ISOPHORONE

Ambient Water Quality Criteria

Criteria and Standards Division
Office of Water Planning and Standards
U.S. Environmental Protection Agency
Washington, D.C.

CRITERION DOCUMENT

ISOPHORONE

CRITERIA

Aquatic Life

The data base for freshwater aquatic life is insufficient to allow use of the Guidelines. The following recommendation is inferred from toxicity data for saltwater organisms.

For isophorone the criterion to protect freshwater aquatic life as derived using the Guidelines is 2,100 µg/l as a 24-hour average and the concentration should not exceed 4,700 µg/l at any time.

For isophorone the criterion to protect saltwater aquatic life as derived using the Guidelines is 97 µg/l as a 24-hour average and the concentration should not exceed 220 µg/l at any time.

Human Health

For the protection of human health from the toxic properties of isophorone ingested through the consumption of water and fish, the criterion is 460 µg/l.

ISOPHORONE

Introduction

Isophorone is an industrial chemical synthesized from acetone and used commercially as a solvent or cosolvent for finishes, lacquers, polyvinyl and nitro cellulose resins, pesticides, herbicides, fats, oils, and gums. It is also used as a chemical feedstock for the synthesis of 3,5 xylenol, 2,3,5-trimethyl-cyclohexanol, and 3,5-dimethylaniline.

Isophorone is an unsaturated, cyclic ketone or aliphatic enone produced commercially by passing acetone over calcium oxide, calcium hydroxide, calcium carbide or mixtures of these at 350°C and 1 atomosphere of pressure (Mark, et al. 1963). It is also prepared by heating acetone with aqueous, alkali metal hydroxide at approximately 150°C under pressure (Mark, et al. 1963). Blackford (1975) has estimated isophorone production at a level of 28 million pounds for 1973.

Isophorone (γ-isophorone) has the chemical name 3,5,5-trimethyl-2-cyclohexen-1-one, and is also known as trimethyl cyclohexanone or isoacetophorone (Rohm and Haas, 1971). Although isophorone is normally produced as the γ-isomer, it may exist also as a β-isomer having the chemical name 3,5,5-trimethyl-3-cyclohexen-1-one (Schering Ag. 1972). The technical or industrial grade of isophorone normally contains 3.0 percent or less of the β-isomer, causing a slight deviation in the melting and boiling points reported for pure isophorone (α-isomer) (Schering Ag. 1972; Rohm and Haas, 1971).

The pure compound (γ-isophorone) is a water-white liquid which exhibits low volatility, possesses a camphor or peppermint-like odor, and turns yellow upon standing (Schering Ag. 1972; Browning, 1965; Patty, 1962; Sax, 1975). It has the empirical formula $C_9H_{14}O$ and a molecular weight of 138.21. The physical properties include: melting point, -8.1°C; boiling point, 215.2°C; vapor pressure, 0.31 Hg at 20°C and 1 mm Hg g at 38°C; and a density of 0.9229 at 20°C (Mark, 1963; Sax, 1975; Browning, 1965). The compound is soluble in water up to 1.2 gm/100 ml at 20°C and is readily soluble in fats, oils, and other hydrophobic substances (Patty, 1962; Rohm and Haas, 1971; Jacob, 1949).

Isophorone is considered chemically stable (Patty, 1962). At 150°C, however, it will form salts with sulfuric acid and a tricyclic γ-, β-unsaturated ketone in the presence of 60 percent aqueous sodium hydroxide (Marx, 1971). Such reactions may be of little significance since the conditions required for their completion are generally not found in the environment.

In aqueous solutions, isophorone forms three different tricyclic diketodimers when exposed to direct sunlight (Jennings, 1965). The molecular weights of these compounds are double that of isophorone and the melting points range from 182 to 186.5°C. Following ultraviolet irradiation for one and ten days, conversions to the dimer were 10 and 50 percent, respectively (Craven, 1963). In a similar study, irradiation for 40 and 80 days resulted in dimer conversions of 76 and

83 percent, respectively (Craven, 1962). The significance of these laboratory studies with respect to the stability of isophorone in the environment is not known.

The microbiological degradation of isophorone, measured as percent biooxidation, was investigated by Price, et al. (1974) in domestic waste water and synthetic saltwater using a modification of the standard BOD test. The observed biooxidation levels of isophorone were 13, 47, and 42 percent in the domestic waste water at 10, 15, and 20 days, respectively. The biooxidation in synthetic saltwater reached only nine percent after 20 days incubation.

Although isophorone has been reported in drinking water, the Delaware River, and effluents of several industrial facilities, little or no information is available regarding bioconcentration, persistence, or fate of isophorone under environmental conditions. However, its broad application as a solvent or cosolvent or chemical feedstock for industrial and agricultural products clearly suggests that the potential for both point source and non-point source water contamination exists (39 FR 37195).

Isophorone has been reported to be toxic to aquatic life, particularly saltwater invertebrate species. Isopphorone also has been shown to be toxic to experimental mammals in acute, subacute, and chronic toxicity tests.

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AQUATIC LIFE TOXICOLOGY*

FRESHWATER ORGANISMS

Introduction

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

Acute Toxicity

The 96-hour LC50 for the bluegill (224,000 g/l) after adjustment for test methods and species sensitivity results in a Final Fish Acute Value for isophorone of 31,000 µg/l (Table 1).

Daphnia magna has been tested and the 48-hour EC50 is 117,000 µg/l (Table 2) which indicates little, if any, difference in sensitivity with the bluegill. The Final Invertebrate Acute Value (4,700 µg/l) also becomes the Final Acute Value since the former is lower than the comparable value for fish.

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*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life [43 FR 21506 (May 18, 1978) and 43 FR 29028 (July 5, 1978)] 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 the calculations for deriving various measures of toxicity as described in the Guidelines.

Chronic Toxicity

No chronic studies have been reported on the effects of isophorone on freshwater organisms.

Plant Effects

The 96-hour EC50 values for cell number production and inhibition of chlorophyll *a* by the alga, *Selenastrum capricornutum*, are 122,000 and 126,000, respectively (Table 3). These effect concentrations are essentially the same as for the bluegill and *Daphnia magna*.

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.

CRITERION FORMULATION

Freshwater-Aquatic Life

Summary of Available Data

The concentrations below have been rounded to two significant figures.

Final Fish Acute Value = 31,000 µg/l

Final Invertebrate Acute Value = 4,700 µg/l

Final Acute Value = 4,700 µg/l

Final Fish Chronic Value = not available

Final Invertebrate Chronic Value = not available

Final Plant Value = 120,000 µg/l

Residue Limited Toxicant Concentration = not available

Final Chronic Value = 120,000 µg/l

0.44 x Final Acute Value = 2,100 µg/l

No freshwater criterion can be derived for isophorone using the Guidelines because no Final Chronic Value for either fish or invertebrate species or a good substitute for either value is available.

Results obtained with isophorone and saltwater organisms indicate how a criterion may be estimated.

For isophorone and saltwater organisms, 0.44 times the Final Acute Value is less than the Final Chronic Value derived from results of an embryo-larval test with the sheepshead minnow. Therefore, it seems reasonable to estimate a criterion for isophorone and freshwater organisms using 0.44 times the Final Acute Value.

The maximum concentration of isophorone is the Final Acute Value of 4,700 µg/l and the estimated 24-hour average concentra-

tion is 0.44 times the Final Acute Value. No important adverse effects on freshwater aquatic organisms have been reported to be caused by concentrations lower than the 24-hour average concentration.

CRITERION: For isophorone the criterion to protect freshwater aquatic life as derived using procedures other than the Guidelines is 2,100 µg/l as a 24-hour average and the concentration should not exceed 4,700 µg/l at any time.

Table 1 Freshwater fish acute values for isophorone (U S EPA, 1978)

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)
Bluegill, *Lepomis macrochirus*	S	U	96	224,000	122,000

* S = static

** U = unmeasured

Geometric mean of adjusted values = 122,000 µg/l $\frac{122,000}{3.9}$ = 31,000 µg/l

Table 2 Freshwater invertebrate acute values for isophorone (U.S. EPA, 1978)

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)
Cladoceran, Daphnia magna	S	U	48	117,000	99,100

* S = static

** U = unmeasured

Geometric mean of adjusted values = 99,100 µg/l $\frac{99,100}{21}$ = 4,700 µg/l

Table 3 Freshwater plant effects for isophorone (U S. EPA, 1978)

Organism	Effect	Concentration (ug/l)
Alga, *Selenastrum capricornutum*	EC50 96-hr cell numbers	122,000
Alga, *Selenastrum capricornutum*	EC50 96-hr chlorophyll *a*	126,000

Lowest plant value = 122,000 µg/l

Table 4. Freshwater residues for isophorone (U.S. EPA, 1978)

Organism	Bioconcentration Factor	Time (days)
Bluegill, *Lepomis macrochirus*	7	28

SALTWATER ORGANISMS

Introduction

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.

Acute Toxicity

The 96-hour LC50 for the sheepshead minnow (U.S. EPA, 1978) was determined to be between 166,000 and 295,000 µg/l (Table 8). No Final Fish Acute Value can be derived but it would be higher than the equivalent value for invertebrate species (220 µg/l) which is derived from an unadjusted 96-hour LC50 value of 12,900 g/l for the mysid shrimp, Mysidopsis bahia (Table 5).

Chronic Toxicity

The chronic value for the sheepshead minnow obtained from an embryo-larval test (U.S. EPA, 1978) is 51,614 µg/l (Table 6). The limits on this test were 74,000 to 144,000 µg/l which is about 0.5 of the LC50 range (Table 8). The Final Fish Chronic Value, and the Final Chronic Value since no invertebrate species has been tested, is 7,700 µg/l.

Plant Effects

Chlorophyll a was inhibited and cell numbers were reduced by 50 percent after 96-hour exposures of the alga, Skeletonema costatum (U.S. EPA, 1978), to isophorone concentrations of 110,000 and 105,000 µg/l, respectively (Table 7).

CRITERION FORMULATION

Saltwater-Aquatic Life

Summary of Available Data

The concentrations below have been rounded to two significant figures.

Final Fish Acute Value = not available

Final Invertebrate Acute Value = 220 µg/l

Final Acute Value = 220 µg/l

Final Fish Chronic Value = 7,700 µg/l

Final Invertebrate Chronic Value = not available

Final Plant Value = 110,000 µg/l

Residue Limited Toxicant Concentration = not available

Final Chronic Value = 7,700 µg/l

0.44 x Final Acute Value = 97 µg/l

The maximum concentration of isophorone is the Final Acute Value of 220 µg/l and the 24-hour average concentration is 0.44 times the Final Acute Value. No important adverse effects on saltwater organisms have been reported to be caused by concentrations lower than the 24-hour average concentration.

CRITERION: For isophorone the criterion to protect saltwater aquatic life as derived using the Guidelines is 97 µg/l as a 24-hour average and the concentration should not exceed 220 µg/l at any time.

Table 5 Marine invertebrate acute values for isophorone (U S EPA, 1978)

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)
Mysid shrimp, Mysidopsis bahia	S	U	96	12,900	10,926

* S = static

** U = unmeasured

Geometric mean of adjusted values = 10,926 µg/l $\frac{10,926}{49}$ = 220 µg/l

Table 6 Marine fish chronic values for isophorone (U S. EPA, 1978)

Organism	Test*	Limits (ug/l)	Chronic Value (ug/l)
Sheepshead minnow, Cyprinodon variegatus	E-L	74,000-144,000	51,614

* E-L = embryo-larval

Geometric mean of chronic values = 51,614 µg/l $\frac{51,614}{6.7}$ = 7,700 µg/l

Lowest chronic value = 51,614 µg/l

Table 7 Marine plant effects for isophor[redacted] (U S EPA, 1978)

Organism	Effect	Concentration (ug/l)
Alga, *Skeletonema costatum*	EC50 96-hr chlorophyll *a*	110,000
Alga, *Skeletonema costatum*	EC50 96-hr cell number	105,000

Lowest plant value = 105,000 µg/l

Table 8. Other marine data for isophorone (U S. EPA, 1978)

Organism	Test Duration	Effect	Result (ug/l)
Sheepshead minnow, Cyprinodon variegatus	96 hrs	LC50	>166,000 <295,000

ISOPHORONE

REFERENCES

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

Mammalian Toxicology and Human Health Effects

Introduction

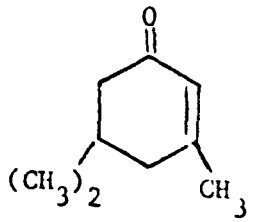
Isophorone is a high-boiling colorless liquid of low volatility with an odor resembling peppermint. Its salient physical properties are summarized in Table 1. Isophorone is an excellent solvent for many oils, fats, gums and natural and synthetic resins (Rowe and Wolf, 1963), but it is used mainly as 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 carbomate 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- trimethyl cyclohexanol, 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 less 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

TABLE 1

Physical Properties of Isophorone
(EPA, 1979a; Union Carbide, 1968; NIOSH, 1978)

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
Air Saturation	0.06%
Evaporation Rate (ether =1)	200
Water Solubility (weight % at 20°C)	1.2
Commercial Purity[a] (weight %)	96-98%
Impurities:	
β-isophorone	2-4%
mesitylene (1,3,5-trimethylbenzene)	trace
mesityl oxide (2-methyl-2 pertene-4-one)	trace
phorone (2,6-dimethyl-2,5-heptachiene-4-one)	trace
isoxylitones	trace
water	trace
Structure	3,5,5-trimethyl-2-cyclohexene-1-one



[a]Isophorone plus trimethylcyclohexenone

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 28 million pounds.

NIOSH (1978) estimates that more than 1.5 million workers are exposed to isophorone. In the industrial handling of isophorone inhalation of the vapors is the most likely mode of contact, although skin and eye contact with the liquid may also occur. Because of the odor and 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.

EXPOSURE

Ingestion from Water

Isophorone has been detected in several samples of drinking water (Table 2), 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 Environmental Protection Agency has quantified levels of isophorone in finished drinking water in the New Orleans area (EPA, 1974a). 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, initiated in 1974, was designed to provide an estimate of the nationwide distribution of organic compounds in drinking water (EPA, 1975). In a comprehensive organic analysis of the finished drinking waters of ten cities, isophorone was identified only in Cincinnati, 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 (FL), Seattle (WA), Ottumwa (IA), Philadelphia (PA), Tucson (AR), New York (NY), Lawrence (MA), Grand Forks (ND), 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 (EPA, 1975). Two hundred and fifty-three compounds were compiled from an extensive search of the

TABLE 2

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	EPA (1975)
X					1.5-2.9 µg/l, treated river water, New Orleans area	EPA (1974)
	X				trace (<0.01 ppb), Delaware River	Sheldon and Hites (1978)
		X	X			Shackelford and Keith (1976)
				X	0.04 mg/l	Jungclaus, et al. (1976)

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 Foods

No reports have been published concerning the possible presence of isophorone in food.

A bioconcentration factor (BCF) relates the concentration of a chemical in water to the concentration in aquatic organisms, but BCF's are not available for the edible portion of all four major groups of aquatic organisms consumed in the United States. Since data indicate that the BCF for lipid-soluble compounds is proportional to percent lipids, BCF's can be adjusted to edible portions using data on percent lipids and the amounts of various species consumed by Americans. A recent survey on fish and shellfish consumption in the United States (Cordle, et al. 1978) found that the per capita consumption is 18.7 g/day. From the data on the nine-

teen major species identified in the survey and data on the fat content of the edible portion of these species (Sidwell, et al. 1974), the relative consumption of the four major groups and the weighted average percent lipids for each group can be calculated:

Group	Consumption (Percent)	Weighted Average Percent Lipids
Freshwater fishes	12	4.8
Saltwater fishes	61	2.3
Saltwater molluscs	9	1.2
Saltwater decapods	18	1.2

Using the percentages for consumption and lipids for each of these groups, the weighted average percent lipids is 2.3 for consumed fish and shellfish.

A measured steady-state bioconcentration factor of 7 was obtained for isophorone using bluegills containing about one percent lipids (U.S. EPA, 1978). An adjustment factor of 2.3/1.0 = 2.3 can be used to adjust the measured BCF from the 1.0 percent lipids of the bluegill to the 2.3 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 2.3 = 16.

Inhalation

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

Dermal

No direct information is available on the importance of dermal absorption in total human exposure to isophorone. It has been demonstrated that isophorone can be absorbed across the skin of rabbits (see Acute, Sub-acute, 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 entry.

PHARMACOKINETICS

Absorption

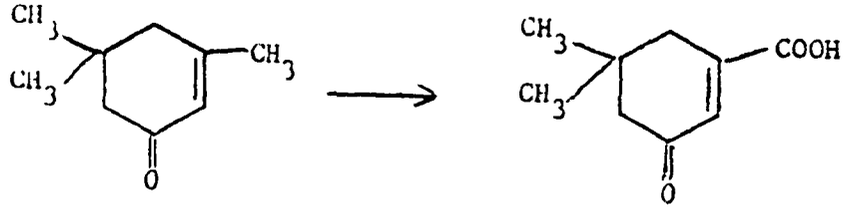
No direct quantitative information is available on the absorption of isophorone in animals or man. The demonstrated toxicity of isophorone by oral, inhalation and dermal exposures (Acute, Sub-acute, and Chronic Toxicity section) indicates that it is capable of passage across epithelial membranes.

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, Sub-acute, and Chronic Toxicity

Effects on Experimental Mammals: The acute toxicology of isophorone is summarized in Table 3. Oral LD_{50} values in the area of 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 no details regarding the number of animals exposed nor any other aspects of the experimental protocol were 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 sarcosis (Table 4). Exposures lasting 12 hours or more

resulted in increased heart rates. Opacity of the cornea or corneal necrosis, as revealed by Fluorescin staining, was found in the guinea pigs following exposures to 840 ppm isophorone lasting four hours or more. Corneal effects were never observed in the rats.

TABLE 3

Acute Toxicology 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, et al. (1976)
	Mice	n.s.	2.00 g/kg	--	LD_{50}	Bukhalovskii, et al. (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 4

Symptoms Resulting From Acute Exposure of Guinea Pigs to Isophorone Vapors[a,b]
(Smyth and Seaton, 1940)

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)

(1) At very start of exposure.
(2) Not observed within maximum exposure period.

[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).

Eight hour inhalation exposures to 4600 ppm isophorone did not result in any deaths to guinea pigs, but in rats a four hour exposure to 1840 ppm was the minimum lethal level (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, et al. 1941; 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.

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; 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 eight hour inhalation exposure to air saturated with isophorone (calculated concentration approximately 600 ppm) killed one of six rats.

In 1942, Smyth and coworkers 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 ten rats and ten guinea pigs were reportedly exposed to isophorone vapors at concentrations ranging from 25 to 500 ppm for eight 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 5. Although about half the animals exposed to isophorone at 500 ppm died before the thirtieth exposure; no guinea pigs died from exposures at 100 ppm or less, and no rats died from inhalation of vapors 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, et al. 1941; 1942). The microscopic picture 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 5

Subacute Inhalation Toxicity of Isophorone
(Smyth, 1941)

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

[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 (EPA, 1979a).

In the rat study, CFE albino weanlings were divided into 4 groups of 20 males and females each and fed 0, 750, 1500 or 3000 ppm isophorone in the daily diet (EPA, 1979a). 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 ten rats of each sex from the control and 3000 ppm groups were examined histologically. The livers and kidneys from five rats/sex from the 750 and 1500 ppm groups were also examined.

Two rats died during the study, one in the control group and one in the 3000 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 weight of the 3000 ppm male group was 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 observerd 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 (EPA, 1979a). Food consumption was within normal limits and body weight was not affected by treatment.

The hematology, biochemical, and urinalyses tests indicated a lack of untoward 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 for a few minutes to measured concentrations of 40, 85, 200 and 400 ppm isophorone in a small room experienced eye, nose and throat irritation, but it appears that these exposure concentrations were higher than actually present (see discussion on page C-13). 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 1200 ft^3 chamber. They found that exposure to 25 ppm isophorone produced irritation of the eyes, nose, and throat,

and that isophorone vapors were considered by the subjects to be the most irritating of all the ketonic solvents tested. The highest tolerable level for an eight 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 (NIOSH, 1978).

Union Carbide (1963) indicated that 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}'s 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 evidenced 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. Sig-

nificant 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.

Teratogenicity

Isophorone has apparently not been tested for teratogenicity.

Mutagenicity

No mutagenicity data for isophorone were encountered in the published literature.

Carcinogenicity

Isophorone has tentatively been selected for carcinogenesis testing in rats and mice by gavage by the National Cancer Institute (NCI, 1979). 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 (Personal communication, 1979).

CRITERION FORMULATION

Existing Guidelines and Standards

The current eight-hour time-weighted average threshold limit value (TLV) for isophorone established by the American Conference of Governmental Industrial Hygienists (1977) is 5 ppm (~ 28 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 (Am. Conf. Gov. Ind. Hyg., 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 U.S. Federal standard for occupational exposure to isophorone is 25 ppm (140 mg/m^3) as an eight-hour time-weighted average concentration limit in the air of the working environment (Occup. Safety Health Admin., 1974). This standard is based on the TLV adopted by the ACGIH in 1968, and is intended to prevent irritative and narcotic effects. The National Institute for Occupational Safety and Health (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 (Natl. Inst. Occup. Safety Health, 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 pesticide formulations

before a crop emerges from the soil, and for post-emergence use both on rice before the crop begins to head and on sugar and table beets (U.S. EPA, 1974b).

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 (9.5 µg/l; U.S. EPA, 1975) by assuming that 100 percent exposure comes from the ingestion of water and fish and shellfish from contaminated waters. Assuming: (a) an average daily consumption of 2 liters of water plus 18.7 grams fish/shellfish; (b) a bioconcentration factor of 16 (U.S. EPA, 1979b); and (c) 100 percent gastrointestinal absorption of the ingested isophorone; then the daily intake of isophorone from water would be 21.8 µg/day (9.5 µg/l x [2 liters + (16 x 0.0187)] 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.

Based on the available data on the toxicological effects of isophorone absorption in both man and experimental animals, a calculated water quality criterion for isophorone can only be based upon a non-carcinogenic end point. Water quality criteria may therefore be derived from the TLV, acute oral LD_{50} values, or from subacute oral toxicity data using non-carcinogenic biological responses. Criteria derivations based on all three approaches are presented below.

Criterion Based on TLV: Stokinger and Woodward (1958) presented a method for calculating equivalent water quality levels from TLV's. Essentially, this method consists of deriving an acceptable daily intake (ADI) from the TLV by making assumptions on breathing rate, and respiratory and gastrointestinal absorption. Stokinger and Woodward assumed that the daily total pollutant uptake from air at the TLV concentration can be safely tolerated, and that this safe quantity of pollutant per day can be similarly tolerated via oral exposure. The ADI is then partitioned into permissible amounts from drinking water and from other sources.

The International Commission on Radiological Protection (1974) has estimated that the "reference man" breathes 7.6 m^3 of air during eight-hours of "light activity." Since respiratory absorption rates are unknown, 50 percent absorption of inhaled isophorone will be assumed. In addition, the five day per week TLV may be converted to a seven day per week equivalent to reflect the more continuous pattern of exposure

via drinking water. An ADI for man can be thus calculated from the TLV by multiplying by these factors:

$$28\ mg/m^3 \times 7.6\ m^3 \times 0.5 \times 5\ days/7days = 76\ mg/day$$

Since estimates of isophorone exposure from non-water sources are not available, it will be assumed that total isophorone exposure is attributable to the ingestion of drinking water and fish and shellfish. For the purpose of estimating a criterion it will be further assumed that the maximal daily intake of water is 2 liters, that the consumption of fish/shell fish amounts to 18.7 grams/day, and that the gastrointestinal absorption of isophorone is 100 percent. Also a bioconcentration factor of 16 has been calculated for fish (U.S. EPA, 1979b). A water quality criterion may then be calculated as:

$$\frac{76\ mg/man}{(2\ l + [16 \times 0.0187]) \times 1.0} = 33\ mg/l$$

It should be noted that the TLV is based on the prevention of the irritant effects of isophorone from inhalation exposures, rather than on chronic effects. Consequently, the development of a criterion by this approach probably has little validity in this case.

Criterion Based on Acute Oral Toxicity Data: McNamara (1976) has suggested that data from acute exposures can be used to estimate chronic no-effect levels for toxic responses to chemical absorption. Based on an extensive review of the literature comparing the results of acute and chronic toxicity bioassays, McNamara noted that "for 95 percent of chemical compounds...[on which data were available]...$LD_{50}/1000$ will

produce no effects in a lifetime." Using this approximation for isophorone, and an average oral LD_{50} value of 2 g/kg (Effects section), the no-observable-effect level for isophorone in rats can be estimated at 2 mg/kg/day. This value may be converted into an ADI by applying an appropriate uncertainty factor to account for species extrapolation and limitations of the data. Since the chronic no-effect dose is merely an estimate based on observed relationships between acute and chronic toxicity, an uncertainty factor of 1,000 is recommended (see Natl. Acad. Sci., 1977, p. 804). Thus, the estimated ADI for man is µg/kg or 140 µg/man, assuming a 70 kg body weight. By assum ing that man consumes 2 liters of water per day, that man is additionally exposed daily to 18.7 grams of fish and shellfish which bioaccumulate isophorone from water by a factor of 16, and that gastrointestinal absorption is 100 percent, the corresponding no-adverse-effect level in water can be calculated as follows:

$$\frac{140\ \mu g/day}{(2\ l + [16 \times 0.0187]) \times 1.0} = 61\ \mu g/l$$

Based on these calculations, the criterion for isophorone should not exceed 0.06 mg/l.

Criterion Based on Subacute Oral Data: As summarized in the Effects section, no significant effects were produced in beagle dogs by feeding isophorone in gelatin capsules at levels up to 150 mg/kg/day for 90 days (U.S. EPA, 1979a). Due to the fact that this study did not involve a truly chronic ex-

posure, the Natl. Acad. Sci. (1977) guidelines for establising an acceptable daily intake for man are not directly applicable McNamara (1976) has suggested, however, that subacute exposures can be used to estimate chronic no-effect exposure levels.

McNamara (1976) found that for 95 percent of chemical compounds for which data were available, a three-month no-effect dose/10 will yield a level which should produce no adverse effects in a lifetime. By using this relationship, the chronic no-effect dose for dogs is calculated to be:

$$\frac{150 \text{ mg/kg}}{10} = 15 \text{ mg/kg}$$

The application of an uncertainty factor of 1000 is suggested to convert this value to an ADI (see Natl. Acad. Sci., 1977, p. 804). Therefore, an estimated ADI for man is 15 µg/kg or 1,050 µg/man, assuming a 70 kg body weight. Consumption of 2 liters of water daily and of 18.7 grams of contaminated aquatic organisms which have a bioconcentration factor of 16 would result in, assuming 100 percent gastrointestional absorption of isophorone, a maximum permissible concentration of 0.46 mg/l for the ingested water:

$$\frac{1050 \text{ µg/day}}{(2 \text{ l} + [16 \times 0.0187]) \times 1.0} = 457 \text{ µg/l}$$

In conclusion, criterion levels for isophorone can be estimated on the basis of a TLV (33 mg/l), acute oral toxicity data (0.06 mg/l), and a 90-day feeding study in dogs (0.46 mg/l).

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 0.46 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 15 µg/kg/day, is 0.46 mg/l. Drinking water contributes 87 percent of the assumed exposure while eating contaminated fish products accounts for 13 percent. The criterion level can similarly be expressed as 3.5 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:

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

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