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16. ABSTRACT

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with specific chemicals or compounds. The Office of Emergency and Remedial Response (Superfund) uses these documents in preparing cost-benefit analyses under Executive Order 12991 for decision-making under CERCLA. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data are available. The interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed. Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval. The RfD is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan. For compounds for which there is sufficient evidence of carcinogenicity, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

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HEALTH EFFECTS ASSESSMENT FOR ISOPHORONE

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
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DISCLAIMER

This document has been reviewed in accordance with the U.S. Environmental Protection Agency's peer and administrative review policies and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with isophorone. All estimates of acceptable intake and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to May, 1986. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980a. 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. EPA 400/5-80-056. NTIS PB81-117673.

U.S. EPA. 1980b. Hazard 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, Washington, DC.

U.S. EPA. 1986a. 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.

U.S. EPA. 1986b. Integrated Risk Information System (IRIS). Reference Dose (RfD) for Oral Exposure for Isophorone. Online (verification date 11/16/86). Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincirnati, OH.

The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S (formerly AIS) or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan).

This type of exposure estimate has not been extensively used, or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for RfD_S estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure. These values are developed for both inhalation (RfD_{SI}) and oral (RfD_{SO}) exposures.

The RfD (formerly AIC) is similar in concept and addresses chronic exposure. It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980c) for a discussion of this concept]. The RfD is route-specific and estimates acceptable exposure for either oral (RfD_O) or inhalation (RfD_I) with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for identifying reportable quantities and the methodology for their development is explained in U.S. EPA (1983).

For compounds for which there is sufficient evidence of carcinogenicity RfD_S and RfD values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980c). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. For carcinogens, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

The U.S. EPA (1986a) computed a q_1^* for human oral exposure to isophorone of 4.1×10^{-3} $(mg/kg/day)^{-1}$ based on the increased incidence of kidney and preputial gland tumors in male rats in a 2-year gavage study (NTP, 1986). In the same study, increased incidence of liver tumors and tumors of the skin were observed in male mice.

No data concerning the potential carcinogenicity of isophorone following inhalation exposure were located in the literature. Therefore, an inhalation q_1^* was not calculated.

ACKNOWLEDGEMENTS

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
CAS	Chemical Abstract Service
CS	Composite score
DNA	Deoxyribonucleic acid
K_{oc}	Soil sorption coefficient
MED	Minimum effective dose
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
PEL	Permissible exposure limit
ppm	Parts per million
RfD	Reference dose
RfD_S	Subchronic reference dose
RV_d	Dose-rating value
RV_e	Effect-rating value
TLV	Threshold limit value
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTRY AND FATE

Selected chemical and physical properties and environmental fate of isophorone are presented in Table 1-1.

In the atmosphere, isophorone should exist primarily in the vapor phase and is expected to react with ozone and photochemically generated HO radical. The atmospheric half-life listed in Table 1-1 has been based on the contribution of both ozone and HO radical reactions. It is also estimated using an estimated ozone reaction rate constant of 5.0×10^{-16} cm^3/molecule-sec at 25°C, an ambient ozone concentration of 1×10^{12} molecules/cm^3, an estimated hydroxyl reaction rate constant of 8.14×10^{-11} cm^3/molecule-sec at 25°C and an ambient hydroxyl concentration of 8.0×10^5 molecule/cm^3 (U.S. EPA, 1986c). Considering its relatively high water solubility, dissolution of isophorone into clouds and removal in rainfall may be significant fate processes. The half-life of isophorone in water and soil was not located in the literature searched; however, biodegradation may be an important fate process both in water and soil (Tabar et al., 1981). Adsorption to suspended solids and sediments in water and bioaccumulation in aquatic organisms are not expected to be significant fate processes. Based on its estimated K_{oc} value of 25, isophorone should be highly mobile in soil (Swann et al., 1983) and leaching into ground water may occur.

TABLE 1-1

Selected Chemical and Physical Properties
and Environmental Fate of Isophorone

CAS number:	78-59-1	
Chemical class:	unsaturated monocyclic ketone	
Molecular weight:	138.2	
Vapor pressure:	0.38 mm Hg at 20°C 0.44 mm Hg at 25°C	Verschueren, 1983 U.S. EPA, 1980a
Water solubility:	12.000 mg/ℓ at 20°C	U.S. EPA, 1976
Log octanol/water partition coefficient:	2.22 (estimated) 1.7 (estimated)	U.S. EPA, 1986b Callahan et al., 1979
Bioconcentration factor:	7, bluegill sunfish (Lepomis macrochirus)	U.S. EPA, 1980a
Soil adsorption coefficient:	25 (estimated)	Lyman et al., 1982
Half-lives:		
Air	32 minutes (estimated)	U.S. EPA, 1986c
Water	NA	NA
Soil	NA	NA

NA = Not available

2. ABSORPTION IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

Quantitative data regarding the absorption of isophorone from the oral route of administration could not be located in the available literature. Isophorone is absorbed by the gastrointestinal tracts of rats and rabbits as indicated in a study by Dutertre-Catella et al. (1978), where unchanged isophorone and metabolites were detected in the urine of rats and rabbits 24 hours after oral dosing with isophorone.

2.2. INHALATION

Quantitative data regarding the absorption of isophorone from the inhalation route could not be located in the available literature. Absorption of isophorone after inhalation can be inferred from studies by Smyth et al. (1942) and Hazelton Labs, Inc. (1968) that show systemic toxicity following inhalation exposure to isophorone.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. AME, Inc. (1972a) fed groups of 20 male and 20 female CFE weanling rats isophorone in their diets at 0, 750, 1500 or 3000 ppm for 90 days (TWA doses of 0, 61.1, 123.1 or 250.5 mg/kg/day, males; 0, 82.7, 170.4 or 323.8 mg/kg/day, females). The only effect observed was a significant ($p<0.01$) decrease in mean body weight gain after 6 weeks in males receiving 250.5 mg/kg/day. The parameters examined were appearance, behavior, hematology, clinical chemistry, urinalysis, organ weights, and gross and histopathological examination of major organs.

AME, Inc. (1972b) dosed groups of four male and four female beagle dogs orally with isophorone in gelatin capsules at 0, 35, 75 or 150 mg/kg/day for 7 days/week for 90 days. Dogs treated with 75 or 150 mg/kg/day had soft and loose stools. No effects on appearance, behavior, hematology, clinical chemistry, urinalysis, organ weights and pathology of organs were noted at any dose level.

NTP (1986) conducted a 13-week study, in which groups of 10 male and 10 female Fischer 344/N rats and equal numbers of B6C3F1 mice received isophorone in corn oil by gavage. Rats and mice received doses of 0, 62.5, 125, 500 or 1000 mg/kg/day, 5 days/week. Histopathological examination was performed only on controls and high-dose rats and mice. Rats treated with 1000 mg/kg/day were lethargic after dosing. In addition, deaths of one female rat and three female mice at 1000 mg/kg/day were considered to be compound-related. There were no effects or gross appearance at necropsy or histological appearance of a comprehensive selection of organs and tissues from high-dose rats and mice, when compared with controls.

3.1.2. Inhalation. In a study by Hazelton Labs, Inc. (1968), groups of 10 male and 10 female young adult Charles River CD rats were exposed to isophorone at average daily air concentrations of 0 or 0.208 mg/ℓ (208 mg/m³), 6 hours/day, 5 days/week for 4 weeks. The effects observed in the exposed rats were transient nasal bleeding, increased percentages of lymphocytes, decreased percentages of neutrophils and increased hemoglobin concentration in males and females. Significantly lower terminal body weights and significantly decreased absolute and relative liver weights of exposed males, as compared with controls, were also observed.

An earlier subchronic inhalation study, using commercial samples of isophorone, with rats and guinea pigs, was conducted by Smyth et al. (1942). The U.S. EPA (1980a) has stated that if pure isophorone had been used in this study, the air concentrations of isophorone reported by Smyth et al. (1942) could not have been attained under the conditions employed. Because the results of the Smyth et al. (1942) study are seriously compromised, details of this study will not be reviewed here. Effects observed in rats and guinea pigs exposed to isophorone at unspecified concentrations were pale or brown kidneys, pale livers, congested spleens and lungs, and discolored bile.

3.2. CHRONIC

3.2.1. Oral. In the NTP (1986) study, groups of 50 male and 50 female F344 rats and equal numbers of B6C3F1 mice were dosed with 0, 250 or 500 mg/kg isophorone in corn oil by gavage, 5 days/week for 103 weeks. During the study, body weights were recorded and clinical signs were noted. At 103 weeks, survivors were necropsied, organs were examined for gross lesions and examined microscopically. Tumor incidences are presented in Section 4.2.1.

In rats, mean body weights of high-dose males averaged ~5% lower than vehicle controls after 1 week. Mean body weights of high-dose females averaged ~8% lower than vehicle controls after week 43. No compound-related clinical signs were noted. Survival of the high-dose group of male rats was significantly lower than vehicle controls after 196 weeks.

In the kidneys of dosed male rats, tubular cell mineralization was increased. This lesion, characterized by basophilic aggregates of mineral, was often found in medullary collecting ducts and occurred coincidentally with lesions of chronic nephropathy. Fatty metamorphosis of the adrenal cortex was observed to increase in dosed male but not female rats; this lesion was most often observed in the zona fasciculata.

In mice, mean body weights of high-dose females averaged 5% lower than vehicle controls during the second year of the study. No body weight differences were noted between male treated and control mice. No compound-related clinical signs were noted. Survival of treated female mice was significantly ($p<0.005$) greater than vehicle controls. In males, survival was adversely affected by fighting. Histopathological examination of the kidneys of male mice revealed a dose-related increase in chronic focal inflammation.

3.2.2. Inhalation. Ware (1973) indicated that workers exposed to isophorone at levels of 5-8 ppm for 1 month complained of fatigue and malaise. When levels were reduced to 1-4 ppm, the complaints ceased.

Further information regarding the effects of chronic inhalation exposure to isophorone could not be located in the available literature.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. No pertinent data regarding teratogenic and reproductive effects after oral exposure were located in the available literature.

3.3.2. Inhalation. The CMA sponsored two inhalation teratogenicity studies. In the first study, groups of 12 pregnant Fischer 344 rats and 12 CD1 mice were exposed to isophorone at 0, 50, 100 or 150 ppm (0, 141, 283 or 848 mg/m^3) 6 hours/day, on days 6-15 of gestation (Bio Dynamics, Inc., 1984). The animals were weighed and examined externally on gestation days 3, 6, 9, 12 and 16. On day 16, the animals were killed, the number of live and dead fetuses were counted and the fetuses were examined for abnormalities.

The results indicated no consistent changes in body weights of dams. Food consumption for rats exposed to 150 ppm isophorone was lower than food consumption for controls. Food consumption for mice was not reported. Signs of toxicity observed in rat dams, especially those exposed to 100 and 150 ppm, were alopecia, excessive lacrimation, yellow stains in the ano-genital area and tan, yellow or red material around the mouth, eyes or lower jaw. At least one of these signs was observed in all rats exposed to 100 or 150 ppm isophorone. Similar toxic signs were observed in only two mice exposed to 100 ppm and two mice exposed to 150 ppm isophorone. The only fetal effect noted in rats was a late resorption in one 150 ppm litter in which one rat had brain tissue protruding from the cranium. In mice, exencephaly was observed in two 150 ppm litters. In one of those litters exencephaly was observed in a later resorption, and in the other litter, the same abnormality was observed in two live fetuses. No abnormalities were observed in control litters.

3.4. TOXICANT INTERACTION

Smyth et al. (1969, 1970) studied the toxicity of all possible pairs of 27 industrial chemicals, including isophorone. Female albino rats were given the chemicals by gavage and LD_{50}s were determined. Isophorone, paired with the other chemicals, did not cause the LD_{50} to deviate greatly from predicted.

4. CARCINOGENICITY

4.1. HUMAN DATA

Pertinent data concerning carcinogenicity of isophorone in humans by either oral or inhalation routes could not be located in the available literature.

4.2. BIOASSAYS

4.2.1. Oral. In an NTP (1986) study, groups of 50 male and 50 female Fischer 344/N rats and equal numbers of B6C3F1 mice were treated by gavage with isophorone (94-97% pure) in corn oil at doses of 250 or 500 mg/kg/day, 5 days/week for 103 weeks. Control groups of rats and mice received corn oil. At 105 weeks, surviving animals were sacrificed; complete necropsies and comprehensive histological examinations were performed on all rats and mice that died during the study (unless precluded by advanced autolysis or cannibalism), that were moribund and killed during the study or that were killed at the end of the study.

After 96 weeks,the survival of the high-dose male rats was significantly reduced. This decline occurred late enough in the study so that late developing tumors could be detected. Results (Table 4-1) showed that male rats had an increased incidence (adjusted for intercurrent mortality) of tubular cell adenoma or adenocarcinoma (combined) of the kidney. These effects on the kidney were significant for the high-dose group by the life table test and significant for dose-related trend by the life table and incidental tumor tests, but not significant by the Cochran-Armitage or Fisher Exact tests. The occurrence of kidney tumors is noteworthy in that kidney tumors are rarely observed in this strain of rats; comparison of incidence in the low-dose group and high-dose group with historical controls (0.4%) showed a significant increase ($p=0.002$) by the Fisher Exact test.

TABLE 4-1

Carcinogenic Potency of Isophorone (94-97% pure) in Corn Oil Orally Administered to Male Fischer 344/N Rats and Male B6C3F1 Mice[a]

Species	Dose[b] (mg/kg/day)	Duration of Treatment (weeks)	Duration of Study (weeks)	Target Organ	Tumor Type	Tumor Incidence[c]	Cochran-Armitage and Fisher Exact (p value)
Rat	0	103	105	kidney	tubular cell	0/50	0.101
	250				adenoma or	3/50	0.121
	500				adenocarcinoma	3/50	0.121
Rat	0	103	105	preputial gland	carcinoma	0/50	0.006[d]
	250					0/50	--
	500					5/50	0.028[e]
Mouse	0	103	105	liver	hepatocellular	18/48	0.025[d]
	250				adenoma or	18/50	0.522
	500				carcinoma	29/50	0.033[e]
Mouse	0	103	105	integumentary	fibroma, sarcoma	6/48	0.033[d]
	250			system	fibrosarcoma or	8/50	0.419
	500				neurofibrosarcoma	14/50	0.048[e]
Mouse	0	103	105	hematopoietic	malignant	7/48	0.316
	250			system	lymphoma	18/50	0.013
	500					5/50	0.351

[a]Source: NTP, 1986

[b]Dosing 5 days/week

[c]Number of animals with tumors/number of animals examined at this site

[d]Statistically significant for positive trend by the Cochran-Armitage test

[e]Incidence compared with matched controls, statistically significant by the Fisher Exact test

In male rats, the increased incidence of carcinoma of the preputial gland showed a significant dose-related trend by all statistical methods. Tumors of this type have been observed at a very low incidence (12/1094) in historical corn oil vehicle control rats; therefore NTP (1986) stated that carcinoma of the preputial gland may be compound-related. A significantly higher incidence of acinar cell carcinoma of the pancreas was also observed in the high-dose male rats as compared with controls. Because the historical incidence of acinar cell tumors in corn oil treated rats is relatively high, NTP (1986) suggested that isophorone was possibly acting as a co-carcinogen or promotor of the effect of corn oil. There were no significantly increased incidences of tumors observed in female rats. From the results of this study, NTP (1986) concluded that there was some evidence of carcinogenicity in rats as a result of the increased incidence of renal tubular cell adenomas and adenocarcinomas in male rats treated with 250 or 500 mg/kg/day and of the increased incidence of preputial gland carcinomas in males treated with 500 mg/kg/day.

Results in male mice (see Table 4-1) showed an increase in the incidence of hepatocellular adenoma or carcinoma (combined), and an increase in fibromas, sarcomas, fibrosarcomas or neurofibrosarcomas (combined) of the integumentary system as compared with controls. These increases were significant when analyzed by the incidental tumor, the Cochran-Armitage and the Fisher Exact tests. The incidence of lymphoma in male mice was increased significantly in the low-dose group, but not in the high-dose group. There were no significant increases in tumor incidence observed in female mice. From these results, NTP (1986) concluded that there was equivocal evidence of carcinogenicity in male mice.

4.2.2. Inhalation. No pertinent data regarding the carcinogenicity of isophorone after inhalation exposure were located in the available literature.

4.3. OTHER RELEVANT DATA

Isophorone has been examined for mutagenicity and genotoxicity by CMA (1984) and NTP (1986). Isophorone was negative in reverse mutation assays, with and without S-9 metabolic activation, using Salmonella typhimurium TA100, TA1535, TA1537 and TA98 (NTP, 1986). CMA (1984) found isophorone to be negative in a forward mutation assay using L5178Y/TK$^{+/-}$ mouse lymphoma cells in the presence and absence of S-9 metabolic activation at concentrations of 0.06-9 µg/mℓ. At higher concentrations (400-1200 mg/mℓ), NTP (1986) found a slightly positive response in the absence of S-9 in the mouse lymphoma assay. Isophorone was negative in the micronucleus test in male and female mice, for unscheduled DNA synthesis in rat primary hepatocytes (CMA, 1984) and for chromosome aberrations in Chinese hamster ovary cells with and without S-9 metabolic activation (NTP, 1986). NTP (1986) found a positive response for sister chromatid exchange in Chinese hamster ovary cells in the absence of S-9.

4.4. WEIGHT OF EVIDENCE

The NTP (1986) study is the only available one concerning the carcinogenicity of isophorone. In this study, kidney tumors and preputial gland carcinomas in male rats and hepatic and integumentary system tumors in male mice showed a significant increase above controls. This evidence is sufficient to place isophorone in IARC Group C and, according to the EPA classification scheme (U.S. EPA, 1986d), isophorone can be placed in Group C, Possible Human Carcinogen.

5. REGULATORY STANDARDS AND CRITERIA

The interim ambient water quality criteria is 5.2 mg/ℓ (U.S. EPA, 1980a). This value is based on an oral ADI of 0.15 mg/kg/day that was calculated from a 90-day study using dogs that determined a NOAEL of 150 mg/kg/day (U.S. EPA, 1980a). This criterion was based on ingestion of 2 ℓ of water and 6.5 g of fish and shellfish/day.

NIOSH (1978) has recommended a PEL for isophorone of 4 ppm (23 mg/m^3) as a TWA concentration for up to a 10-hour workshift. The ACGIH (1986) ceiling limit is 5 ppm (~25 mg/m^3) for occupational exposure. Both the NIOSH PEL and ACGIH ceiling limit are based on a report by Ware (1973), which indicates that workers at Western Electric Co. complained of fatigue and malaise at 5-8 ppm (28-45 mg/m^3) but not at 1-4 ppm (6-23 mg/m^3). The OSHA standard for occupational exposure to isophorone is 25 ppm (140 mg/m^3) as an 8-hour TWA concentration limit in workroom air (OSHA, 1981).

The Federal Food, Drug and Cosmetic Act exempts isophorone from the requirement of a tolerance when it is used as a solvent and cosolvent for pesticide formulation used before crops emerge from soil, and for post-emergent use on rice before the rice begins to head, and on sugar and table beets (U.S. EPA, 1974).

6. RISK ASSESSMENT

6.1. SUBCHRONIC REFERENCE DOSE (RfD_S) AND REFERENCE DOSE (RfD)

Isophorone has been shown to be a carcinogen in animals; therefore, it is not appropriate for the purposes of this document to derive acceptable intake values.

6.2. CARCINOGENICITY POTENCY (q_1^*)

6.2.1. Oral. In a recent U.S. EPA (1986a) analysis, a q_1^* has been calculated using the data from the NTP (1986) study, which showed an increase in kidney tubular cell adenomas and carcinomas and preputial gland carcinomas in male rats, and in liver and integumentary system tumors in male B6C3F1 mice. Although the increased incidence of tumors in the male mice was statistically significant, the incidence of liver tumors in male mice may be highly variable and judged by NTP (1986) to represent "equivocal" evidence of carcinogenicity. NTP (1986) judged the incidence of kidney and preputial gland tumors in treated male rats to represent "some evidence of carcinogenicity" because of the absence of these tumors in matched contemporary controls and the very low incidence in historical controls. The U.S. EPA (1986a) combined the incidences of kidney and preputial gland tumors in male rats to calculate a human q_1^* for oral exposure to isophorone of 4.1×10^{-3} mg/kg/day, using the multistage model of Howe and Crump (1982). The data used in this computation are presented in Table 6-1.

6.2.2. Inhalation. No pertinent data concerning the potential carcinogenicity of isophorone were located in the literature; therefore, an inhalation q_1^* will not be calculated.

TABLE 6-1

Cancer Data Sheet for Derivation of q_1^*

Compound: isophorone

Reference: NTP, 1986

Species/strain/sex: rat, Fischer 344/N, male

Route/vehicle: gavage, corn oil

Length of exposure (le) = 103 weeks

Length of experiment (LE) = 105 weeks

Lifespan of animal (L) = 105 weeks

Body weight = 0.40 kg (measured)

Tumor site and type: kidney (tubular cell) adenoma or carcinoma; preputial gland carcinoma

Experimental Doses or Exposures (mg/kg/day, 5 days/week)	Transformed Dose (mg/kg/day)	Incidence No. Responding/No. Examined
0	0	0/48
250	175	3/50
500	350	8/50

Unadjusted $q_1^* = 7.33 \times 10^{-4}$ $(mg/kg/day)^{-1}$

Human $q_1^* = 4.1 \times 10^{-3}$ $(mg/kg/day)^{-1}$

7. REFERENCES

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APPENDIX

Oral Summary Table for Isophorone in the Male Rat*

Experimental Exposure	Effect	q_1*
0, 250, 500 mg/kg/day, 5 days/week for 103 weeks	kidney (tubular cell) adenoma or carcinoma and preputial gland carcinoma	4.1×10^{-3}

*Source: NTP, 1986; U.S. EPA, 1986a