

TOXICOLOGICAL PROFILE FOR  
ISOPHORONE

Agency for Toxic Substances and Disease Registry (ATSDR)  
U.S. Public Health Service

In collaboration with  
U.S. Environmental Protection Agency (EPA)

December 1989

**DISCLAIMER**

Mention of company name or product does not constitute endorsement by the Agency for Toxic Substances and Disease Registry.

## FOREWORD

The Superfund Amendments and Reauthorization Act of 1986 (Public Law 99-499) extended and amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law (also known as SARA) directed the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare toxicological profiles for hazardous substances which are most commonly found at facilities on the CERCLA National Priorities List and which pose the most significant potential threat to human health, as determined by ATSDR and the Environmental Protection Agency (EPA). The lists of the most significant hazardous substances were published in the Federal Register on April 17, 1987, and on October 20, 1988.

Section 110 (3) of SARA directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. Each profile must include the following content:

- (A) An examination, summary and interpretation of available toxicological information and epidemiological evaluations on the hazardous substance in order to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects,
- (B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure which present a significant risk to human health of acute, subacute, or chronic health effects, and
- (C) Where appropriate, an identification of toxicological testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and EPA. The original guidelines were published in the Federal Register on April 17, 1987. Each profile will be revised and republished as necessary, but no less often than every 3 years, as required by SARA.

The ATSDR toxicological profile is intended to characterize succinctly the toxicological and health effects information for the hazardous substance being described. Each profile identifies and reviews the key literature that

describes a hazardous substance's toxicological properties. Other literature is presented but described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

Each toxicological profile begins with a public health statement, which describes in nontechnical language a substance's relevant toxicological properties. Following the statement is material that presents levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health will be identified by ATSDR, the National Toxicology Program of the Public Health Service, and EPA. The focus of the profiles is on health and toxicological information; therefore, we have included this information in the front of the document.

The principal audiences for the toxicological profiles are health professionals at the federal, state, and local levels, interested private sector organizations and groups, and members of the public. We plan to revise these documents as additional data become available.

This profile reflects our assessment of all relevant toxicological testing and information that has been peer reviewed. It has been reviewed by scientists from ATSDR, EPA, the Centers for Disease Control, and the National Toxicology Program. It has also been reviewed by a panel of nongovernment peer reviewers and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.



Walter R. Dowdle, Ph.D.  
Acting Administrator  
Agency for Toxic Substances and  
Disease Registry

## CONTENTS

FOREWORD . . . . .	iii
LIST OF FIGURES . . . . .	ix
LIST OF TABLES . . . . .	xi
1. PUBLIC HEALTH STATEMENT . . . . .	1
1.1 WHAT IS ISOPHORONE? . . . . .	1
1.2 HOW MIGHT I BE EXPOSED TO ISOPHORONE? . . . . .	1
1.3 HOW CAN ISOPHORONE ENTER AND LEAVE MY BODY? . . . . .	1
1.4 HOW CAN ISOPHORONE AFFECT MY HEALTH? . . . . .	2
1.5 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO ISOPHORONE? . . . . .	2
1.6 WHAT LEVELS OF EXPOSURE HAVE RESULTED IN HARMFUL HEALTH EFFECTS? . . . . .	2
1.7 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH? . . . . .	7
1.8 WHERE CAN I GET MORE INFORMATION? . . . . .	7
2. HEALTH EFFECTS . . . . .	9
2.1 INTRODUCTION . . . . .	9
2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE . . . . .	9
2.2.1 Inhalation Exposure . . . . .	10
2.2.1.1 Death . . . . .	10
2.2.1.2 Systemic Effects . . . . .	15
2.2.1.3 Immunological Effects . . . . .	19
2.2.1.4 Neurological Effects . . . . .	19
2.2.1.5 Developmental Effects . . . . .	20
2.2.1.6 Reproductive Effects . . . . .	21
2.2.1.7 Genotoxic Effects . . . . .	22
2.2.1.8 Cancer . . . . .	22
2.2.2 Oral Exposure . . . . .	22
2.2.2.1 Death . . . . .	22
2.2.2.2 Systemic Effects . . . . .	28
2.2.2.3 Immunological Effects . . . . .	31
2.2.2.4 Neurological Effects . . . . .	32
2.2.2.5 Developmental Effects . . . . .	32
2.2.2.6 Reproductive Effects . . . . .	32
2.2.2.7 Genotoxic Effects . . . . .	33
2.2.2.8 Cancer . . . . .	33
2.2.3 Dermal/Ocular Exposure . . . . .	33
2.2.3.1 Death . . . . .	33
2.2.3.2 Systemic Effects . . . . .	36
2.2.3.3 Immunological Effects . . . . .	36
2.2.3.4 Neurological Effects . . . . .	36
2.2.3.5 Developmental Effects . . . . .	37

2.2.3.6	Reproductive Effects . . . . .	37
2.2.3.7	Genotoxic Effects. . . . .	37
2.2.3.8	Cancer . . . . .	37
2.3	RELEVANCE TO PUBLIC HEALTH . . . . .	37
2.4	LEVELS IN HUMAN TISSUES AND FLUIDS ASSOCIATED WITH HEALTH EFFECTS. . . . .	44
2.5	LEVELS IN THE ENVIRONMENT ASSOCIATED WITH LEVELS IN HUMAN TISSUES AND/OR HEALTH EFFECTS. . . . .	44
2.6	TOXICOKINETICS . . . . .	45
2.6.1	Absorption. . . . .	45
2.6.1.1	Inhalation Exposure. . . . .	45
2.6.1.2	Oral Exposure. . . . .	45
2.6.1.3	Dermal Exposure. . . . .	45
2.6.2	Distribution. . . . .	46
2.6.2.1	Inhalation Exposure. . . . .	46
2.6.2.2	Oral Exposure. . . . .	46
2.6.2.3	Dermal Exposure. . . . .	46
2.6.3	Metabolism. . . . .	46
2.6.4	Excretion . . . . .	47
2.6.4.1	Inhalation Exposure. . . . .	47
2.6.4.2	Oral Exposure. . . . .	47
2.6.4.3	Dermal Exposure. . . . .	47
2.7	INTERACTIONS WITH OTHER CHEMICALS. . . . .	47
2.8	POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE . . . . .	49
2.9	ADEQUACY OF THE DATABASE . . . . .	49
2.9.1	Existing Information on Health Effects of Isophorone . . . . .	49
2.9.2	Data Needs. . . . .	51
2.9.3	On-going Studies. . . . .	56
3.	CHEMICAL AND PHYSICAL INFORMATION . . . . .	57
3.1	CHEMICAL IDENTITY. . . . .	57
3.2	PHYSICAL AND CHEMICAL PROPERTIES . . . . .	57
4.	PRODUCTION, IMPORT, USE, AND DISPOSAL . . . . .	61
4.1	PRODUCTION . . . . .	61
4.2	IMPORT . . . . .	61
4.3	USE. . . . .	61
4.4	DISPOSAL . . . . .	62
4.5	ADEQUACY OF THE DATABASE . . . . .	62
4.5.1	Data Needs. . . . .	62
5.	POTENTIAL FOR HUMAN EXPOSURE. . . . .	63
5.1	OVERVIEW . . . . .	63
5.2	RELEASES TO THE ENVIRONMENT. . . . .	63
5.2.1	Air . . . . .	63
5.2.2	Water . . . . .	64
5.2.3	Soil. . . . .	64
5.3	ENVIRONMENTAL FATE . . . . .	64
5.3.1	Transport and Partitioning. . . . .	64

5.3.2	Transformation and Degradation. . . . .	66
5.3.2.1	Air. . . . .	66
5.3.2.2	Water. . . . .	66
5.3.2.3	Soil . . . . .	67
5.4	LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT . . . . .	67
5.4.1	Air . . . . .	67
5.4.2	Water . . . . .	67
5.4.3	Soil. . . . .	70
5.4.4	Other Media . . . . .	71
5.5	GENERAL POPULATION AND OCCUPATIONAL EXPOSURE . . . . .	71
5.6	POPULATIONS WITH POTENTIALLY HIGH EXPOSURE . . . . .	74
5.7	ADEQUACY OF THE DATABASE . . . . .	74
5.7.1	Data Needs. . . . .	76
5.7.2	On-going Studies. . . . .	77
6.	ANALYTICAL METHODS. . . . .	79
6.1	BIOLOGICAL MATERIALS . . . . .	79
6.2	ENVIRONMENTAL SAMPLES. . . . .	79
6.3	ADEQUACY OF THE DATABASE . . . . .	81
6.3.1	Data Needs. . . . .	81
6.3.2	On-going Studies. . . . .	82
7.	REGULATIONS AND ADVISORIES. . . . .	83
8.	REFERENCES. . . . .	87
9.	GLOSSARY. . . . .	99
APPENDIX	. . . . .	103



**LIST OF FIGURES**

2-1	Levels of Significant Exposure to Isophorone - Inhalation . . . . .	14
2-2	Levels of Significant Exposure to Isophorone - Oral . . . . .	27
2-3	Metabolic Scheme for Isophorone . . . . .	48
2-4	Existing Information on Health Effects of Isophorone . . . . .	50



## LIST OF TABLES

1-1	Human Health Effects from Breathing Isophorone. . . . .	3
1-2	Animal Health Effects from Breathing Isophorone . . . . .	4
1-3	Human Health Effects from Eating or Drinking Isophorone . . . . .	5
1-4	Animal Health Effects from Eating or Drinking Isophorone. . . . .	6
2-1	Levels of Significant Exposure to Isophorone - Inhalation . . . . .	11
2-2	Levels of Significant Exposure to Isophorone - Oral . . . . .	23
2-3	Levels of Significant Exposure to Isophorone - Dermal . . . . .	34
2-4	Genotoxicity of Isophorone In Vitro and In Vivo . . . . .	42
3-1	Chemical Identity of Isophorone . . . . .	58
3-2	Physical and Chemical Properties of Isophorone. . . . .	59
5-1	Detection of Isophorone in Water. . . . .	68
5-2	Detection of Isophorone in Fish Near Lake Michigan . . . . .	72
5-3	Occupational Monitoring of Isophorone . . . . .	75
6-1	Analytical Methods for Isophorone . . . . .	80
7-1	Regulations and Guidelines Applicable to Isophorone . . . . .	84



## 1. PUBLIC HEALTH STATEMENT

### 1.1 WHAT IS ISOPHORONE?

Isophorone is a clear liquid with a peppermint-like odor. It evaporates faster than water but slower than charcoal starter or paint thinner, and it will not mix completely with water. Isophorone is a manmade chemical for use commercially, but it has been found to occur naturally in cranberries. It is used as a solvent in some printing inks, paints, lacquers, and adhesives. Isophorone does not remain in the air very long, but can remain in water for possibly more than 20 days. The length of time that isophorone will remain in soil is not known, but it probably is about the same as the length of time it remains in water. More information can be found in Chapters 3 and 4.

### 1.2 HOW MIGHT I BE EXPOSED TO ISOPHORONE?

Exposure to isophorone may take place where you work or in very low concentrations at home. Because it is used in some inks, paints, lacquers, and adhesives, people who work with these products may be exposed to isophorone. Isophorone has been found in the drinking water of Cincinnati, Philadelphia, and New Orleans at amounts less than 10 parts of isophorone in 1 billion parts of water (10 ppb). In one instance (a screen print shop), isophorone was found in amounts as high as 26 parts in 1 million parts of air (26 ppm), but the usual amounts in the workplace are much lower. At this time, isophorone has been found in at least 9 out of 1177 National Priorities List (NPL) hazardous waste sites in the United States. Exposure to isophorone at these sites may occur by touching contaminated soil, water, or sediment. For more information please read Chapter 5.

### 1.3 HOW CAN ISOPHORONE ENTER AND LEAVE MY BODY?

Isophorone can enter your body if you breathe its vapor, have skin contact with it, drink contaminated water, or eat contaminated food. If isophorone is present at a waste site near homes that use local wells as a source of water, the well water could be contaminated with isophorone. Experiments in animals show that after doses by mouth, isophorone enters easily and spreads to many organs of the body, but most of it leaves the body within 24 hours in the breath and in urine. Isophorone may enter the lungs of workers exposed to isophorone where it is used indoors as a solvent. Isophorone disappears quickly from outside air, so the chance of breathing outdoor air contaminated with isophorone is small. If isophorone is spilled at a waste site and evaporates, however, a person nearby may breathe isophorone before it disappears from the air. In addition, soil around waste sites may contain isophorone, and a person, such as a child playing in the dirt, may eat or have skin contact with the contaminated soil. How much isophorone enters the body through the skin is not known.

## 1. PUBLIC HEALTH STATEMENT

More information on how isophorone can enter and leave-the body can be found in Chapter 2.

### 1.4 HOW CAN ISOPHORONE AFFECT MY HEALTH?

The only effects of isophorone reported in humans are irritation of the skin, eyes, nose, and throat, and possibly dizziness and fatigue. These effects have occurred in workers who breathe vapors of isophorone and other solvents during use in the printing industry. Short-term exposure of animals to high vapor amounts and short- or long-term exposure of animals to high doses by mouth cause death or a shortened lifespan. Short-term exposure to high amounts of vapors or high doses by mouth has caused inactivity and coma in animals. Inconclusive studies suggested that isophorone may have caused birth defects and growth retardation in the offspring of rats and mice that breathed the vapors during pregnancy. Some harmful health effects were seen in adult female animals in these studies. It is not known whether isophorone could cause birth defects in humans. In a long-term study in which rats and mice were given high doses of isophorone by mouth, the male rats developed kidney disease and kidney tumors. Male rats also developed tumors in a reproductive gland. Some male mice developed tumors in the liver, in connective tissue, and in lymph glands (tissues of the body that help fight disease), but the evidence was not strong. It is not known whether isophorone causes cancer in humans. More information on the health effects of isophorone in animals and humans can be found in Chapter 2.

### 1.5 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO ISOPHORONE?

No medical test is known to determine human exposure to isophorone. A few studies in rats and rabbits have shown that isophorone and its metabolites can be found in the urine of these animals, so it may be possible to find a method for testing the urine of humans to determine exposure to isophorone. It is not known, however, whether such a measurement would predict how much exposure had occurred or the possible health effects. For more information see Chapter 2.

### 1.6 WHAT LEVELS OF EXPOSURE HAVE RESULTED IN HARMFUL HEALTH EFFECTS?

Tables 1-1 through 1-4 show the link between exposure to isophorone and known health effects. A Minimal Risk Level (MRL) is also included in Table 1-3. This MRL was derived from animal data for long-term exposure, as described in Chapter 2 and in Table 2-2. The MRL provides a basis for comparison with levels that people might encounter in food. If a person is exposed to isophorone at an amount below the MRL, it is not expected that harmful (noncancer) health effects will occur. Because this level is based on information that is currently available, some uncertainty is always associated with it. Also, because the method for deriving MRLs does not use any information about cancer, a MRL does not imply anything about the

## 1. PUBLIC HEALTH STATEMENT

TABLE 1-1. Human Health Effects from Breathing Isophorone\*

Short-term Exposure (less than or equal to 14 days)		
<u>Levels in Air (ppm)</u>	<u>Length of Exposure</u>	<u>Description of Effects**</u>
25	4 minutes	Eye, nose, throat irritation
Long-term Exposure (greater than 14 days)		
<u>Levels in Air (ppm)</u>	<u>Length of Exposure</u>	<u>Description of Effects**</u>
5	1 month	Fatigue, depression

\*See Section 1.2 for a discussion of exposures encountered in daily life.

\*\*These effects are listed at the lowest level at which they were first observed. They may also be seen at higher levels.

## 1. PUBLIC HEALTH STATEMENT

TABLE 1-2. Animal Health Effects from Breathing Isophorone

Short-term Exposure (less than or equal to 14 days)		
<u>Levels in Air (ppm)</u>	<u>Length of Exposure</u>	<u>Description of Effects*</u>
28	5 minutes	Lung irritation in mice
89	4 hours	Behavior problems in mice
620	6 hours	Lung congestion in rats and mice
885	6 hours	Death in rats
Long-term Exposure (greater than 14 days)		
<u>Levels in Air (ppm)</u>	<u>Length of Exposure</u>	<u>Description of Effects*</u>
37	4 weeks	Poor weight gain in rats
250	18 months	Slight liver effects, eye and nose irritation in rats and rabbits
500	4-6 months	Death in rats

\*These effects are listed at the lowest level at which they were first observed. They may also be seen at higher levels.

## 1. PUBLIC HEALTH STATEMENT

TABLE 1-3. Human Health Effects from Eating or Drinking Isophorone\*

Short-term Exposure (less than or equal to 14 days)		
<u>Levels in Food (ppm)</u>	<u>Length of Exposure</u>	<u>Description of Effects</u>
		The health effects resulting from short-term human exposure to food containing specific levels of isophorone are not known.
<u>Levels in Water (ppm)</u>		The health effects resulting from short-term human exposure to water containing specific levels of isophorone are not known.
Long-term Exposure (greater than 14 days)		
<u>Levels in Food (ppm)</u>	<u>Length of Exposure</u>	<u>Description of Effects</u>
7		Minimal risk level (based on animal data, see Section 1.6 for discussion)
<u>Levels in Water (ppm)</u>		The health effects resulting from long-term human exposure to water containing specific levels of isophorone are not known.

\*See Section 1.2 for a discussion of exposures encountered in daily life.

## 1. PUBLIC HEALTH STATEMENT

TABLE 1-4. Animal Health Effects from Eating or Drinking Isophorone

Short-term Exposure (less than or equal to 14 days)		
<u>Levels in Food (ppm)</u>	<u>Length of Exposure</u>	<u>Description of Effects*</u>
8000	1 day	Fatigue, staggering in mice
<u>Levels in Water (ppm)</u>		
11,000	1 day	Death in mice
15,000	1 day	Death in rats
Long-term Exposure (greater than 14 days)		
<u>Levels in Food (ppm)</u>	<u>Length of Exposure</u>	<u>Description of Effects*</u>
1900	2 years	Liver disease, stomach irritation in mice
5000	2 years	Kidney disease in rats
8000	13 weeks	Death in mice
15,000	16 days	Death in mice
<u>Levels in Water (ppm)</u>		
The health effects resulting from long term animal exposure to drinking water containing specific levels of isophorone are not known.		

\*These effects are listed at the lowest level at which they were first observed. They may also be seen at higher levels.

## 1. PUBLIC HEALTH STATEMENT

presence, absence, or level of risk of cancer. The information on health effects in humans or animals for short-term or long-term exposure to isophorone in air, for short-term exposure in food or water, and for longterm exposure in water was either not available or not suitable to derive MRLS.

The amounts listed in Table 1-1 that cause eye, nose, and throat irritation (25 ppm) with short-term exposure and fatigue and depression (5 ppm) with long-term exposure are much higher than the amount at which the odor is first noticed, which is about 0.2 ppm. This means that you can probably smell isophorone before you would have harmful health effects. The levels of isophorone in air that cause death and lung congestion in animals are much higher than the amounts that workers breathe in industry when using isophorone as a solvent. The amount that causes lung irritation in animals is about the same as the amount that causes eye, nose, and throat irritation in humans.

Besides the harmful health effects from exposure to isophorone in air, food, and water, skin irritation or eye damage occurred in animals after a few drops of isophorone had been applied directly to the skin or eyes.

### 1.7 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The Environmental Protection Agency (EPA) has determined that the level of isophorone in natural waters (lakes, streams) should be limited to 5.2 parts isophorone per million parts of water (5.2 ppm) to protect human health from the harmful effects of isophorone from drinking the water and from eating contaminated fish and other animals found in the water. The Occupational Safety and Health Administration (OSHA) has set a permissible exposure limit of 4 parts of isophorone per million parts of workroom air (4 ppm) during an 8-hour work shift to protect workers. The National Institute for Occupational Safety and Health (NIOSH) recommends that the amount in workroom air be limited to 4 ppm averaged over a 10-hour work shift. Further information on government recommendations can be found in Chapter 7.

### 1.8 WHERE CAN I GET MORE INFORMATION?

If you have more questions or concerns, please contact your State Health or Environmental Department or:

Agency for Toxic Substances and Disease Registry  
Division of Toxicology  
1600 Clifton Road, E-29  
Atlanta, Georgia 30333