

Isophorone; CASRN 78-59-1

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the [IRIS assessment development process](#). Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the [guidance documents located on the IRIS website](#).

STATUS OF DATA FOR Isophorone

File First On-Line 01/31/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	09/01/1989
Inhalation RfC (I.B.)	message	03/01/1991
Carcinogenicity Assessment (II.)	yes	10/01/1992

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Isophorone

CASRN — 78-59-1

Last Revised — 09/01/1989

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of

substances that are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
No observed effects	NOEL: 150 mg/kg/day	1000	1	2E-1 mg/kg/day
90-Day Dog Feeding Study	LEL: None			
Nor-Am Agricultural Products, Inc., 1972a				
Kidney pathology	NOEL: None			
2-Year Rat Gavage Study	LEL: 250 mg/kg/day (179 mg/kg/day)			
NTP, 1984				

*Conversion Factors: The LEL of 179 mg/kg/day is based on a 5 day/week treatment schedule

I.A.2. Principal and Supporting Studies (Oral RfD)

Nor-Am Agricultural Products, Inc. 1972a. MRID No. 00123976. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

NTP (National Toxicology Program). 1984. NTP Technical Report on the Toxicology and Carcinogenesis Studies of Isophorone in F344/N Rats and B63F1 Mice (Gavage). NIH Publication No. 84-2547, NTP-83-168.

Beagle dogs (4/sex/dose) were administered gelatin capsules containing 0, 35, 75, or 150 mg isophorone/kg/day 7 days/week for 90 days (Nor-Am Agricultural Products, 1972a). All dogs survived the study in good condition. Food consumption was within normal limits and body weight was not affected by treatment. All organs appeared normal at gross examination and no significant changes in organ weight were produced with the ingestion of isophorone. There were no definitive signs of cellular change in any of the tissues examined. A NOEL for systemic toxicity was established at 150 mg/kg/day (HDT) due to the lack of effects produced at any dose tested.

NTP (1984) administered 0, 250, or 500 mg isophorone/kg/day, 5 days/week for 103 weeks by corn oil gavage to groups of 50 F344/N rats/sex and 50 B63F1 mice/sex (averaged daily doses: 0, 179, and 357 mg/kg/day). Doses selected for the 2-year studies were based on 16-day repeated-administration studies in which rats and mice of each sex received 0-2000 mg/kg/day and on 13-week studies in which rats and mice of each sex received doses ranging from 0-1000 mg/kg/day by corn oil gavage.

Dosed male rats showed a variety of proliferative lesions of the kidney (tubular cell hyperplasia, 0/50, 1/50, 4/50; tubular cell carcinoma, 0/50, 0/50, 2/50; tubular cell adenocarcinoma, 0/50, 3/50, 0/50; and epithelial hyperplasia of the renal pelvis, 0/50, 5/50, 5/50 in the 0, 250, and 1000 mg/kg/day, respectively). Dosed male rats also exhibited increased mineralization of the medullary collecting ducts (1/50, 31/50, 20/50 in the 0, 250, and 1000 mg/kg/day, respectively), and male rats receiving 250 mg/kg/day showed a more severe nephropathy than is commonly seen in aging F344/N rats. With the exception of a moderate increase in nephropathy, female rats did not show chemically related increased incidences of neoplastic or nonneoplastic lesions.

I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF — An uncertainty factor of 100 was used to account for the inter- and intraspecies differences. An additional UF of 10 was used to account for the use of a subchronic study. (The use of the chronic study to estimate the RfD would not evoke this latter 10-fold factor, but would necessitate a 10-fold factor for the use of a LOAEL. In either case the RfD is the same.)

MF — None

I.A.4. Additional Studies/Comments (Oral RfD)

Data Considered for Establishing the RfD

1) 90-Day Feeding - dog: Principal study - see previous description; core grade minimum

2) NTP 2-Year Bioassay - rats and mice: Co-principal study - see previous description; no core grade (NTP, 1984)

3) 90-Day Feeding - rat: Isophorone was fed in the diet to CFE weanling rats (20/sex/dose) at levels of 0, 750, 1500, and 3000 ppm (Male: 0, 57, 102.5, and 233.8 mg/kg/day; Female: 0, 78.9, 163.8, and 311.8 mg/kg/day) for 90 days. The only effect noted was decreased body weights for males in the high-dose group for several weeks. Body weights were not different from controls by the end of the study. (Note: Dosing in the 90-day rat study was in the diet [prepared weekly], but in the two principal studies animals were dosed by gavage. Since the stability of isophorone in feed has not been determined, the actual dosage levels in the 90-day rat study are unknown); (Nor-Am Agricultural Prod., Inc., 1972b)

Data Gap(s): Chronic Rat Feeding Study, Chronic Dog Feeding Study, Rat Reproduction Study, Rat Teratology Study, Rabbit Teratology Study, Mouse Oncogenicity Study

I.A.5. Confidence in the Oral RfD

Study — Medium

Database — Low

RfD — Low

The critical study is of adequate quality and is given a medium confidence rating. Since numerous data gaps exist for isophorone, the database is given a low confidence rating. Low confidence in the RfD follows.

I.A.6. EPA Documentation and Review of the Oral RfD

Source Document — U.S. EPA, 1980

The ADI in the Ambient Water Quality Criteria Document was extensively reviewed by the Agency and was reviewed by the public.

Other EPA Documentation — Pesticide Registration Files

Agency Work Group Review — 12/02/1985, 02/05/1986, 05/15/1986, 03/22/1989, 05/18/1989

Verification Date — 05/18/1989

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfD for Isophorone conducted

in August 2003 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Isophorone
CASRN — 78-59-1

The health effects data for isophorone were reviewed by the U.S. EPA RfD/RfC Work Group and determined to be inadequate for derivation of an inhalation RfC. For additional information on health effects of this chemical, interested parties are referred to the EPA documentation listed below.

U.S. EPA. 1980. Ambient Water Quality Criteria Document for Isophorone. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. NTIS PB 81-117673.

U.S. EPA. 1986. Health and Environmental Effects Profile for Isophorone. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC. NTIS PB 88-242359/AS.

Agency Work Group Review — 11/15/1990

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfC for Isophorone conducted in August 2003 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

EPA Contacts:

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Isophorone

CASRN — 78-59-1

Last Revised — 10/01/1992

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

II.A. Evidence for Human Carcinogenicity

II.A.1. Weight-of-Evidence Characterization

Classification — C; possible human carcinogen

Basis — Based on no data in humans; limited evidence of carcinogenicity of one tumor type in one sex of one animal species as shown by an increase of preputial gland carcinomas in male rats. The apparent renal tubular cell tumor in the male rat is associated with alpha-2u-globulin, considered to be of questionable relevance to humans.

II.A.2. Human Carcinogenicity Data

None.

II.A.3. Animal Carcinogenicity Data

Limited. Evidence of carcinogenicity is limited to one sex of one animal species as shown by an increased incidence of preputial gland tumors in male rats; an apparent increase in hepatocellular and integumentary tumors in male mice was complicated by high mortality. No increases were seen in females of either species.

NTP (1986) administered isophorone via corn oil gavage to F344/N rats (50/sex/group) at 0, 250 and 500 mg/kg/day, 5 days/week for 103 weeks. Preputial gland carcinomas were reported in 5 males in the high-dose group; no tumors were reported in the control or low-dose groups.

Survival of high-dose male rats (28%) was significantly reduced after 96 weeks compared with controls (66%) and low-dose males (66%). The first preputial gland tumor appeared at week 56. The tumor incidences, after adjustment for survival, were 0/49, 0/46 and 5/44 for control, low- and high- dose groups, respectively. The positive trend in tumor incidence was statistically significant by the Life Table Test. The tumor incidence in the high-dose group was statistically significantly elevated when compared with the NTP historical controls (i.e., 12/1094 as of 1986) by the Fisher Exact Test. After survival adjustment, this group differed from the concurrent control as well. The treated male rats showed renal cell hyperplasia and a small number of renal tubular cell adenomas and adenocarcinomas after week 99 when the survival rate was down to 32%. Female rats showed a moderate increase in nephropathy, with no neoplastic lesions.

Detailed review and analysis show that the isophorone induced male rat kidney tumor has met the criteria established by the U.S. EPA for associating renal tumors with alpha-2u-globulin (U.S. EPA, 1991a). The criteria were met as follows: (1) there was an increased number and size of hyaline droplets in renal proximal tubule cells of treated male rats; (2) the accumulating protein in the hyaline droplets was alpha-2u-globulin (Strasser et al., 1988); (3) additional aspects of the pathological sequence of lesions associated with alpha-2u-globulin nephropathy were present; (4) sex and species-specificity were demonstrated: the formation of renal tumors was specific to male rats; (5) there was noncovalent binding between isophorone and alpha-2u-globulin (Thier et al., 1990); and (6) the presence of isophorone decreased alpha-2u- globulin degradation (Lehman-McKeeman et al., 1990). The renal tubular cell tumor induced by isophorone in the male rat is associated with alpha-2u- globulin, a protein specific to male rats, and is, therefore, considered to have questionable relevance to humans (U.S. EPA, 1991a).

In the same study by NTP (1986), B6C3F1 mice (50/sex/group) were administered isophorone by gavage at 0, 250 and 500 mg/kg/day, 5 days/week for 2 years. Survival of male mice was very low for control and treated animals (32, 32 and 38% for control, low- and high-dose mice, respectively). Dosed male mice showed an increased frequency of coagulative necrosis and hepatocytomegaly as compared to controls. In the high-dose male mice, isophorone exposure

appeared to be associated with increased incidence of hepatocellular adenomas or carcinomas (combined incidence: control, 18/48; low-dose, 18/50; and high-dose, 29/50) and of mesenchymal tumors of the integumentary system such as fibromas, fibrosarcomas, neurofibrosarcomas or sarcomas (incidence of combined tumors: control, 6/48; low-dose, 8/50; and high-dose, 14/50). An increased incidence of lymphomas or leukemias was reported in the low-dose male mice (18/50) when compared to vehicle controls or high-dose males (8/48 and 5/50, respectively). The survival of male mice, however, was low (final rates: control, 16/50; low-dose, 16/50; and high-dose, 19/50). No significant elevation or trends for these sites was found when the data were analyzed with the Life Table Test. The survival was so low in both the treatment and control groups that the NTP and U.S. EPA consider the results in male mice to be "equivocal." No treatment-related neoplasms were observed in female mice.

II.A.4. Supporting Data for Carcinogenicity

Isophorone was not mutagenic in Salmonella/microsome assays, but a positive response was reported at moderately high concentrations (greater than or equal to 400 ug/mL) without S9 activation in the L5178Y tk+/tk- mouse lymphoma cell forward mutation assay (McGregor et al., 1988). In the absence of S9 mix, isophorone induced sister chromatid exchanges in the Chinese hamster ovary cell but chromosomal aberrations in these cells were not induced either with or without S9 mix (NTP, 1986).

II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

II.B.1. Summary of Risk Estimates

Oral Slope Factor — 9.5E-4 per (mg/kg)/day

Drinking Water Unit Risk — 2.7E-8 per ug/L

Extrapolation Method — Linearized multistage procedure, extra risk

Drinking Water Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	4E+3 ug/L

Risk Level	Concentration
E-5 (1 in 100,000)	4E+2 ug/L
E-6 (1 in 1,000,000)	4E+1 ug/L

II.B.2. Dose-Response Data (Carcinogenicity, Oral Exposure)

Tumor Type — preputial gland carcinoma

Test Animals — rat/F344/N, male

Route — oral, gavage

Reference — NTP, 1986

----- Dose -----		Tumor Incidence
Administered (mg/kg)/day	Human Equivalent (mg/kg)/day	
0	0	0/49
179	32	0/46
357	64	5/44

II.B.3. Additional Comments (Carcinogenicity, Oral Exposure)

The tumor incidences were adjusted for survival by subtracting the animals that died before the first tumor appearance at week 56 from the initial number of 50 animals in each denominator.

The human equivalent dose was determined using a surface area correction factor. The daily adjusted animal dose (i.e., the administered animal dose multiplied by 5/7 to adjust from 5 to 7 days), is divided by a ratio of the human weight (70 kg) to rat weight (0.4 kg) raised to the 1/3 power.

The unit risk should not be used if the water concentration exceeds 4E+5 ug/L, since above this concentration the slope factor may differ from that stated.

II.B.4. Discussion of Confidence (Carcinogenicity, Oral Exposure)

An adequate number of rats were observed and treated for an adequate duration of exposure at two dose levels and controls. The compound was given to the animals by gavage rather than in feed or drinking water. Exposure to a chemical by gavage can give different results than through drinking water. The crude adjustment for survival may not result in the same unit risk that would be obtained using a model also incorporating time-to-tumor, because the dose groups differed significantly in their survival experiences.

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

Not available.

II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

II.D.1. EPA Documentation

Source Document — U.S. EPA, 1991b

The 1991 Drinking Water Health Advisory for Isophorone has received Agency Review.

II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Work Group Review — 05/03/1989, 10/05/1989, 06/02/1992, 06/03/1992, 08/05/1992

Verification Date — 08/05/1992

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the cancer assessment for Isophorone conducted in August 2003 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

II.D.3. EPA Contacts (Carcinogenicity Assessment)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

III. [reserved]

IV. [reserved]

V. [reserved]

VI. Bibliography

Substance Name — Isophorone
CASRN — 78-59-1

VI.A. Oral RfD References

Nor-Am Agricultural Products, Inc. 1972a. MRID No. 00123976. Available from EPA. Write to FOI, EPA, Washington DC. 20460.

Nor-Am Agricultural Products, Inc. 1972b. MRID No. 00123977. Available from EPA. Write to FOI, EPA, Washington DC. 20460.

NTP (National Toxicology Program). 1984. NTP Technical Report on the Toxicology and Carcinogenesis Studies of Isophorone in F344/N Rats and B63F1 Mice (Gavage). NIH Publication No. 84-2547, NTP-83-168.

U.S. EPA. 1980. Ambient Water Quality Criteria Document for Isophorone. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste, Washington, DC. EPA 440/5-80-056. NTIS PB 81-117673.

VI.B. Inhalation RfC References

U.S. EPA. 1980. Ambient Water Quality Criteria Document for Isophorone. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office,

Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. NTIS PB 81-117673.

U.S. EPA. 1986. Health and Environmental Effects Profile for Isophorone. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC. NTIS PB 88-242359/AS.

VI.C. Carcinogenicity Assessment References

Lehman-McKeeman, L.D., M.I. Rivera-Torres and D. Caudill. 1990. Lysosomal degradation of a₂u-globulin and a₂u-globulin-xenobiotic conjugates. *Toxicol. Appl. Pharmacol.* 103(3): 539-548.

McGregor, D.B., A. Brown, P. Cattanaach et al. 1988. Response of the L5178Y tk⁺/tk⁻ mouse lymphoma cell forward mutation assay. III. 72 coded chemicals. *Environ. Molec. Mut.* 12: 85-154.

NTP (National Toxicology Program). 1986. Toxicology and carcinogenesis studies of isophorone (CAS No. 78-59-1) in F344/N rats and B6C3F1 mice (gavage studies). NTP TR-291. NIH Pub. No. 86-2547.

Strasser, J., Jr., M. Charbonneau, S.J. Borghoff, M.J. Turner and J.A. Swenberg. 1988. Renal protein droplet formation in male Fischer 344 rats after isophorone (IPH) treatment. *Toxicologist.* 8(1): 136.

Thier, R., H. Peter, H.J. Wiegand and H.M. Bolt. 1990. DNA binding study of isophorone in rats and mice. *Arch. Toxicol.* 64: 684-685.

U.S. EPA. 1991a. Alpha(2u)Globulin: Association with Chemically Induced Renal Toxicity and Neoplasia in the Male Rat. EPA/625/3-91/019F.

U.S. EPA. 1991b. Drinking Water Health Advisory on Isophorone. Office of Water, Washington, DC.

VII. Revision History

Substance Name — Isophorone
CASRN — 78-59-1

Date	Section	Description
06/01/1989	I.A.	Withdrawn; new Oral RfD verified (in preparation)
09/01/1989	I.A.	Oral RfD summary replaced; RfD changed
07/01/1990	II.	Carcinogen summary on-line
03/01/1991	I.B.	Inhalation RfC message on-line
10/01/1992	II.	Carcinogenicity assessment replaced; new oral quant.
10/28/2003	I.A.6., I.B., II.D.2.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — Isophorone
CASRN — 78-59-1
Last Revised — 01/31/1987

- 78-59-1
- Isoacetophorone
- Isoforon
- Isophoron
- alpha-Isophoron
- Isophorone
- alpha-Isophorone
- 3,5,5-Trimethyl-2-cyclohexenone