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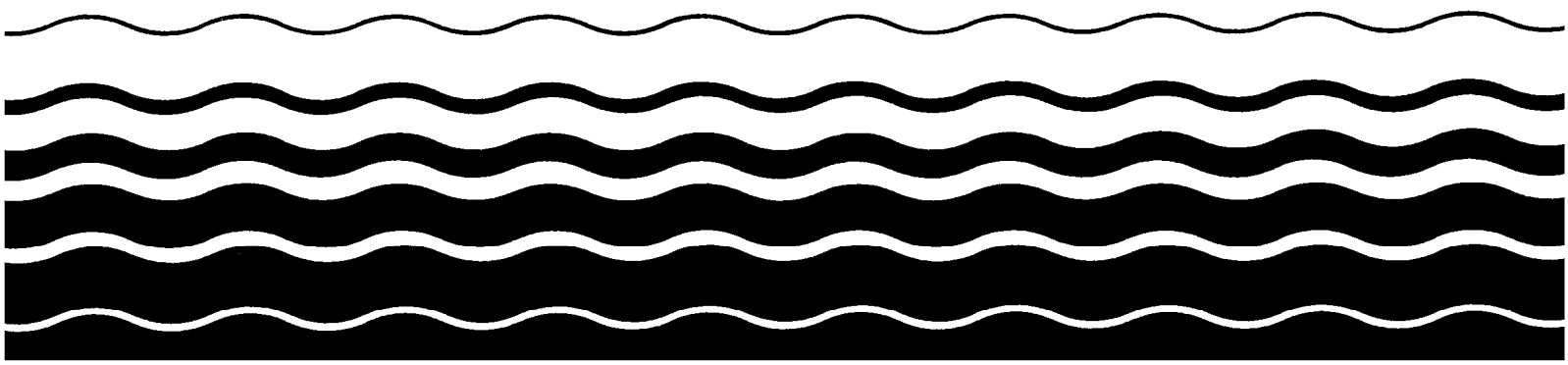
Ambient Water Quality Criteria for Isophorone



AMBIENT WATER QUALITY CRITERIA FOR

ISOPHORONE

Prepared By
U.S. ENVIRONMENTAL PROTECTION AGENCY

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FOREWORD

Section 304 (a)(1) of the Clean Water Act of 1977 (P.L. 95-217), requires the Administrator of the Environmental Protection Agency to publish criteria for water quality accurately reflecting the latest scientific knowledge on the kind and extent of all identifiable effects on health and welfare which may be expected from the presence of pollutants in any body of water, including ground water. Proposed water quality criteria for the 65 toxic pollutants listed under section 307 (a)(1) of the Clean Water Act were developed and a notice of their availability was published for public comment on March 15, 1979 (44 FR 15926), July 25, 1979 (44 FR 43660), and October 1, 1979 (44 FR 56628). This document is a revision of those proposed criteria based upon a consideration of comments received from other Federal Agencies, State agencies, special interest groups, and individual scientists. The criteria contained in this document replace any previously published EPA criteria for the 65 pollutants. This criterion document is also published in satisifaction of paragraph 11 of the Settlement Agreement in Natural Resources Defense Council, et. al. vs. Train, 8 ERC 2120 (D.D.C. 1976), modified, 12 ERC 1833 (D.D.C. 1979).

The term "water quality criteria" is used in two sections of the Clean Water Act, section 304 (a)(1) and section 303 (c)(2). The term has a different program impact in each section. In section 304, the term represents a non-regulatory, scientific assessment of ecological effects. The criteria presented in this publication are such scientific assessments. Such water quality criteria associated with specific stream uses when adopted as State water quality standards under section 303 become enforceable maximum acceptable levels of a pollutant in ambient waters. The water quality criteria adopted in the State water quality standards could have the same numerical limits as the criteria developed under section 304. However, in many situations States may want to adjust water quality criteria developed under section 304 to reflect local environmental conditions and human exposure patterns before incorporation into water quality standards. It is not until their adoption as part of the State water quality standards that the criteria become regulatory.

Guidelines to assist the States in the modification of criteria presented in this document, in the development of water quality standards, and in other water-related programs of this Agency, are being developed by EPA.

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ISOPHORONE

CRITERIA

Aquatic Life

The available data for isophorone indicate that acute toxicity to freshwater aquatic life occurs at concentrations as low as 117,000 µg/l and would occur at lower concentrations among species that are more sensitive than those tested. No data are available concerning the chronic toxicity of isophorone to sensitive freshwater aquatic life.

The available data for isophorone indicate that acute toxicity to saltwater aquatic life occurs at concentrations as low as 12,900 µg/l and would occur at lower concentrations among species that are more sensitive than those tested. No data are available concerning the chronic toxicity of isophorone to sensitive saltwater aquatic life.

Human Health

For the protection of human health from the toxic properties of isophorone ingested through water and contaminated aquatic organisms, the ambient water criterion is determined to be 5.2 mg/l.

For the protection of human health from the toxic properties of isophorone ingested through contaminated aquatic organisms alone, the ambient water criterion is determined to be 520 mg/l.

INTRODUCTION

Isophorone is a high-boiling colorless liquid of low volatility with an odor resembling peppermint. Its salient physical properties are summarized in Table 1. Isophorone is an excellent solvent for many oils, fats, gums, natural, and synthetic resins (Rowe and Wolf, 1963), but it is used mainly as a solvent for vinylic resins applied by roller coating (Blackford, 1975). Isophorone is also used as a solvent for cellulose derivatives, lacquers, and pesticide formulations, particularly anilide and carbamate herbicides. Because of its structure, isophorone is useful as a chemical intermediate and is utilized in the synthesis of 3,5-xylenol, 3,3,5-trimethylcyclohexanol, and plant growth retardants (Haruta, et al. 1974).

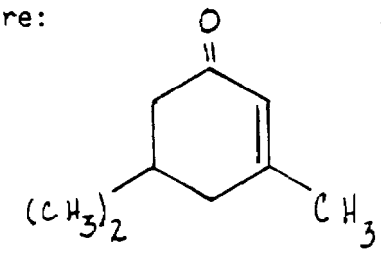
Isophorone is prepared commercially by two methods, both of which require acetone as a starting material (Rowe and Wolf, 1963). Acetone is passed over calcium oxide, hydroxide, carbide, or mixtures of these at 350°C, or is heated at 200-250°C under pressure. The isophorone is separated from the resultant products by distillation. Because fewer than three companies manufacture isophorone, production figures are not published by the U.S. Tariff Commission. The production of isophorone can, however, be estimated from acetone consumption data. In 1973, 35 million pounds of acetone were consumed for isophorone production (Blackford, 1975). Blackford estimated that, for every pound of methyl isobutyl ketone produced, 1.25 pounds of acetone are required. This corresponds to a yield of slightly above 90 percent. Assuming a 90 percent yield, and an acetone consumption figure of 35 million pounds, the estimated 1973 production of isophorone was 31.5 million pounds.

TABLE 1

Physical Properties of Isophorone*

Empirical Formula	$C_9H_{14}O$
Molecular Weight	138.21
Freezing Point	-8.1°C
Boiling Point (760 mm)	215.2°C
Specific Gravity (20/20°C)	0.9229 g/cc
Refractive Index n_D (20°C)	1.4781
Vapor Pressure (25°C)	0.44 mm Hg
Air Saturation	0.06%
Evaporation Rate (ether = 1)	200
Water Solubility (weight % at 20°C)	1.2
Commercial Purity** (weight %)	96-98%
Impurities:	
α-isophorone	2-4%
mesitylene (1,3,5-trimethylbenzene)	trace
mesityl oxide (2-methyl-2 pertene-4-one)	trace
phorone (2,6-dimethyl-2,5-heptadiene-4-one)	trace
isoxylitones	trace
water	trace

Structure: 3,5,5-trimethyl-2-cyclohexene-1-one



* Source: U.S. EPA, 1979; Union Carbide, 1975; National Institute for Occupational Safety and Health (NIOSH), 1978.
**Isophorone plus trimethylcyclohexenone.

The National Institute for Occupational Safety and Health (NIOSH, 1978) estimates that more than 1.5 million workers are exposed annually to isophorone. In the industrial handling of isophorone, inhalation of the vapor is the most likely mode of contact, although skin and eye contact with the liquid may also occur. Because of the odor and the taste of isophorone, ingestion is not expected unless by accident. In the environment, isophorone has been detected in a few samples of drinking water, but not in ambient air, soil, or food.

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Aquatic Life Toxicology*

INTRODUCTION

Static acute toxicity tests have been reported for isophorone and the bluegill and Daphnia magna. The 50 percent effect concentrations were between 117,000 and 224,000 µg/l. A bioconcentration test with bluegill indicated negligible uptake of isophorone.

As with freshwater organisms, most of the available data for the effects of isophorone on saltwater organisms result from static tests with unmeasured concentrations. An embryo-larval test has been conducted with the sheepshead minnow.

EFFECTS

Acute Toxicity

Daphnia magna has been tested and the 48-hour EC_{50} is 117,000 µg/l (Table 1) which indicates little, if any, difference in sensitivity compared with the bluegill. The 96-hour LC_{50} for the bluegill is 224,000 µg/l.

The 96-hour LC_{50} for the mysid shrimp is 12,900 µg/l and this species is much more sensitive than the sheepshead minnow. The 96-hour LC_{50} for the sheepshead minnow (U.S. EPA, 1978) was between 166,000 and 295,000 µg/l (Table 5).

Chronic Toxicity

The chronic value for the sheepshead minnow obtained from an embryo-larval test (U.S. EPA, 1978) is 110,000 µg/l (Table 2). The limits on this test were 80,000 to 156,000 µg/l which is just below the acute LC_{50} range (Table 5) and results in an acute-chronic ratio between 1.5 and 2.7.

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*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life and Its Uses in order to better understand the following discussion and recommendation. The following tables contain the appropriate data that were found in the literature, and at the bottom of each table are calculations for deriving various measures of toxicity as described in the Guidelines.

Plant Effects

The 96-hour EC_{50} values for cell number production and inhibition of chlorophyll a by the freshwater alga, Selenastrum capricornutum, are 122,000 and 126,000, respectively (Table 3). These effect concentrations are essentially the same as those for the bluegill and Daphnia magna.

Chlorophyll a was inhibited and cell numbers were reduced by 50 percent after 96-hour exposures of the saltwater alga, Skeletonema costatum, to isophorone concentrations of 110,000 and 105,000 µg/l, respectively (Table 3).

Residues

A 28-day exposure (U.S. EPA, 1978) to ^{14}C-isophorone resulted in bioconcentration by the bluegill to 7 times that in the water (Table 4). The half-life of isophorone in the whole body was one day. Thin-layer chromatography was used to verify the analytical results.

Summary

The cladoceran, Daphnia magna, and bluegill have been acutely tested with isophorone and the 50 percent effect concentrations were 117,000 and 224,000 µg/l, respectively. The EC_{50} values for a freshwater alga were within that range. The bioconcentration factor for the bluegill was 7 with a half-life of one day.

The mysid shrimp was much more sensitive than the sheepshead minnow with a 96-hour LC_{50} value of 12,900 µg/l for the former and between 166,000 and 295,000 µg/l for the latter. The acute LC_{50} value for the sheepshead minnow was only slightly higher than the chronic value of 110,000 µg/l for the same species. The EC_{50} values for an alga were 105,000 and 110,000 µg/l.

CRITERIA

The available data for isophorone indicate that acute toxicity to freshwater aquatic life occurs at concentrations as low as 117,000 µg/l and would occur at lower concentrations among species that are more sensitive than those tested. No data are available concerning the chronic toxicity of isophorone to sensitive freshwater aquatic life.

The available data for isophorone indicate that acute toxicity to saltwater aquatic life occurs at concentrations as low as 12,900 µg/l and would occur at lower concentrations among species that are more sensitive than those tested. No data are available concerning the chronic toxicity of isophorone to sensitive saltwater aquatic life.

Table 1. Acute values for isophorone (U.S. EPA, 1978)

Species	Method*	LC50/EC50 (µg/l)	Species Acute Value (µg/l)
	FRESHWATER SPECIES		
Cladoceran, *Daphnia magna*	S, U	117,000	117,000
Bluegill, *Lepomis macrochirus*	S, U	224,000	224,000
	SALTWATER SPECIES		
Mysid shrimp, *Mysidopsis bahia*	S, U	12,900	12,900

* S = static, U = unmeasured

No Final Acute Values are calculable since the minimum data base requirements are not met.

Table 2. Chronic values for isophorone (U.S. EPA, 1978)

Species	Test*	Limits (µg/l)	Chronic Value (µg/l)
SALTWATER SPECIES			
Sheepshead minnow, Cyprinodon variegatus	ELS	80,000-156,000	110,000

* ELS = early life stage

Acute-Chronic Ratio

Species	Chronic Value (µg/l)	Acute Value (µg/l)	Ratio
Sheepshead minnow, Cyprinodon variegatus	110,000	166,000-295,000	1.5-2.7

Table 3. Plant values for Isophorone (U.S. EPA, 1978)

Species	Effect	Result (µg/l)
	FRESHWATER SPECIES	
Alga, *Selenastrum capricornutum*	Cell number 96-hr EC50	122,000
Alga, *Selenastrum capricornutum*	Chlorophyll a 96-hr EC50	126,000
	SALTWATER SPECIES	
Alga, *Skeletonema costatum*	Cell number 96-hr EC50	105,000
Alga, *Skeletonema costatum*	Chlorophyll a 96-hr EC50	110,000

Table 4. Residues for Isophorone (U.S. EPA, 1978)

Species	Tissue	Bioconcentration Factor	Duration (days)
	FRESHWATER SPECIES		
Bluegill, *Lepomis macrochirus*	whole body	7	28

Table 5. Other data for Isophorone (U.S. EPA, 1978)

Species	Duration	Effect	Result (µg/l)
	SALTWATER SPECIES		
Sheepshead minnow, *Cyprinodon variegatus*	96 hrs	LC50	166,000-295,000*

* Author did not calculate the LC50.

REFERENCES

U.S. EPA. 1978. In-depth studies on health and environmental impacts of selected water pollutants. U.S. Environ. Prot. Agency. Contract No. 68-01-4646.

Mammalian Toxicology and Human Health Effects

EXPOSURE

Ingestion from Water

Isophorone has been detected in several samples of drinking water (Table 1), but these identifications cannot be used to imply a continuous occurrence. The sources of the isophorone contamination were not identified, but they would appear to be of industrial origin.

The U.S. EPA has quantified levels of isophorone in finished drinking water in the New Orleans area (U.S. EPA, 1974). At the Carrollton Water Plant (City of New Orleans), and at two water treatment sites in Jefferson Parish, the highest measured isophorone concentrations were 1.5, 2.2, and 2.9 µg/l, respectively.

The National Organics Reconnaissance Survey (NORS), initiated in 1974, was designed to provide an estimate of the nationwide distribution of organic compounds in drinking water (U.S. EPA, 1975). In a comprehensive organic analysis of the finished drinking waters of 10 cities, isophorone was identified only in Cincinnati (Ohio), at a level of 0.02 µg/l. The Cincinnati water source was categorized as being contaminated with industrial discharges. Isophorone was not found in the waters of Miami (Fla.), Seattle (Wash.), Ottumwa (Iowa), Philadelphia (Pa.), Tucson (Ariz.), New York (N.Y.), Lawrence (Mass.), Grand Forks (N.Dak.), or Terrebonne Parish (La.).

EPA also maintains an inventory of organic compounds that have been isolated and identified in drinking water in the United States (U.S. EPA, 1975). Two hundred and fifty-three compounds

TABLE 1

Water Types Contaminated with Isophorone

Finished Drinking Water	River	Effluent from Latex Plant	Effluent from Chemical Plant	Effluent from Tire Plant	Concentration	Reference
X					9.5 µg/l highest concentration reported in a nationwide survey	U.S. EPA (1975)
X					1.5-2.9 µg/l, treated river water, New Orleans area	U.S. EPA (1974)
	X				trace (<0.01 ppb), Delaware River	Sheldon and Hites (1978)
		X	X		levels not reported	Shackelford and Keith (1976)
				X	0.04 mg/l	Jungclaus, et al. (1976)

were compiled from an extensive search of the chemical literature and from EPA reports generated from the Agency's analytical activities. Although the compounds included in the inventory were based upon an analysis of only a few (unspecified) public water supplies, isophorone was nevertheless detected at concentrations as high as 9.5 µg/l.

In a primarily qualitative study, Sheldon and Hites (1978) recently found trace quantitites (<0.01 ppb) of isophorone in water samples from the Delaware River near a highly industrialized region. Isophorone was also identified as a contaminant (approximate concentration, 0.04 mg/l) in the wastewater from a tire manufacturing plant (Jungclaus, et al. 1976). Shackelford and Keith (1976) have reported that isophorone has been detected in the effluents from latex and chemical plants in Alabama, but no levels were reported.

Ingestion from Food

Pertinent data could not be located in the available literature concerning the presence of isophorone in food.

A bioconcentration factor (BCF) relates the concentration of a chemical in aquatic animals to the concentration in the water in which they live. The steady-state BCFs for a lipid-soluble compound in the tissues of various aquatic animals seems to be proportional to the percent lipid in the tissue. Thus, the per capita ingestion of a lipid-soluble chemical can be estimated from the per capita consumption of fish and shellfish, the weighted average percent lipids of consumed fish and shellfish, and a steady-state BCF for the chemical.

Data from a recent survey on fish and shellfish consumption in the United States was analyzed by SRI International (U.S. EPA, 1980). These data were used to estimate that the per capita consumption of freshwater and estuarine fish and shellfish in the United States is 6.5 g/day (Stephan, 1980). In addition, these data were used with data on the fat content of the edible portion of the same species to estimate that the weighted average percent lipids for consumed freshwater and estuarine fish and shellfish is 3.0 percent.

A measured steady-state bioconcentration factor of 7 was obtained for isophorone using bluegills (U.S. EPA, 1978). Similar bluegills contained an average of 4.8 percent lipids (Johnson, 1980). An adjustment factor of 3.0/4.8 = 0.625 can be used to adjust the measured BCF from the 4.8 percent lipids of the bluegill to the 3.0 percent lipids that is the weighted average for consumed fish and shellfish. Thus, the weighted average bioconcentration factor for isophorone and the edible portion of all aquatic organisms consumed by Americans is calculated to be 7 x 0.625 = 4.38.

Inhalation

No monitoring information is available on the levels of isophorone in ambient air.

Dermal

No information is available on the importance of dermal absorption in total human exposure to isophorone. It has been demonstrated that isophorone can be absorbed through the skin of

rabbits (see Acute, Subacute, and Chronic Toxicity section). For those humans exposed only to background levels of isophorone, however, dermal absorption is not likely to be a significant route of exposure.

PHARMACOKINETICS

Absorption

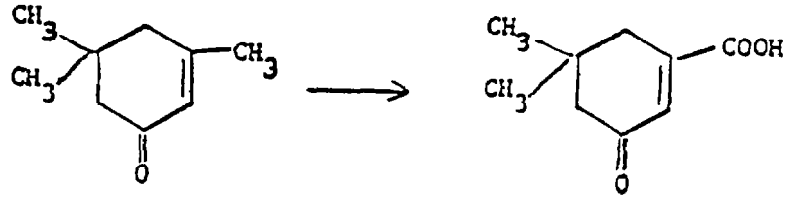
No quantitative information is available on the absorption of isophorone in animals or man. The demonstrated toxicity of isophorone by oral, inhalation and dermal exposures (see Acute, Subacute, and Chronic Toxicity section) indicates that it is capable of passage across epithelial membranes.

Distribution

The tissue distribution and accumulation of isophorone has not been studied.

Metabolism and Excretion

Isophorone appears to undergo oxidation at the 3-methyl group following oral administration of 1 g/kg to rabbits (Truhaut, et al. 1970). This reaction, shown below, precedes glucuronide conjugation and urinary elimination.



The complete reaction sequence for isophorone biotransformation has not been determined and no quantitative data on the extent of glucuronic acid conjugation are available.

Isophorone has been detected as a urinary metabolite of 3,5,5-trimethylcyclohexanone in rats and rabbits (Truhaut, et al. 1973). A large percentage of the metabolite was present as a glucuronide conjugate.

EFFECTS

Acute, Subacute, and Chronic Toxicity

Effects on Experimental Mammals: The acute toxicity of isophorone is summarized in Table 2. Oral LD_{50} values of about 2 gm/kg body weight have been reported for rats and mice by several authors.

The Union Carbide Corporation reported a single skin penetration LD_{50} value of 1.39 g/kg in rabbits in a 1975 technical data booklet. Single skin penetration refers to a 24-hour covered skin contact with the isophorone, but details regarding the number of animals exposed and any other aspects of the experimental protocol were not presented.

Smyth and Seaton (1940) reported that 750 ppm was the highest concentration of isophorone to which rats and guinea pigs could be exposed for several hours with no symptoms other than slight eye and nose irritation. The symptoms exhibited by the animals following exposures to higher concentrations included eye and nose irritation, lacrimation, swelling of the nose, instability, respiratory difficulty or irregularity, marked increase in intestinal peristalsis, and light narcosis (Table 3). Exposures lasting 12

TABLE 2

Acute Toxicity of Isophorone

Route	Animal	Number Treated per dose level[a]	Dose	Duration	Mortality	Reference
Oral	Rats	n.s.	1.87 g/kg	--	LD_{50}	Union Carbide (1975)
	Rats	5	2.10 g/kg	--	14-day LD_{50}	Smyth, et al. (1969)
	Rats	5	2.12 g/kg	--	14-day LD_{50}	Smyth, et al. (1970)
	Rats	n.s.	2.37 g/kg	--	LD_{50}	Bukhalovskii, & Shugeav (1976)
	Mice	n.s.	2.00 g/kg	--	LD_{50}	Bukhalovskii, & Shugeav (1976)
Dermal	Rabbits	n.s.	1.39 g/kg	--	LD_{50}	Union Carbide (1975)
Inhalation[b]	Rats and Guinea Pigs	n.s.	750 ppm	"several" hours	No death or serious symptoms	Smyth and Seaton (1940)
	Rats	n.s.	1840 ppm	4 hrs.	Caused death in some animals	Smyth and Seaton (1940)
	Guinea Pigs	n.s.	4600	8 hrs.	No deaths	Smyth and Seaton (1940)
	Rats	6	Air saturated with isophorone	8 hrs.	One death	Union Carbide (1975)

[a] n.s. = not specified.

[b] 600 ppm is the maximum attainable concentration of Isophorone in air (see discussion on page C-13 and appendix).

TABLE 3

Symptoms Resulting From Acute Exposure of Guinea Pigs to Isophorone Vapors[a,b,*]

Symptoms	Concentration in PPM					
	4,600	1,840	1,370	880	750	300
Maximum exposure period (minutes)	480	360	480	720	1,440	1,440
Nasal irritation (rub nose)	(1)	(1)	(1)	(1)	15	(2)
Eye irritation (blink)	(1)	(1)	(1)	(1)	15	(2)
Lacrimation	5	15	20	75	(2)	(2)
Nose swollen	8	20	30	75	(2)	(2)
Instability	40	50	80	135	(2)	(2)
Respiratory difficulty	60	120	180	360	(2)	(2)
Diarrhea	120	180	240	480	(2)	(2)
Light narcosis	180	200	255	600	(2)	(2)
First death	(2)	(2)	(2)	(2)	(2)	(2)

*Source: Smyth and Seaton, 1940

[a]Numbers are time in minutes for first animal to display symptom indicated. Time required for similar effects to be displayed by rats was about 2/3 of that for guinea pigs

[b]600 ppm is the maximum attainable concentration of Isophorone in air (see discussion on page C-13 and appendix)

(1) At very start of exposure

(2) Not observed within maximum exposure period

hours or more resulted in increased heart rates. Corneal opacity or necrosis, as revealed by fluorescein staining, was found in the guinea pigs following exposures of four hours or longer to isophorone at 840 ppm. Corneal effects were never observed in the rats.

Eight-hour inhalation exposures to isophorone at 4,600 ppm did not result in any deaths to guinea pigs, but in rats four hours at 1,840 ppm was the minimum lethal exposure (Smyth and Seaton, 1940). When death occurred it was usually during the exposure period due to paralysis of the respiratory center (narcosis). A few deaths were attributed to lung irritation.

It must be noted that Rowe and Wolf (1963) have indicated that the isophorone vapor concentrations reported by Smyth and Seaton in this study (1940), and those in a related subacute study described subsequently (Smyth, 1941; Smyth, et al. 1942), could not have been attained under the conditions employed. Later investigation led to the conclusion that the material used in the Smyth studies was an impure commercial product containing appreciable amounts of material(s) more volatile than isophorone (Rowe and Wolf, 1963). Smyth maintained vapor concentrations in a flow-through chamber by bubbling air through the solvent in a constant temperature bath and diluting the vapor stream with pure air, and monitored the concentrations with an interferometer. Since the concentration of vapors within the exposure chamber was measured by means of an interferometer calibrated against pure isophorone, it was apparently assumed that the vapors present in the chamber were isophorone only.

A calculation of the maximum attainable concentration of isophorone in air at standard temperature and pressure, presented in the appendix, yields a value of approximately 600 ppm. This calculation indicates that the allegation of Rowe and Wolf is probably correct and implies that the value of the Smyth data is seriously compromised.

The microscopic pathology of those animals surviving acute exposure by 14 days was almost never severe and was essentially reversible (Smyth and Seaton, 1940). Pathological findings were reported for 95 percent of the lungs (general congestion; alveolar and bronchiolar secretion, red cell leakage and epithelial cell desquamation; and secondary pneumonia), 56 percent of the kidneys (cloudy swelling, dilation, granular detritis and hyaline casts in convoluted tubules; dilation of Bowman's capsule; general congestion), 30 percent of the hearts (dilation of coronary vessels), 17 percent of the livers (congestion; hemorrhages into parenchyma; cloudy swelling) and 10 percent of the spleens (congestion). The typical hematologic response to acute isophorone intoxication was a temporary drop in red cells and hemoglobin, with white cells appearing to be unchanged.

Union Carbide (1975) reported that a single 8-hour inhalation exposure to air saturated with isophorone (calculated concentration approximately 600 ppm) killed 1 of 6 rats.

In 1942, Smyth, et al. compared the subacute inhalation toxicity of isophorone in rats and guinea pigs. The mortality and pathological details of this study were originally reported by Smyth (1941). Groups of 10 rats and 10 guinea pigs were re-

portedly exposed to isophorone vapor at 25 to 500 ppm for 8 hrs/day, five days a week for six weeks, but the experimental methods utilized were similar to those described for the Smyth and Seaton (1940) study. Since it appears that this experiment was also conducted with impure material and that the concentration of the isophorone tested is not accurately known (Rowe and Wolf, 1963), these results are also of limited value. The dose-related effects produced by the 25 to 500 ppm exposures are summarized in Table 4. Although about half the guinea pigs exposed to isophorone at 500 ppm died before the 30th exposure, no guinea pigs died from exposures at 100 ppm or less, and no rats died from inhalation of vapor at 50 ppm or less.

When death resulted from subacute inhalation exposure it appeared to be due to a combination of kidney and lung damage, although none of the surviving animals showed any severe grade of injury to these organs (Smyth, 1941; Smyth, et al. 1942). The microscopic findings of various tissues from the survivors was rather uniform, varying in degree with the concentration breathed. The lungs were frequently injured, showing primarily congestion and leakage of red blood cells into alveoli. Cloudy swelling with increased secretion and dilation of Bowman's capsule was a common finding in the kidney, but the action of isophorone on the liver, heart and spleen was negligible. Guinea pigs exposed to 500 ppm showed an increase in polymorphonuclear white cells and a corresponding fall in lymphocytes, but no other consistent changes in hematologic parameters were found.

TABLE 4

Subacute Inhalation Toxicity of Isophorone*

Animal	Concentration[a] (ppm)	Hr/Day	Duration (Days)	Mortality[b]	Details
Rats male, Wistar, 90-120 g	25	8	42 (30 exposures, 5 days/wk x 6 wks)	0%	No apparent signs of toxicity
	50	8	42 (30 exposures, 5 days/wk x 6 wks)	0%	Evidence of lung and kidney pathology
	100	8	42 (30 exposures, 5 days/wk x 6 wks)	20%	Evidence of lung, spleen and kidney pathology
	200	8	42 (30 exposures, 5 days/wk x 6 wks)	10%	Evidence of lung, spleen and kidney pathology; conjunctivitis and nasal irritation; urine albumin
Guinea Pigs both sexes, 250-300 g	25	8	42 (30 exposures, 5 days/wk x 6 wks)	0%	No apparent signs of toxicity
	100	8	42 (30 exposures, 5 days/wk x 6 wks)	0%	Evidence of lung and kidney pathology; weight loss
	200	8	42 (30 exposures, 5 days/wk x 6 wks)	25%	Evidence of lung and kidney pathology; weight loss
	500	8	42 (30 exposures, 5 days/wk x 6 wks)	40%	Evidence of lung, kidney and liver pathology; conjunctivitis and nasal irritation; weight loss; increase in polymorphonuclear white cells with a corresponding fall in lymphocytes

*Source: Smyth, 1941

[a]Rowe and Wolf (1963) have indicated that the isophorone used in this study was impure and that the reported concentrations are higher than actually present (see discussion on page C-13 and appendix).

[b]percentage of animals dying; usually 10 animals were tested at each dosage.

Smyth (1941) indicated that during the course of the study, both control and exposed animals, especially the guinea pigs, were troubled with infections (parasites, intestinal protozoa and bacteria). Although the affected animals were reportedly eliminated from consideration, the significance of the infection on the other animals is difficult to ascertain.

Subacute (90 day) feeding studies on isophorone in rats and dogs have also been conducted (Parkin, 1972).

In the rat study, CFE albino weanlings were divided into 4 groups of 20 males and females each and fed isophorone at 0, 750, 1,500 or 3,000 ppm in the daily diet (Parkin, 1972). Individual body weights, food and compound consumption were tabulated weekly. After four weeks and at 90 days, five rats/sex/group were killed and blood was collected for hematological and clinical chemistry determinations. Urine was collected from an additional five males and five females per group at the same time and was also comprehensively analyzed. The rats sacrificed after four weeks were examined for gross pathology only; but after 90 days, tissues from 10 rats of each sex from the control and 3,000 ppm groups were examined histologically. The livers and kidneys from five rats/sex from the 750 and 1,500 ppm groups were also examined. Two rats died during the study, one in the control group and one in the 3,000 ppm group, of an unspecified infection unrelated to the administration of isophorone. The body weights and food consumption were not significantly affected at the end of the study by feeding isophorone although the body weights of the males in the

3,000 ppm group were significantly depressed for several weeks during the study. There was no significant difference between the treated and control groups regarding hematology, blood chemistry, or urinalysis, and no pathological lesions were observed by either gross or microscopic examination.

In the dog study, four male and four female beagles were fed isophorone for 90 days at doses of 0, 35, 75, and 150 mg/kg/day, in gelatin capsules (food containing isophorone was refused). The dogs were weighed weekly and bled monthly for hematological blood chemistry evaluation, and urine was collected and analyzed on the same schedule as the blood. All the animals survived the study and were killed after 90 days and examined grossly. Twenty-eight selected tissues from the control and high level (150 mg/kg) groups were examined histologically, as were liver and kidney specimens from the intermediate exposure groups.

All dogs survived the study in excellent condition (Parkin, 1972). Food consumption was within normal limits and body weight was not affected by treatment.

The hematology, biochemical, and urinalysis tests indicated a lack of adverse effect of 90 doses of isophorone. All organs appeared normal at gross examination and no significant changes in organ weight were produced with the ingestion of isophorone. There was no evidence of any definitive signs of cellular change in any of the tissues examined.

Isophorone has been shown to be weakly irritating to the skin of rabbits, but its effect was stronger on the ocular mucosa where it induced reversible irritation of the conjunctiva and corneal

opacity (Truhaut, et al. 1972). These latter results are consistent with the moderate rabbit eye irritation ratings for isophorone reported by Carpenter and Smyth (1946) and Union Carbide (1963).

Effects on Humans: The most significant consequence of human exposure to low levels of isophorone vapor is irritation of mucosal membranes. In this respect isophorone is probably the most irritating of all ketonic solvents. Smyth and Seaton (1940) reported that groups of 11 or 12 human subjects exposed in a small room for a few minutes to measured isophorone concentrations of 40, 85, 200, and 400 ppm experienced eye, nose, and throat irritation, but it appears that these measured concentrations were higher than the isophorone that was actually present (see previous discussion regarding mammals). A few complaints of nausea, headache, dizziness, faintness, inebriation, and a feeling of suffocation resulted from inhalation of isophorone at 200 and 400 ppm in air. However, the symptoms of irritation and narcotic action were less severe at concentrations of 40 and 85 ppm.

In a sensory threshold study, Silverman, et al. (1946) exposed humans to the vapors of several industrial solvents including isophorone. Twelve unconditioned subjects of both sexes were exposed to the vapors for 15-minute periods in a 1,200 ft^3 chamber. They found that exposure to isophorone at 25 ppm produced irritation of the eyes, nose, and throat, and that isophorone vapor was considered by the subjects to be the most irritating of all the ketonic solvents tested. The highest tolerable level for an 8-hour isophorone exposure was judged to be 10 ppm by a

majority of the subjects. It should be noted that the concentration of isophorone in the exposure chamber was calculated (nominal) rather than measured analytically, so the true concentration may have been different than reported [National Institute Occupational Safety and Health (NIOSH), 1978].

Union Carbide (1963) indicated than one minute exposures to 200 ppm isophorone are intolerable for humans. A concentration of 40 ppm was intolerable to half of an unspecified number of human volunteers after four minutes. Union Carbide also noted that isophorone did not cause allergic contact sensitization in any of the ten human volunteers.

Synergism and/or Antagonism

Smyth and coworkers (1969, 1970) have examined the joint toxic action of isophorone with 26 industrial liquid chemicals based on acute LD_{50} data from oral intubations of female albino rats. In the initial study (Smyth, et al. 1969), LD_{50}s were determined for each of the compounds alone and for 1:1 (v/v) mixtures of the compounds. Based on the assumption of simple similar action, isophorone exhibited greater than additive toxicity in combination with nine compounds and less than additive toxicity in combination with 17 compounds. The significance of the interactions was determined by modifying the interactive ratios (predicted/observed LC_{50}) so that the distribution approximated normality. Significant interaction was then defined as those ratios which were beyond 1.96 standard deviations from the mean ratio. By this criterion, none of the mixtures containing isophorone deviated significantly from the assumption of simple

similar action. In a subsequent study (Smyth, et al. 1970), equal volume mixtures of isophorone and propylene oxide showed markedly less than additive toxicity, but equitoxic mixtures showed slightly greater than additive toxicity. An equitoxic mixture was defined as a mixture of chemicals in volumes directly proportional to their respective rat oral LD_{50} values, so that each component contributed the same degree of toxicity to the mixture.

Teratogenicity and Mutagenicity

Pertinent data could not be located in the available literature.

Carcinogenicity

Isophorone is being tested for carcinogenicity in rats and mice by gavage by the National Cancer Institute (NCI, 1979a). Apparently, isophorone was selected on the basis of its reported presence in municipal water supplies, the large number of workers exposed industrially (>1,500,000), a projected increase in production levels (>25 million pounds are currently being produced), and the existing paucity of epidemiological, animal, and metabolic information (NCI, 1979b).

CRITERION FORMULATION

Existing Guidelines and Standards

The current 8-hour time-weighted average (TWA) threshold limit value (TLV) for isophorone established by the American Conference of Governmental Industrial Hygienists (ACGIH, 1977) is 5 ppm (~25 mg/m^3). The TLV was lowered from 25 ppm (~140 mg/m^3) to 5 ppm in response to a June 1973 communication from the Western Electric Company to the TLV committee regarding fatigue and malaise among workers exposed to levels of 5 to 8 ppm for one month (ACGIH, 1974). When isophorone levels in air were lowered to 1 to 4 ppm (~6-23 mg/m^3) by increasing exhaust ventilation, no further complaints were received.

The current Federal standard for occupational exposure to isophorone is 25 ppm (140 mg/m^3) as an 8-hour time-weighted average concentration limit in the air of the working environment (39 FR 23540). This standard is based on the TLV adopted by the ACGIH in 1968, and is intended to prevent irritative and narcotic effects. NIOSH currently recommends a permissible exposure limit of 4 ppm (23 mg/m^3) as a TWA concentration for up to a 10-hour workshift, 40-hour work week (NIOSH, 1978). The NIOSH recommended standard is essentially based on the 1974 ACGIH TLV documentation.

Isophorone was exempted from the requirement of a tolerance under the Federal Food, Drug and Cosmetic Act when used as an inert solvent or cosolvent in pre-emergence pesticide formulations and for post-emergence use both on rice before the crop begins to head and on sugar and table beets (39 FR 37195).

Current Levels of Exposure

As detailed in the Exposure section of this report, only limited monitoring data are available regarding levels of isophorone in water, and virtually no information is available on ambient levels in air or food. Since there is a lack of extensive monitoring data on isophorone levels in drinking water, it is difficult to predict the magnitude or extent of human population exposure.

Although isophorone has been detected at levels of less than 3 ppt in several water samples, a maximum daily intake can be calculated from the highest reported level of 9.5 µg/l; (U.S. EPA, 1975) by assuming: (a) that 100 percent exposure comes from an average daily consumption of 2 liters of water plus 6.5 grams fish/shellfish; (b) a bioconcentration factor of 4.38 (U.S. EPA, 1979); and (c) 100 percent gastrointestinal absorption of the ingested isophorone. Thus, the daily intake of isophorone from water would be 19.3 µg/day (9.5 µg/l x [2 liters + (4.38 x 0.0065)] x 1.0).

Special Groups at Risk

Certain occupations (particularly individuals who are exposed to isophorone as a solvent) have elevated levels of exposure relative to the general population.

Basis and Derivation of Criterion

The data base for deriving an ambient water quality criterion for isophorone is relatively poor. The compound has not been

tested for carcinogenicity, mutagenicity, teratogenicity or chronic toxicity. With the exception of its irritant properties, no information is available on the effects of isophorone on humans.

The only suitable data for deriving a criterion comes from the 90 day feeding study in rats and dogs (Parkin, 1972). In this study, dogs evidenced no-observable-effects (based on hematology, blood chemistry, urinalyses and gross or microscopic pathology) at dose levels of 35, 75, and 150 mg/kg/day. In the rats, the only effect was transient weight loss in the 3,000 ppm group, with no effects noted in the 750 and 1,500 ppm exposure groups. Assuming a food consumption of approximately 10 percent of the body weight per day, the data on rats supports the NOEL of 150 mg/kg/day in dogs. This NOEL can be used to estimate an acceptable daily intake (ADI) for man by applying a safety factor of 1,000. This safety factor is justified because of the existence of only scanty human data and the lack of chronic toxicity data in animals. Thus, the estimated ADI for man is 150 µg/kg or 10.5 mg/man assuming a 70 kg body weight.

An ambient water quality criterion can be calculated using the following assumptions:

1. Two liters of water consumed per day.
2. 0.0065 kg of fish consumed per day.
3. Bioconcentration factor of 4.38.
4. 100 percent gastrointestinal absorption.

Therefore:

$$\frac{10.5 \text{ mg}}{(2\ 1 + [4.38 \times 0.0065]) \times 1.0} = 5.18 \text{ mg/l (or} \approx 5.2 \text{ mg/l).}$$

An alternate criterion could be derived from the TLV using the approach recommended by Stokinger and Woodward (1958). This approach would be compromised by three factors. First, the criterion is based on irritant effects from vapor exposures rather than chronic effects from oral exposures. Secondly, at the current TLV of 5 ppm, malaise and fatigue have been noted in exposed workers. Lastly, the lack of pharmacokinetic data precludes any firm estimate of equivalent oral doses based on inhalation exposures. Consequently, the TLV-based criterion would be a tenuous approximation at best.

The most prudent approach at this time would be to recommend only an interim criteria level pending the results of future research, including the planned NCI bioassay. An interim criterion of 5.2 mg/l could be recommended in cases where ambient water is the sole source of exposure to isophorone, because the basis for this value is a well defined no-effect level derived from a higher vertebrate species (dog) subjected to subchronic oral exposure. Since current levels of isophorone in water are usually less than 3 µg/l, although amounts as high as 9.5 µg/l have been reported, an ample margin of safety apparently exists.

In summary, based on the use of subchronic dog toxicological data and an uncertainty factor of 1,000, the criterion level of isophorone corresponding to an acceptable daily intake of 10.5 µg/kg/day, is 5.2 mg/l. Drinking water contributes 99 percent of

the assumed exposure while eating contaminated fish products accounts for 1 percent. The criterion level can similarly be expressed as 520 mg/l if exposure is assumed to be from the consumption of fish and shellfish products alone.

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APPENDIX

Calculation of appropriate isophorone concentration in saturated air.

For a sample of ideal gas,

$$PV = nRT$$

where

P = pressure

V = volume

n = number of moles

R = universal gas constant

T = absolute temperature

Since $n = \frac{g}{mw}$, the ideal gas equation can be rearranged as follows to calculate the approximate number of grams of compound contained in a particular volume of gas at a specified temperature and pressure:

$$PV = \frac{g}{mw} RT$$

$$g = \frac{PV(mw)}{RT}$$

At 25°C, the vapor pressure of isophorone is 0.44mm. Assuming a 1 liter volume of air,

$$g = \frac{\frac{0.44mm}{760mm} \times 1 \text{ liter} \times 138.21 \frac{g}{mole}}{0.082 \frac{\text{liter-atm}}{\text{mole-°K}} \times 298°K}$$

$$= 0.00327 \text{ g} = 3.27 \text{ mg}$$

The approximate ppm equivalent concentration of isophorone in saturated air can then be calculated from the relationship:

$$\frac{(\text{mg/l})\ (24{,}450\ \text{ml/mole})}{\text{mw}} = \text{ppm}$$

$$\frac{(3.27\ \text{mg/l})\ (24{,}450\ \text{ml/mole})}{138.21\ \text{g/mole}} = 578\ \text{ppm}.$$