakness, anorexia, muscle pain, apathy, slow speech, monotonous tone of voice, emotionless "mask-like" facial expression, and slow clumsy movement of the limbs. In general, these effects are irreversible.

An epidemiological study was conducted by Kondakis et al (1989) to investigate the possible correlation between long-term manganese exposure from drinking water and neurological effects in elderly people. The levels of manganese in the drinking-water of 3 different geographical areas were 3.6-14.6 µg/L in the control area and 81-253 µg/L and 1800-2300 µg/L in the manganese-containing areas. The total population in the three areas being studied range from 3,200 to 4,350 people. The study included individuals over the age of fifty drawn from a random sample of 10% of the households. The number of subjects sampled were 62, 49, and 77 for control, low-, and high-exposed groups. The authors performed a neurological examination of the subjects (weakness/fatigue, gait disturbances, tremors, dystonia, etc.) and expressed the results as composite scores. They found no differences in the manganese content in the blood, but a statistically-significant difference in both the manganese content in the hair and composite neurological scores between the high exposed area (concentrations 1,800-2,300 µg/L) and the control area, suggesting neurological impairment in the high exposed area.

Reproductive and Developmental Studies

Men afflicted with clinical manganism may also experience loss of libido and impotence from occupational exposure to manganese. Impaired fertility, as measured by fewer children/married couple, has been observed in men who were exposed to manganese dust at levels that did not produce obvious symptoms of manganism (EPA, 2004).

Mutagenicity

The genotoxic potential of high manganese exposure in humans is not known.

Carcinogenicity

No studies are available on the potential carcinogenicity of high exposure to manganese in humans (ATSDR, 2000).

Variation in Human Sensitivity

Individuals with impaired liver function can be at risk from exposure to manganese because the liver is the main organ for excreting manganese. This group may include the elderly who may have declining organ function, the very young who may have immature and developing organs, and those with liver disease. Neurological symptoms and changes in brains MRI scans have been observed in patients with chronic liver disease (EPA, 2004).

Infants are considered a potential sensitive population due to the increased retention of manganese. Increased retention leads to increased manganese levels in the brain. This is a concern because the nervous system is the primary target organ (EPA, 2004).

Manganese is an essential trace nutrient. However, excess exposure, particularly via the inhalation route, is associated with symptoms that resemble Parkinsonism. The US EPA has estimated that an intake of 10 mg Mn/day (0.14 mg Mn/kg-day, assuming a body weight of 70 kg) in the diet is safe for a lifetime of exposure. This level of manganese represents a NOAEL for chronic ingestion of manganese by adults. Application of an uncertainty factor of 1 was used to derive the dietary RfD of 0.14 mg Mn/kg-day (U.S. EPA, 1997).

U.S. EPA (2008) recommends use of a modifying factor of 3 when assessing exposure to manganese from drinking water. Four reasons for this recommendation include:

1. Uptake of manganese from water appears to be greater in fasted individuals.
2. The study by Kondakis et al. (1989) raises concern for possible adverse health effects associated with a lifetime consumption of drinking water containing 2 mg/L of manganese.
3. Infants seem to absorb more manganese from the gastrointestinal tract, and excrete less of the absorbed manganese than adults.
4. Infant formula typically contains a much higher concentration of manganese than human or cows' milk. Powdered formula reconstituted with drinking water represents an additional source of manganese intake for a potentially sensitive population.

In order to enhance consumer acceptance of water resources, this advisory recommends reducing manganese concentrations to or below 0.050 mg/L, the EPA's Secondary Maximum Contaminant Level (SMCL) for Mn. The SMCL is based on staining and taste considerations.

The lifetime health advisory value of 0.3 mg/L will protect against potential neurological effects. In addition, this document provides a 1-day and 10-day health advisory of 1 mg/L for acute exposure. However, it is advised that for infants younger than 6 months of age, the lifetime HA of 0.3 mg/L be used even for an acute exposure of 10 days, because of the concerns for differences in manganese content in human milk and formula and the possibility of a higher absorption and lower excretion in young infants.

Regulatory Summary

MCL	None
MCLG	None
RfD	0.14 mg/kg/day
Drinking Water Equivalent Level (DWEL)	600 µg/L
Lifetime Health Advisory	300 µg/L
Cancer Classification	Group D: Not classifiable

State Drinking Water Standards and Advisories

California	500 µg/L
Connecticut	500 µg/L
Maine	500 µg/L
Minnesota	100 µg/L
New York	300 µg/L
Vermont	840 µg/L

Recommendations and Conclusions

The Wisconsin Department of Health Services recommends adoption of the federal lifetime health advisory for manganese as a groundwater enforcement standard. Because manganese is not known to have mutagenic or carcinogenic effects, a 20% preventive action limit is proposed.

Recommended Enforcement Standard	300 µg/L
Recommended Preventive Action Limit	60 µg/L

References

ATSDR, 2000. Toxicological Profile for Manganese.

Bleich, S., D. Degner, R. Sprung, A. Riegel, W. Poser, E. Ruther. 1999. Chronic manganism: Fourteen years follow-up. J. Neuropsych. Clin. Neurosci. 11: 117.

Holzgraefe, M., W. Poser, H. Kijewski, W. Beuche. 1986. Chronic enteral poisoning caused by potassium permanganate: A case report. J. Toxicol. Clin. Toxicol. 24:235-244 [erratum in: J.Toxicol. Clin. Toxicol. 24:462].

Institute of Medicine, 2000. Dietary Reference Concentrations for Micronutrients. Washington, DC.

Kondakis XG, Makris N, Leotsinidis M, Prinou M, and Papapetropoulos T. 1989. Possible Health Effects of High Manganese Concentration in Drinking Water. Archives of Environmental Health, 44(3): 175-178.

US EPA. 2004. Drinking Water Health Advisory for Manganese.

US EPA. 2008. IRIS document for Manganese.

METOLACHLOR ETHANE SULFONIC AND OXANILIC ACID METABOLITES

(Combined Standard)

Metolachlor is a selective herbicide that can be incorporated into the soil before planting or applied to surface soils as a pre-emergent to control annual grasses, certain broadleaf weeds in field corn (except fresh and popcorn), soybeans, peanuts, and grain sorghum. Metolachlor is marketed in two emulsifiable concentrate products (68.5 and 86.4 percent active ingredient) and in combination with atrazine or propachlor to provide broad spectrum weed control. In the US, the Novartis Corporation is the sole registrant and manufacturer of metolachlor. Metolachlor ethane sulfonic acid (ESA) and metolachlor oxanilic acid (OXA) are commonly seen environmental degradates.

	Metolachlor oxanilic acid	Metolachlor ethane sulfonic acid
CAS no.	194992-44-4	947601-85-6
Molecular Formula	C15H21NO4	C15H22NO4S
Molecular Weight	279.33	312.40
Physical State	Na salt, colorless crystal	Na salt, beige crystal
Water Solubility	Freely soluble in water	Freely soluble in water
Density at 20 deg C	Not available	Not available
Synonyms	Metolachlor OXA, CGA 51202	Metolachlor ESA, CGA 354743

Occurrence

More than 70 wells, including 27 monitoring wells, 22 private drinking water wells, and 23 municipal wells in Wisconsin have been sampled for alachlor, metolachlor, acetolachlor, and their ethane sulfonic acid (ESA) and oxanilic acid (OA) metabolites. Wells were selected based on previous detections of pesticides or proximity to agricultural fields to increase the likelihood of exposure to the compounds of interest. Alachlor, metolachlor, and metolachlor are chloroacetanilide herbicides that are commonly used on corn and other crops in Wisconsin. Sample results showed over 80 percent of the monitoring wells and drinking water wells contained the ESA and OXA metabolites of alachlor and metolachlor. Acetolachlor metabolites were detected less frequently. Analytical results for metolachlor OXA ranged from below the level of detection to 32 µg/L with detects in 63% of the monitoring wells, 86% of the private wells and 35% of the public water supplies. Analytical results for metolachlor ESA ranged from below the level of detection to 14 µg/L with detects in 78% of the monitoring wells, 91% of the private wells and 39% of the public water supplies (WDATCP, 2000).

Toxicity

A series of acute, subchronic, developmental and mutagenicity studies have been conducted with the OXA and ESA metabolites of metolachlor and s-metolachlor. The acute toxicity of these metabolites was essentially the same as the parent herbicide with LD50s >5,000 mg/kg.

In a 90-day rat feeding study (MRID 44931710) 10 male and 10 female CD BR rats were given the ESA metabolite at 0, 25.1, 86.2, 427, or 1545 mg/kg/day for males and 0, 28.4, 98.3, 519 and 1,685 in females. No deaths or clinical signs of toxicity were seen. In addition, no statistically significant changes in body weight, body weight gain, food consumption, food efficiency, ophthalmologic examination, urinalysis, or histopathology were reported. Changes in hematological parameters including increased white blood cell counts in females and mean red blood cell volumes (MCVs) in males were seen at the 6,000 ppm dose, however these effects were not dose-dependent and were within historic reference ranges. Reviewers

assigned the study a NOEL of 427 mg/kg/day in males (6,000 ppm) and a NOAEL 1,545 mg/kg/day. A LOAEL was not established. (Oak Ridge National Laboratory, 2000).

In another 90-day feeding study (MRID 44929509), 10 male and 10 female albino rats were fed diets containing 0, 18.7, 62.1 or 1,000 (males) or 0, 20.6, 67.3 or 1020 mg/kg/day metolachlor OXA. The investigators reported that all animals survived to termination and no treatment related signs were observed. Platelet counts were decreased 16% ($p<0.01$) in high dose males and total protein was decreased slightly in both sexes, however, these effects were not considered biologically significant. The NOAEL was determined to be 1,000 mg/kg/day in males and 1,020 mg/kg/day in females (Oak Ridge National Laboratory, 2000).

Purebred beagle dogs (4/sex/dose) were dosed with CGA-354743 at levels of 0, 50, 200, 500 or 1000 mg/kg/day for 13 weeks (MRID 44931709). There were no significant treatment-related effects on mortality, body weights, food intake, ophthalmological findings, hematology and urinalysis parameters. Vomiting was observed in females at 1,000 mg/kg/day. Absolute and relative liver weights were increased in females at 500 and 1,000 mg/kg/day, however these effects were considered mild and not toxicologically relevant. Reviewers concluded that NOAEL was greater than 1,000 mg/kg/day (Oak Ridge National Laboratory, 2000).

Developmental Toxicity

At the limit dose of 1,000 mg/kg/day, the ESA and OXA metabolites of metolachlor did not induce any maternal or developmental effects in rats. Therefore, the NOAELs for both substances were >1000 mg/kg/day and LOAELs were not established. MRIDs 44929510 and 44931711 (Oak Ridge National Laboratory, 2000).

Carcinogenicity

Metolachlor ESA and OXA have not been tested for carcinogenicity.

Mutagenicity

In vitro studies using bacterial assays and mammalian cells indicate that metolachlor ESA and OXA are not mutagenic (EPA, 2001).

Environmental Fate

Soil and Groundwater: The principal environmental breakdown products of metolachlor include the ethane sulfonic acid (ESA) and oxanilic acid (OA) metabolites which are more mobile in soils and more persistent in the environment than to the parent herbicide (EPA, 2001). These metabolites leach readily and have been detected in a high percentage of groundwater and surface waters in the Midwestern US (Kolpin et al. 2000; WDATCP, 2000).

Surface Water: Metolachlor ESA and OXA have been detected in surface waters in areas of use (Kolpin et al., 2000).

Regulatory Summary

	Metolachlor OXA	Metolachlor ESA
LOAEL	Not established	Not established
NOAEL	1,000 mg/kg/day	1,545 mg/kg/day
RfD	None	None
MCL	None	None
MCLG	None	None
DWEL	None	None
LHA	None	None
Cancer Classification	Not classified	Not classified

State Drinking Water/Groundwater Standards

None found

Recommendations and Conclusions

The Department of Health Services recommends that NOAELs from 90-day rat feeding studies for metolachlor ESA and OXA be averaged and used as the point of departure for a combined groundwater enforcement standard (GWES). A combined standard is justified because these metabolites frequently occur together in the environment, have a common source and are similar in molecular structure. Their toxicity profiles are very similar with both chemicals having minimal effects on food utilization and weight gain in experimental animals. Because these substances are considered unlikely to have carcinogenic or mutagenic effects, a 20% preventive action limit (PAL) is appropriate. An uncertainty factor of 10,000 is recommended. This UF includes four factors of 10 each to account for the use of a subchronic study, intra- and inter-species variability, and data gaps. Data gaps for these substances include the lack of a subchronic LOAEL, the lack of studies in a second species, and the lack chronic toxicity information. Existing toxicity information indicates that these metabolites have low toxicity and are unlikely to cause cancer.

(1,000 + 1,545 mg/kg/day)/2 = 1270 mg/kg/day (averaged NOAEL for ESA and OXA metabolites)

$$\frac{1270 \text{ mg/kg/day} \times 10\text{-kg} \times 100\% \text{ exposure}}{10{,}000 \times 1 \text{ liter/day}} = 1{,}270 \text{ µg/L (rounded to 1.3 mg/L)}$$

Recommended GWES	1.3 mg/L
Recommended PAL	260 µg/L

References

Kolpin DW, Nations BK, Goolsby DA; Thurman EM. (1996) Metolachlor in the hydrologic system in the midwestern united states, 1994. ES&T 30(5):1459-1464.

US EPA. (2004). Method 535 -Analytical Method Development for Chloroacetanilide and Other Acetamide Degradation Products in Drinking Water - Research Summary J.A. Shoemaker and M.V. Bassett, National Exposure Research Laboratory, Office of Research and Development U. S. Environmental Protection Agency, Cincinnati, OH accessed at *http://www.regulations.gov/fdmspublic/component/main?main=DocketDetail&d=EPA-HQ-OW-2004-0001* on January 12, 2009.

US EPA (2001). Memo from Virginia Dobozy to Christina Jarvis. Re: Toxicology Chapter for Metolachlor/S-metolachlor. DP Barcode D274326.

US EPA. UCMR Contaminants and Corresponding Analytical Methods accessed at http://www.epa.gov/OGWDW/ucmr/ucmr2/methods.html on October 1, 2008.

Oakridge National Laboratory (2000). Data Evaluation Report, Metolachlor OA Subchronic Oral Toxicity Feeding - Rat. MRID 44929509. January 2000. accessed at http://www.epa.gov/pesticides/foia/reviews.

Oak Ridge National Laboratory (2000). Data Evaluation Report, Metolachlor OA Developmental Toxicity - Rat. MRID 44929510. January 2000. accessed at http://www.epa.gov/pesticides/foia/reviews.

Oak Ridge National Laboratory (2000). Data Evaluation Report: Metolachlor ESA Subchronic oral toxicity feeding – dog. MRID 44931709. accessed at http://www.epa.gov/pesticides/foia/reviews.

Oak Ridge National Laboratory (2000). Data Evaluation Report: Metolachlor ESA Subchronic oral toxicity feeding – Rat. MRID 44931710. accessed at http://www.epa.gov/pesticides/foia/reviews.

Oak Ridge National Laboratory (2000). Data Evaluation Report, Metolachlor ESA Developmental Toxicity - Rat. MRID 44931711. January 2000. accessed at http://www.epa.gov/pesticides/foia/reviews

WDATCP. 2000. Chloroacetanilide herbicide metabolites in Wisconsin groundwater: Final Report.

PERCHLORATE

Perchlorate refers to the dissociated anion of perchlorate salts such as ammonium, potassium, and sodium perchlorate. Perchlorate and its salts are used in solid propellant for rockets, missiles, and fireworks. It is also used in the production of matches, flares, pyrotechnics, munitions, and explosives. The production and use of perchlorate has resulted in releases to the environment and contamination of groundwater.

	Sodium Perchlorate	Ammonium Perchlorate	Potassium Perchlorate
CAS no	7601-89-0	7790-98-9	7778-74-7
Molecular formula	$NaHClO_4^-$	NH_4ClO_4	$KClHO_4$
Molecular weight	81.0	117.49	138.55
Physical state	White crystals	White crystals	Colorless crystals
Density g/cu cm	2.52	1.95	2.53
Water solubility at 25 deg C	2096 g/L	20 g/L	15 g/L
Synonyms	IRENAT, perchloric acid	None	Irenal, Astrumal, Peroidin

Occurrence

An American Water Works Association (AWWA, 2005) study of perchlorate occurrence found the rocket-fuel contaminant in 26 states and Puerto Rico, mostly at levels below 12 µg/L. Analysis of breast milk samples suggests that exposure is widespread in the US. Perchlorate was detected in 36 of 36 breast milk samples collected from a wide geographic area at an average concentration of 10.5 ug/L and ranging up to 92 ug/L. These exposure levels substantially exceed recommended exposure levels for infants and may pose a risk of thyroid-related developmental disorders. Sampling conducted between 2001 and 2005 at all public water supply systems serving more than 10,000 people found no detectable perchlorates.

Toxicity

Perchlorate has been used medicinally to control hyperthyroidism. However, it was determined that the doses needed could cause fatal aplastic anemia and it is no longer used for this purpose except in very unusual circumstances (Hardman et al. 1996).

Springborn Laboratories studied the subchronic toxicity of ammonium perchlorate in Sprague-Dawley rats (Siglin et al. 2000). The study consisted of a control group and five treatment groups that were exposed for 14 or 90 days via the drinking water at dosage levels of 0.01, 0.05, 0.2, 1.0, and 10.0 mg/kg/day. Significantly increased thyroid weights, follicular cell hypertrophy with microfollicle formation and colloid depletion was observed in male and female rats at the 10 mg/kg/day dose level in

both treatment groups. These changes were reversible after a recovery period of 30 days. Statistically significant changes in TSH and thyroid hormone levels were observed at all dose levels. However, no thyroid organ weight or histopathological changes were observed at doses below 10 mg/kg/day.

Greer et al. (2002) studied 21 healthy women and 16 healthy men (mean age 38 years, range 18-57 years) who were given potassium perchlorate in doses of 0.007, 0.02, 0.1 and 0.5 mg perchlorate/kg body weight per day for 14 days. The dose was administered in 400 ml of water with instructions that 100 ml be consumed four times each day. Thyroid uptake of radioiodide was measured at 8 and 24 hours after radioiodide administration: at baseline, on days 2 and 14 of perchlorate administration, and 15 days after cessation of dosing. On day 14, the mean 24-hour radioiodide uptake was 98.2% of the baseline value in the seven subjects given 0.007 mg/kg/day; 83.6% of the baseline value in the subjects given 0.02 mg/kg/day, 55.3% of the baseline value in those given 0.1 mg/kg/day, and 32.9% of the baseline value in those given 0.5 mg/kg/day. The effects of perchlorate in these healthy adults did not change over time, as indicated by very similar results for thyroid radioiodide uptake measurements on day 2 of perchlorate administration compared to day 14 in the three higher dose groups. The 8-hour thyroid radioiodide uptake values 15 days after exposure were very similar to the baseline values, indicating rapid recovery after the exposure ended. The no observed effect level (NOEL) for perchlorate-induced inhibition of thyroid iodide uptake was 0.007 mg/kg/day. There were no changes in serum thyroxine (T4), triiodothyronine (T3) and thyroid stimulating hormone (TSH) concentrations, except for a very small decrease in serum TSH concentrations in the subjects given 0.5 mg/kg/day. One woman had a slightly elevated TSH at baseline, and it was slightly lower on day 14 of perchlorate administration at 0.007 mg/kg/day.

The National Academy of Sciences established a panel of experts to assess the health implications of perchlorate ingestion. The committee addressed a number of charge questions covering key scientific issues associated with perchlorate risk, and in January 2005 recommended a reference dose of 0.0007 mg/kg per day (NRC 2005a). The NAS committee was not unanimous in its view of the RfD with one dissenting member recommending an RfD value of 0.00023 mg/kg per day. The NRC findings were summarized in the 2005 "Report in Brief: Health Implications of Perchlorate Ingestion" which is available online at http://www.nap.edu/books. The U.S. EPA adopted the NRC recommended reference dose in February 2005 and established an official reference dose (RfD) of 0.0007 mg/kg/day for perchlorate.

Carcinogenicity

US EPA Cancer Classification: Not Likely/Likely depending on dose

Under U.S. EPA's 1999 Draft Revised Guidelines for Carcinogen Risk Assessment, perchlorate is not likely to pose a risk of thyroid cancer in humans at doses below those necessary to alter thyroid hormone homeostasis.

Epidemiological evidence is insufficient to determine whether or not there is a causal association between exposure to perchlorate and thyroid cancer. Sufficient evidence is available from rodent studies to indicate that goitrogenic doses of perchlorate cause follicular cell tumors of the thyroid, both following prolonged ingestion and from a two-generation study where a low incidence of early onset adenomas was reported.

In rodents, high doses of perchlorate cause increases in follicular cell nodules (Fernandez Rodriguez et al. 1991), adenomas (Kessler and Kruskemper 1966), and carcinomas (Pajer and Kalisnik 1991). Other

studies have demonstrated the ability of perchlorate to promote thyroid tumors initiated by other chemicals or by irradiation (Hiasa et al. 1987, Fernandez-Santos et al. 2004; Pajer and Kalisnik 1991).

In a two-generation study (Argus 1999), there were follicular cell adenomas in one control male rat in the initial parent (P1) generation and two high-dose (30 mg/kg/day) males in the first offspring (F1) generation at 19 weeks of age. Statistical analysis of the early onset thyroid adenomas concluded that they were increased relative to the entirety of the National Toxicology Program database (Dunson, 2001). The NRC (2005) concluded that the thyroid tumors in the offspring were most likely treatment related, but that they would be expected in high dose male rats in the presence of a markedly goitrogenic dosing regimen, as existed under the conditions of the study.

Mutagenicity

The perchlorate is has not demonstrated mutagenic effects in standard *in vitro* and *in vivo* assays.

Reproductive Effects

Recent research conducted in rats has shown that daily ingestion of water with perchlorate levels as low as 0.01 µg/L can induce significant effects on thyroid hormone levels in pregnant rats, as well as in the fetus and offspring. (Crofton 2001).

Environmental Fate

Terrestrial
Perchlorate is persistent and mobile in most soil types (ATSDR 2005).

Aquatic
When released to water, ammonium perchlorate will dissolve and dissociate to the perchlorate ion. The perchlorate ion is very stable and can persist for decades in groundwater and surface water systems (Gullick et al. 2001).

Regulatory Summary

RfD	0.0007 mg/kg/day
MCL/MCLG	None
DWEL	None
Lifetime HA	None
Cancer classification	Not likely at doses below those that alter thyroid homeostasis

State Drinking Water Regulations and Advisories

Arizona	14 µg/L
California	6 µg/L
Massachusetts	2 µg/L

Recommendations and Conclusions

The Department of Health Services recommends use of the EPA reference dose for development of an enforcement standard for perchlorate. Because perchlorate has demonstrated carcinogenic and endocrine disruptive effects in animals, a 10% PAL is proposed.

$$\frac{0.0007 \text{ mg/kg/day} \times 10\text{-kg}}{1 \text{ liter/day}} = 0.007 \text{ mg/L or } 7 \text{ µg/L}$$

Recommended Enforcement Standard	7.0 µg/L
Recommended Preventive Action Limit	0.7 µg/L

References

Argus Research Laboratories, Inc. 1999. Oral (drinking water) two-generation (one litter per generation) reproduction study of ammonium perchlorate in rats. Horsham, PA: Argus Research Laboratories, Inc.; protocol no. 1416-001. As cited in EPA 2002.

Argus Research Laboratories, Inc. 2001. Hormone, thyroid and neurohistological effects of oral (drinking water) exposure to ammonium perchlorate in pregnant and lactating rats and in fetuses and nursing pups exposed to ammonium perchlorate during gestation or via maternal milk. Horsham, PA. As cited in EPA 2002.

ATSDR; Toxicological profile for Perchlorates. Atlanta, GA: Agency for Toxic Substances and Disease Registry, US Public Health Service (2005)

Brechner, R. J.; Parkhurst, G. D.; Humble, W. O.; Brown, M. B.; Herman, W. H. 2000. Ammonium perchlorate contamination of Colorado River drinking water is associated with abnormal thyroid function in newborns in Arizona. J. Occup. Environ. Med. 42: 777-782.

CalEPA/OEHHA. 2002. Draft Public Health Goal for Perchlorate in Drinking Water. Pesticide and Environmental Toxicology Section.

Crofton, K. M. 2001. Revised analysis of the thyroid hormone data from the rat developmental "effects" study - Argus protocol 1416-003 [memorandum with attachments to Annie M. Jarabek]. Research Triangle Park, NC: U.S. Environmental Protection Agency, National Health Effects and Environmental Research Laboratory; December 14 (revised December 28). As cited in EPA 2002.

Delange F and Ermans AM. 1991. Iodine deficiency. In: The Thyroid. A fundamental and clinical text. Braverman LE, Utiger RD, Eds. JB Lippincott, Philadelphia, pp 368-390.

Environmental Working Group (EWG). 2002. Rocket Fuel in Lettuce. http://www.ewg.org/reports/rocketlettuce.

Goleman, W. L.; Carr, J. A.; Anderson, T. A. 2002. Environmentally relevant concentrations of ammonium perchlorate inhibit thyroid function and alter sex ratios in developing Xenopus laevis. Environ. Toxicol. Chem. 21: 590-597.

Greer MA, Goodman G, Pleus RC, and Greer SE. 2002. Health effects assessment for environmental perchlorate contamination: The dose-response for inhibition of thyroidal radioiodine uptake in humans.

Greer, M.A., Goodman, G., Pleuss, R.C., Greer, S.E. 2002. Health effect assessment for environmental perchlorate contamination: The dose response for inhibition of thyroidal radioiodide uptake in humans. Environ. Health Perspect. 110:927-937.

Gullick RW et al; J Amer Water Works Assoc 93: 66-77 (2001)

Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, O'Heir CE, Mitchell M, Hermos RJ, Waisbren SE, Faix JD, Klein RZ (1999). Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. New England Journal of Medicine. 341:549-555.

Hardman, J.G., L.E. Limbird, P.B. Molinoff, R.W. Ruddon, A.G. Goodman (eds.). Goodman and Gilman's the pharmacological basis of therapeutics. 9th ed. New York, NY: McGraw-Hill, 1996., p. 1401

NRC. 2005. Report in Brief: Health Implications of Perchlorate Ingestion.

Phillips, D. I. W.; Barker, D. J. P.; Fall, C. H. D.; Seckl, J. R.; Whorwood, C. B.; Wood, P. J.; Walker, B. R. 1998. Elevated plasma cortisol concentrations: a link between low birth weight and the insulin resistance syndrome? J. Clin. Endocrinol. Metab. 83: 757-760.

Pop VJ, Kuijpens JL, van Baar AL, Verkerk G, van Son MM, de Vijlder JJ, Vulsma T, Wiersinga WM, Drexhage HA, Vader HL (1999). Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy. Clin Endocrinol 50:149-155.

Prins, G. S.; Birch, L.; Couse, J. F.; Choi, I.; Katzenellenbogen, B.; Korach, K. S. 2001. Estrogen imprinting of the developing prostate gland is mediated through stromal estrogen receptor a: studies with aERKO and bERKO mice. Cancer Res. 61: 6089-6097.

Seckl, J. R. 1997. Glucocorticoids, feto-placental 11b-hydroxysteroid dehydrogenase type 2, and the early life origins of adult disease. Steroids 62: 89-94.

Siglin JC, Mattie DR, Dodd DE, Hildebrandt PK, Baker WH. A 90-day drinking water toxicity study in rats of the environmental contaminant ammonium perchlorate. Toxicol Sci. 2000 Sep;57(1):61-74.

USEPA. 2003. Memorandum re: Status of EPA's Interim Assessment Guidance for Perchlorate. January 22, 2003.

USEPA/ORD. 2002. Perchlorate Environmental Contamination: Toxicological Review and Risk Characterization (External Review Draft). Washington, D.C. NCEA-1-0503.

USEPA/Solid Waste and Emergency Response; Perchlorate Treatment Technology Update; Federal Facilities Forum Issue Paper. p. 11-13. EPA 542-R-05-015 (May 2005). Available at http://www.epa.gov/tio/download/remed/542-r-05-015.pdf as of March 9, 2007.

Versloot, P.M., J.P. Schroder-Van der Elst, D. Van der Heide and L. Boogerd. Effects of marginal iodine deficiency during pregnancy: iodide uptake by the maternal and fetal thyroid. American Journal of Physiology. E1121-E1126.

Yu, K. O. 2000. Consultative letter, AFRL-HE-WP-CL-2000-0038, tissue distribution and inhibition of iodide uptake in the thyroid by perchlorate with corresponding hormonal changes in pregnant and

lactating rats (drinking water study) [memorandum with attachment to Annie Jarabek]. Wright-Patterson Air Force Base, OH: Air Force Research Laboratory; June 28. As cited in EPA 2002.

PROPAZINE

Propazine is a triazine herbicide that is currently registered only for indoors on container-grown ornamentals in greenhouses. Propazine has no existing registered uses in the U.S. on agricultural crops. There is an import tolerance for propazine on sorghum. There are no registered residential uses of propazine in the U.S. These limited uses are unlikely to result in groundwater contamination. However, historical uses or chemical disposal may contribute to ongoing problems. Propazine is available in wettable powder, liquid and water dispersible granular formulations.

CAS #:	139-40-2
Molecular weight	229.7
Physical State	Colorless, crystalline solid
Specific gravity:	1.162
Water solubility:	8.6 ppm at 20 degrees C (1, 9, 20)
Log Kow:	2.94
Synonyms	GEIGY 30,028, Gesamil, Milogard, Plantulin, Primatol P, Propasin, Propazin, Propazine, Prozinex

Occurrence

Triazines are environmentally persistent and leach readily to groundwater. Propazine has been detected in drinking water supplies in areas of use on agricultural cropland. However, the current uses of propazine are limited to indoor greenhouse applications and the chemical is detected much less frequently than atrazine and its residues. In a USDA study published in 1990, propazine was detected in 33 out of 1,097 surface water samples and in 15 out of 906 groundwater samples. Contaminated groundwater samples have been collected from eight states. The maximum concentration found in any sample was 13 ug/l (ppb) for surface water and 300 ug/l (ppb) for groundwater (USDA 1990).

Occurrence data provided by the Wisconsin Department of Agriculture, Trade and Consumer Protection, confirm that propazine is an uncommon contaminant of Wisconsin's groundwater having been detected in only six water supply wells to date.

Toxicity

Propazine is classified as moderately toxic. Administration of lethal or near lethal doses to rats has caused symptoms of lethargy, muscular weakness, runny nose, emaciation, diarrhea, and labored breathing. It is mildly irritating to the skin, eyes, and upper respiratory tract. Contact dermatitis has been reported among workers manufacturing propazine. No cases of poisoning from human ingestion of this herbicide have been recorded.

Principal and Supporting Studies (Oral RfD)

EPA's current reference dose of 0.02 mg/kg/day was developed in 1987 and is based on a 2-yr rat feeding study completed by Ciba-Geigy in 1980 in which the critical effect was a decrease in body weight.

Two hundred and sixty males and 260 female CD rats were selected randomly and given 0, 3, 100 or 1000 ppm of propazine in their diets for 2 years. Seventy animals of each sex were placed in the control and high dose group. Sixty animals of each sex were placed in the low and mid-dose groups. At 1000

ppm there was a significant decrease in body weight in both sexes. There was a significant increase in mammary tumors in females at 1000 ppm. The NOEL for systemic effects was 100 ppm (5 mg/kg/day). The US EPA used the NOEL from this study as the point of departure to develop an oral reference dose. The agency applied an uncertainty factor of 300 which included a factor of 3 to account for the lack of a chronic toxicity study in a second mammalian species and factors of 10 each to account for intra- and inter- species differences. The agency noted that use of a subchronic dog NOEL of 5 mg/kg/day and a 1000 UF, to account for inter- and intraspecies differences and a subchronic-to-chronic extrapolation, would yield a value similar to the RfD.

When given daily to rabbits for one to four months, oral doses of 500 mg/kg propazine were reported to cause a type of anemia (Gosselin et al, 1984). No gross signs of toxicity or pathologic changes were evident in rats that received daily doses of 250 mg/kg for 130 consecutive days. No clinical or physical toxic symptoms were observed in beagle dogs fed 1.25, 5, or 25 mg/kg of propazine formulation in 90-day feeding studies (Worthing, 1983).

The National Academy of Science has established an Acceptable Daily Intake (ADI) of 0.0464 mg/kg/day for propazine (NRC, 1977; USDA, 1990).

Reproductive Effects

There was an increase in the number of deaths of newborns produced by female rats that were given 5 mg/kg of propazine during 18 days of pregnancy (Shepard, 1980). Consumption of propazine at high levels well above the Lifetime Health Advisory level over a long period of time has caused decreased fetal weight gain and delayed fetal bone development in animal studies (USDA, 1990). Maternal doses of 500 mg/kg/day resulted in maternal toxicity and developmental toxicity expressed as increased incidence of extra ribs, incomplete bone formation, and decreased fetal body weights (US EPA, 1988). In a 3-generation study with rats fed 0, 0.15, 5 or 50 mg/kg/day, no effects on fertility, length of pregnancy, pup viability or pup survival were observed. At 50 mg/kg, pup body weights on day 21 of lactation were reduced, and there were pathological changes in organ weights in the 2nd and 3rd generation (US EPA, 1988).

Teratogenic Effects

No teratogenic effects were observed in rats fed 500 mg/kg/ day, the highest dose tested (US EPA, 1988).

Mutagenic Effects

Propazine has shown no mutagenic effects in tests conducted on human and rat liver cells and in live hamsters.

Carcinogenicity

EPA Cancer Classification: N – Not likely to be carcinogenic in humans

No evidence of increased tumor frequency was detected in a 2-year study in mice fed doses up to 450 mg/kg of propazine each day. When rats were fed 0. 0.15, 5, or 50 mg/kg of propazine each day for 2 years, there was an increase in the incidence of mammary gland tumors at the highest dose level. EPA initially classified propazine as a possible human carcinogen. However this classification was changed in 2005 based on mode of action studies.

The Fourth Report of the Cancer Assessment Review Committee stated the following: "In accordance with the EPA Final *Guidelines for Carcinogen Risk Assessment* (March 29, 2005), the Committee classified propazine as "Not Likely To Be Carcinogenic To Humans." This decision was based on the following weight-of-evidence that propazine is not genotoxic and operates via a mode of action for the development of mammary tumors in the female SD rat similar to atrazine and simazine. Atrazine's mode of action of tumor formation appears to be specific to female rats (which maintain constant estrus) and does not appear to have a counterpart in humans, and thus the mammary gland tumors found in atrazine or propazine treated SD female rats are qualitatively not relevant for human risk assessment.

Environmental Fate

Soil and Groundwater

Propazine does not adsorb as strongly to soil particles as other commercial triazine herbicides. In most soils, it binds only weakly to soil particles (Koc = 154 g/m), and, depending on soil temperature, moisture and pH, it can become unbound. Its movement with soil moisture is limited by partial adsorption to soil particles, as well as its low water solubility (Worthing, 1983). Propazine is persistent, moderately mobile in most soils, and it is resistant to breakdown by hydrolysis, photolysis or biodegradation. For these reasons, propazine is one of the pesticide compounds considered by the EPA to have the greatest potential for leaching into groundwater (US EPA, 1987).

A significant portion of the herbicide may be broken down by soil microbes. Several soil microorganisms utilize propazine as a source of energy or nitrogen. Photolysis and volatilization are not important factors in propazine degradation (Worthing, 1983).

Fate in Water

Propazine is resistant to breakdown by hydrolysis. After 28 days, at pH 5, 60% of applied propazine remained unhydrolyzed; at pH 7, 92% remained; and at pH 9, 100% remained (USDA 1990).

US EPA Regulatory Position

NOAEL	5 mg/kg/day
Reference Dose	0.02 mg/kg/day
MCL	None
MCLG	None
Lifetime Health Advisory	10 µg/L
Cancer Classification	N,- Not Likely

State Drinking Water Standards and Advisories

Florida	10 µg/L
Maine	14 µg/L
New York	16 µg/L
Vermont	10 µg/L

Recommendations and Conclusions for Propazine

The Wisconsin Department of Health Services recommends adoption of the US EPA Lifetime Health Advisory for use as a groundwater enforcement standard. Since propazine has been determined to be

unlikely to cause cancer in humans and is not teratogenic or mutagenic, a 20% preventive action limit is appropriate.

Recommended enforcement standard 10 µg/L
Recommended preventive action limit 2 µg/L

References

Gosselin, R. E., et al. 1984. Clinical toxicology of commercial products. Fifth edition. Baltimore, MD: Williams and Wilkins.

Hartley, D and H Kidd, eds. 1983. The Agrochemicals Handbook. Nottingham, England: Royal Society of Chemistry.

National Research Council, Safe Drinking Water Committee. 1977. Drinking water and health. National Academy of Sciences, Washington, DC: National Academy of Sciences.

Shepard, T. H. 1980. Catalogue of teratogenic agents. 3rd Ed. Baltimore, MD: The Johns Hopkins University Press.

U. S. Environmental Protection Agency. 1987. (Feb. 4). Environmental News. Office of Public Affairs (A-107). Washington, DC.

U. S. Environmental Protection Agency. 1988 (Dec.) Guidance for the Reregistration of Pesticide Products Containing Propazine as the Active Ingredient. Office of Pesticides and Toxic Substances, USEPA, Washington, DC.

U.S. Environmental Protection Agency. 1988 (Aug.). Propazine: Health Advisory. Office of Drinking Water, US EPA, Washington, DC.

U.S. Environmental Protection Agency. 1988 (Dec. 20). Pesticide Fact Sheet #189: Propazine. Office of Pesticides and Toxic Substances, Office of Pesticide Programs, USEPA, Washington, DC.

USDA Soil Conservation Service. 1990 (Nov.). SCS/ARS/CES Pesticide Properties Database: Version 2.0 (Summary). USDA - Soil Conservation Service, Syracuse, NY.

Worthing, C. R., ed. 1983. The pesticide manual: A world compendium. Croydon, England: The British Crop Protection Council.

TERTIARY BUTYL ALCOHOL

t-Butyl alcohol is used as a denaturant for ethanol, in the manufacture of flotation agents, flavors and perfumes, as a solvent, as an octane booster in gasoline as well as its use as a dehydrating agent and in the manufacture of methyl methacrylate. t-Butyl alcohol is also a likely degradation product of methyl tert-butyl ether (MTBE) and has been detected in MTBE contaminated wells.

CAS No	75-65-0
Molecular Weight	74.12
Physical State	Colorless liquid
Solubility	Freely soluble in water
Synonyms	T-butanol

Occurrence

t-Butyl alcohol was identified, but not quantified in drinking water samples from at least one of the following cities: Cincinnati, OH, Miami, FL, Ottumwa, IA, Philadelphia, PA, and Seattle, WA(1). t-Butyl alcohol was detected in methyl tert-butyl ether (MTBE) contaminated wells in the US (1993-1998) at concentrations of 5.5-397 µg/L (HSDB, 2005).

Toxicity

Numerous acute toxicity tests are available on t-butyl alcohol. Oral, dermal and inhalation tests all meet OECD and EPA test guidelines. t-Butanol has low acute toxicity. The oral LD50 is 2733 mg/kg; the dermal LD50 is > 2000 mg/kg. By inhalation, the LC50 is >14,100 ppm from a 4 hour whole body exposure to t-butanol vapor; ataxia and dyspnea were seen immediately post exposure at 9700 or 14,100 ppm.

NTP (1995) performed short term and chronic carcinogenesis studies in both mice and rats by administration in drinking water. In rats t-butanol caused kidney toxicity at concentrations of 1.25 to 5 mg/l and increased kidney tumors in male rats at 5 mg/L (420 mg/kg/day). In mice t-butanol caused thyroid toxicity at concentrations of 10 to 20 mg/l and marginally increased thyroid tumors in females at 20 mg/L (US EPA, 2004).

Mutagenesis

There are two Ames assays; both are negative. There are two mouse lymphoma assays; both are negative. There is an *in vitro* sister chromatid exchange assay that was positive without activation, but negative with activation. Blood taken from mice in the 90 day NTP study were analyzed for micronuclei; TBA did not induce an increase in MN. The mutagenicity battery is satisfactory; no further mutagenicity testing was recommended.

Developmental/Reproductive Toxicity

A developmental toxicity study is available in rats. Maternal toxicity (decreased weight gain and feed consumption at 5000 ppm; unsteady gait at 3500 and 5000 ppm and decreased locomoter activity at 2000 ppm) was seen at all exposure concentrations. Developmental delay (reduced fetal weight, reduced ossification) occurred in offspring of dams exposed during gestation to 2000 ppm or greater; however, no increase in malformations was seen. Results from two developmental toxicity studies in mice are available. Neither of the studies is compliant with either OECD or EPA guidelines for developmental toxicity testing; however, neither study demonstrated increased malformations.

No studies of the effect of t-butanol on reproductive function were available. No adverse effects were observed in sex organs in rats or mice in the subchronic or chronic studies of t-butanol conducted by NTP. However, several observations (*i.e.*, decreased fetal body weights in teratology studies, altered postnatal development) suggest that further study of reproductive toxicity is warranted. An enhanced OECD 421 study was proposed and to investigate the effect of t-butanol on mating behavior, preimplantation, embryonic and fetal development, parturition, and postnatal survival and development until weaning.

An enhanced OECD Guideline 421 study on t-butanol was conducted in which t-butanol was administered by gavage to F_0 male and female Sprague-Dawley rats for 4 weeks premating. Males were treated for a total of 9 weeks, after which sperm were analyzed for total number, abnormal morphology, and motility. Females were treated through mating, through day 20 gestation and lactation days 5-21 (US EPA, 2004).

In males at 1000 mg/kg/day, there was an initial reduction in body weight gain, which remained as a 5-7% deficit in weight until termination. During late gestation, there was a reduction in weight gain in females. At 1000 mg/kg/day, there was transient lethargy, and ataxia. At 400 mg/kg/day similar effects were seen in a few females during weeks 2-4. There was no effect on mating or fertility; 11-12 females in each group became pregnant and all delivered a live litter. All but three females mated at the first estrus (one each in 0, 64, and 160 mg/kg/day groups). There was a questionable increase in gestation length at 400 and 1000 mg/kg/day. All females delivered within the normal range of 21-23 days; however, 6 of 11 females at 1000 mg/kg/day and 5 of 12 at 400 mg/kg/day vs. no more than 20% in any of the control and lowest two treatment groups delivered on day 23.

There was no effect on sperm motility or sperm morphology. There was no effect on the number of implantation sites per pregnancy. At 1000 mg/kg/day, there was a significant reduction in the number of live born pups and an increase in the number of still born pups. The NOAEL for paternal and maternal toxicity was 160 mg/kg/day t-butanol. Maternally toxic doses of t-butanol (1000 mg/kg/day) resulted in decreased survival and body weight of pups. The NOAEL for reproduction/development was 400 mg/kg/day.

Carcinogenicity

USEPA, Cancer classification: Not classified.

Male and female F344/N rats and B6C3F1 mice were given t-butyl alcohol (>99% pure) in drinking water for 2 yr.

Groups of 60 F344/N rats were given 0, 1.25, 2.5, or 5 mg/ml t-butyl alcohol (males) or 0, 2.5, 5, or 10 mg/ml t-butyl alcohol (females) in drinking water for 2 yr. These correspond to average daily doses of approximately 90, 200, or 420 mg t-butyl alcohol/kg body weight for males and 180, 330, or 650 mg t-butyl alcohol/kg body weight for females. Groups of 60 male & 60 female B6C3F1 mice were given 0, 5, 10, or 20 mg/ml t-butyl alcohol in drinking water for 2 yr. Exposure levels of 5, 10, or 20 mg/mL delivered average daily doses of approx 540, 1,040, or 2,070 mg t-butyl alcohol/kg to males & approx 510, 1,020, or 2,110 mg/kg to females. Under the conditions of these studies, there was evidence of carcinogenic activity in male rats based on increased incidences of renal tubule adenoma or carcinoma (combined). There was no evidence of carcinogenic activity in female rats. There was equivocal evidence of carcinogenic activity of t-butyl alcohol in male B6C3F1 mice based on the marginally increased incidence of follicular cell adenoma or carcinoma (combined) of the thyroid gland. There was some

evidence of carcinogenic activity of t-butyl alcohol in female B6C3F1 mice based on an increased incidence of follicular cell adenoma of the thyroid gland (NTP, 1995).

The California EPA used the NTP feeding studies to develop a cancer slope factor of 3.0E-3 for t-butyl alcohol (Alexeef, 1999). Using this cancer slope factor, CalEPA developed a drinking water guideline of 12 ug/L.

Environmental Fate

Aquatic
If released into water, t-butyl alcohol is not expected to adsorb to suspended solids and sediment in water based upon the estimated Koc. Volatilization from water surfaces is expected to be an important environmental fate process based upon this compound's Henry's Law constant. Estimated volatilization half-lives for a model river and model lake are 2 and 29 days, respectively. The biodegradation half-life of t-butyl alcohol was reported to range from about 28 to 180 days in aerobic water and 100 to 500 days in anaerobic water. BCF values of less than 5 measured in fish suggest that bioconcentration in aquatic organisms is low. Hydrolysis is not expected to be an important environmental fate process since this compound lacks functional groups that hydrolyze under environmental conditions.

Atmosphere
If released to air a vapor pressure of 40.7 mm Hg at 25 deg C indicates t-butyl alcohol will exist solely as a vapor in the ambient atmosphere. Vapor-phase t-butyl alcohol will be degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals; the half-life for this reaction in air is estimated to be 14 days.

Terrestrial
If released to soil, t-butyl alcohol is expected to have very high mobility based upon an estimated Koc of 37. Volatilization from moist soil surfaces is expected to be an important fate process based upon a Henry's Law constant of 9.05X10-6 atm-cu m/mole. t-Butyl alcohol may volatilize from dry soil surfaces based upon its vapor pressure. Screening tests using sewage or activated sludge inoculum have shown that t-butyl alcohol degrades slower than primary or secondary alcohols. The half-life of t-butyl alcohol under anoxic conditions in a non-amended soil was about 200 days, but the half-lives in the same soil amended with nitrate and sulfate nutrients were 100 and 50 days, respectively.

Regulatory Summary

MCL	None
MCLG	None
LOAEL	180 mg/kg/day
BMDL10	133 mg/kg/day (subchronic rat study)
RfD	None
Cancer class	Not classified by EPA; NTP found evidence of carcinogenicity

State Drinking Water Guidelines

California	12 µg/L
Florida	1,200 µg/L
Michigan	3,900 µg/L

Recommendations and Conclusions

The Department of Health Services recommends use of the cancer slope factor developed by CalEPA in the development of a groundwater standard for t-butyl alcohol. Because this substance has carcinogenic properties, a 10% preventive action limit is proposed.

$$\frac{10\text{-}6 \text{ LCR*} \times 70 \text{ kg}}{3\text{x}10\text{-}3 \text{ /mg/kg/day} \times 2 \text{ liters/day}} = 12 \text{ µg/L}$$

*LCR = lifetime cancer risk of 1 in a million

Recommended Enforcement Standard 12 µg/L
Recommended Preventive Action Limit 1.2 µg/L

References

Alexeef, George. June 2, 1999 Memo to David P. Spath titled: Expedited Evaluation of Risk Assessment for Tertiary Butyl Alcohol in Drinking Water. California Environmental Protection Agency, Sacramento, CA.

Cirvello JD, Radovsky A, Heath JE, Farnell DR, and Lindamood C. Toxicity and carcinogenicity of t-butyl alcohol in rats and mice following chronic exposure in drinking water. Toxicology and industrial health 11(2):151-65, 1995.

HSDB. 2005. Tertiary Butyl Alcohol, accessed March 2, 2009.

NPT, 1995. Toxicology & Carcinogenesis Studies of t-Butyl Alcohol in F344/N Rats and B6C3F1 Mice (Drinking water Studies). Technical Report Series No. 436 (1995) NTIS Publication No. PB96-162748 U.S. Department of Health and Human Services, National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC 27709

US EPA. 2004. HPV Challenge Program Final Submission Overview of Robust Summaries November 24, 2004. Submitted by: Propylene Carbonate / t-Butyl Alcohol HPV Committee Members: Lyondell Chemical Company Huntsman Corporation. Prepared by: ToxWorks, Bridgeton, NJ.