Acenaphthene; CASRN 83-32-9 (11/01/90)

Health risk assessment information on a chemical is included in IRIS only after a comprehensive review of chronic toxicity data by work groups composed of U.S. EPA scientists from several Program Offices. The summaries presented in Sections I and II represent a consensus reached in the review process. The other sections contain U.S. EPA information which is specific to a particular EPA program and has been subject to review procedures prescribed by that Program Office. The regulatory actions in Section IV may not be based on the most current risk assessment, or may be based on a current, but unreviewed, risk assessment, and may take into account factors other than health effects (e.g., treatment technology). When considering the use of regulatory action data for a particular situation, note the date of the regulatory action, the date of the most recent risk assessment relating to that action, and whether technological factors were considered. Background information and explanations of the methods used to derive the values given in IRIS are provided in the five Background Documents in Service Code 5, which correspond to Sections I through V of the chemical files.

STATUS OF DATA FOR Acenaphthene

File On-Line 11/01/90

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	11/01/90
Inhalation RfC Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	no data	
Drinking Water Health Advisories (III.A.)	no data	
U.S. EPA Regulatory Actions (IV.)	no data	
Supplementary Data (V.)	no data	

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_I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

__I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name -- Acenaphthene
CASRN -- 83-32-9
Last Revised -- 11/01/90

The Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. 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 Background Document 1 in Service Code 5 for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of compounds which 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 when a review of that evaluation is completed.

<<< Acenaphthene >>>

___I.A.1. ORAL RfD SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfD
Hepatotoxicity	NOAEL: 175 mg/kg/day	3000	1	6E-2 mg/kg/day
Mouse Oral Subchronic Study	LOAEL: 350 mg/kg/day			
U.S. EPA, 1989				

*Conversion Factors: None

<<< Acenaphthene >>>

___I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

U.S. EPA. 1989. Mouse oral subchronic study with acenaphthene. Study conducted by Hazelton Laboratories, Inc., for the Office of Solid Waste, Washington, DC.

Four groups of CD-1 mice (20/sex/group) were gavaged daily with 0, 175, 350, or 700 mg/kg/day acenaphthene for 90 days. The toxicological evaluations of this study included body weight changes, food consumption, mortality, clinical pathological evaluations (includings hematology and clinical chemistry), organ weights and histopathological evaluations of target organs. The results of this study indicated no treatment-related effects on survival, clinical signs, body weight changes, total food intake, and ophthalmological alterations. Liver weight changes accompanied by microscopic alterations (cellular hypertrophy) were noted in both mid- and high-dose animals and seemed to be dose-dependent. Additionally, high-dose males and mid- and high-dose females showed significant increases in cholesterol levels. Although increased liver weights, without accompanying microscopic alterations or increased cholesterol levels, were also observed at the low dose, this change was considered to be adaptive and was not considered adverse. The LOAEL is 350 mg/kg/day based on hepatotoxicity); the NOAEL is 175 mg/kg/day.

<<< Acenaphthene >>>

___I.A.3. UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

UF = 3000. An uncertainty factor of 3000 reflects 10 each for inter- and intraspecies variability, 10 for the use of a subchronic study for chronic RfD derivation, and 3 for the lack of adequate data in a second species and reproductive/developmental data.

MF = 1.

<<< Acenaphthene >>>

___I.A.4. ADDITIONAL COMMENTS (ORAL RfD)

Reshetyuk et al. (1970) examined the comparative toxicity of acenaphthene and acenaphthylene with respect to naphthalene. On intraperitoneal administration in rats (species/number/sex unspecified), naphthalene was more toxic than acenaphthene and acenaphthylene. Two LD\50? values (0.6 and 1.7 g/kg) were reported, but it is unclear to which of the three chemicals these values belonged. Intraperitoneal and intratracheal administration of naphthalene, acenaphthene, and acenaphthylene produced monotypic effects in the form of vascular disorders, and degeneration in the internal organs and central nervous system. Inflammatory changes were also observed in the lungs; the degree was the same for all three substances. Splenic degeneration was noted among the unscheduled deaths in this study. Reshetyuk et al. (1970) concluded that chronic inhalation of acenaphthene and acenaphthylene had more pronounced toxic effects than naphthalene.

Gershbein (1975) exposed partially hepatectomized rats to 15 mg/kg acenaphthene in the diet for 7 days. The only parameters used to assess toxicity were body weight, absolute liver weight, and liver regeneration. Information on histopathologic alterations and food intake is needed to evaluate the adversity of decreased body weight gain and increased liver weight observed in this study. Increased liver regeneration was reported. Because of its inherent deficiencies, this study is not considered adequate for RfD derivation.

Knobloch et al. (1969) administered 2 g/kg acenaphthene orally to rats and mice for 32 days. Weight loss and mild histopathological alterations in the liver and kidney were observed. It is unclear whether experimental controls were used.

<<< Acenaphthene >>>

___I.A.5. CONFIDENCE IN THE ORAL RfD

Study: Low
Data Base: Low
RfD: Low

Confidence in the study is low, because the observed effects were adaptive and not considered adverse. Confidence in the data base is low because of the lack of supporting chronic toxicity and developmental/reproductive studies. Low confidence in the RfD follows.

<<< Acenaphthene >>>

___I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

Source Document -- This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation -- U.S. EPA, 1980

Agency Work Group Review: 11/15/89

Verification Date: 11/15/89

___I.A.7. EPA CONTACTS (ORAL RfD)

Harlal Choudhury / ORD -- (513)569-7536 / FTS 684-7536

Kenneth A. Poirier / ORD -- (513)569-7462 / FTS 684-7462

__I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

Substance Name -- Acenaphthene
CASRN -- 83-32-9

Not available at this time.

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_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Acenaphthene
CASRN -- 83-32-9

This substance/agent has not been evaluated by the U.S. EPA for evidence of human carcinogenic potential.

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_III. HEALTH HAZARD ASSESSMENTS FOR VARIED EXPOSURE DURATIONS

__III.A. DRINKING WATER HEALTH ADVISORIES

Substance Name -- Acenaphthene
CASRN -- 83-32-9

Not available at this time.

__III.B. OTHER ASSESSMENTS

Substance Name -- Acenaphthene
CASRN -- 83-32-9

Content to be determined.

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_IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- Acenaphthene
CASRN -- 83-32-9

Not available at this time.

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_V. SUPPLEMENTARY DATA

Substance Name -- Acenaphthene
CASRN -- 83-32-9

Not available at this time.

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_VI. BIBLIOGRAPHY

Substance Name -- Acenaphthene
CASRN -- 83-32-9
Last Revised -- 11/01/90

__VI.A. ORAL RfD REFERENCES

Gershbein, L.L. 1975. Liver regeneration as influenced by the structure of aromatic and heterocyclic compounds. Res. Commun. Chem. Pathol. Pharmacol. 11: 445.

Knobloch, K., S. Szendzikowski and A. Slusarczyk-Zalobona. 1969. Acute and subacute toxicity of acenaphthene and acenaphthylene. Med. Pracy. 20: 210-222. (Pol.) (Cited in U.S. EPA, 1980)

Reshetyuk, A.L, E.I. Talakina and P.A. En'yakova. 1970. Toxicological evaluation of acenaphthene and acenaphthylene. Gig. Tr. Prof. Zabol. 14: 46-47.

U.S. EPA. 1980. Ambient Water Quality Criteria Document for Acenaphthene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulation and Standards, Washington, DC. EPA-440/5-80-015. NTIS PB81-117269.

U.S. EPA. 1989. Mouse Oral Subchronic Study with Acenaphthene. Study conducted by Hazelton Laboratories, Inc., for the Office of Solid Waste, Washington, DC.

---------<<< Acenaphthene >>>---------

__VI.B. INHALATION RfC REFERENCES

None

---------<<< Acenaphthene >>>---------

__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

None

---------<<< Acenaphthene >>>---------

__VI.D. DRINKING WATER HA REFERENCES

None

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SYNONYMS

Substance Name -- Acenaphthene
CASRN -- 83-32-9
Last Revised -- 11/01/90

83-32-9
Acenaphthylene, 1,2-dihydro-
Acenaphthene
HSDB 2659
Naphthyleneethylene
NSC 7657
PERI-ETHYLENENAPHTHALENE
1,2-DIHYDROACENAPHTHYLENE
1,8-ETHYLENENAPHTHALENE

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1 Occurrences...

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Sullivan's Ledge
3.9.2 (AM)
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STATUS OF DATA FOR Acetone

File On-Line 03/31/87

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	03/01/88
Inhalation RfC Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	on-line	07/01/90
Drinking Water Health Advisories (III.A.)	no data	
U.S. EPA Regulatory Actions (IV.)	on-line	07/01/90
Supplementary Data (V.)	no data	

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I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name -- Acetone
CASRN -- 67-64-1
Last Revised -- 03/01/88

The Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. 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 Background Document 1 in Service Code 5 for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of compounds which 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 when a review of that evaluation is completed.

<<< Acetone >>>

I.A.1. ORAL RfD SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfD
Increased liver and	NOEL: 100 mg/kg/day	1000	1	1E-1

kidney weight and nephrotoxicity | LOAEL: 500 mg/kg/day | mg/kg/day

Rat Oral Subchronic Study

U.S. EPA, 1986

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*Conversion Factors: none

<<< Acetone >>>

___I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

U.S. EPA. 1986. Ninety-day gavage study in albino rats using acetone. Office of Solid Waste, Washington, DC.

Acetone was evaluated for potential toxicity following administration by oral gavage for 90 days to groups of albino rats (30/sex/group) at levels of 0, 100, 500 or 2500 mg/kg/day. Body weights, food consumption, clinical chemistry, hematology, and histopathologic parameters, as well as organ weights and organ-to-body weight ratios, were measured and analyzed. Animals were sacrificed after 30 and 90 days of exposure. No effects were seen at the 100 mg/kg/day dose level throughout the study. RBC parameters were significantly increased in the 2500 mg/kg group at 30 days (males only) and at 90 days in males and females. Statistical analysis of the organ weight and ratio data revealed significantly increased kidney weights for females in 500 and 2500 mg/kg groups and increased kidney-to-body and brain weight ratios for males and females in the 2500 mg/kg groups. Liver weight and liver/body weight ratios were also increased in the 2500 mg/kg males and females. Histopathologic studies revealed a marked increase in severity in tubular degeneration of the kidneys and hyaline droplet accumulation with increasing doses. This accumulation was significant in the 500 and 2500 mg/kg males and the 2500 mg/kg females.

Based on the above findings, an animal NOEL of 100 mg/kg/day and a LOAEL of 500 mg/kg/day were established. Using the animal NOEL of 100 mg/kg/day and applying an uncertainty factor of 1000, an RfD of 0.1 mg/kg/day (7.0 mg/day for a 70-kg human) for acetone can be calculated.

<<< Acetone >>>

___I.A.3. UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

UF = 1000. An uncertainty factor of 1000 is used; 100 for inter- and intraspecies extrapolation and 10 to extrapolate from subchronic to chronic exposure.

MF = 1.

<<< Acetone >>>

___I.A.4. ADDITIONAL COMMENTS (ORAL RfD)

Limited human studies have shown that workers exposed to acetone vapors (600 to 2150 ppm) experienced transient eye and nose irritation. Animals exposed to acetone vapors at 45,134 mg/cu.m experienced slight, but not significant, decreases in organ and body weights.

<<< Acetone >>>

___I.A.5. CONFIDENCE IN THE ORAL RfD

Study: Medium
Data Base: Low
RfD: Low

Confidence in the principal study is rated medium, since a moderate number of animals/dose/sex and an extensive number of parameters were measured. The data base is rated low because a very limited number of studies are available and no pertinent supporting studies were located. The overall confidence rating for the RfD is low.

<<< Acetone >>>

___I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

The only U.S. EPA documentation at present is on IRIS.

Agency RfD Work Group Review: 12/18/85, 05/30/86

Verification Date: 05/30/86

___I.A.7. EPA CONTACTS (ORAL RfD)

Christopher T. DeRosa / ORD -- (513)569-7534 / FTS 684-7534

Michael L. Dourson / ORD -- (513)569-7544 / FTS 684-7544

__I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

Substance Name -- Acetone
CASRN -- 67-64-1

Not available at this time.

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_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Acetone
CASRN -- 67-64-1
Last Revised -- 07/01/90

Section II provides information on three aspects of the carcinogenic risk assessment for the agent in question; the U.S. EPA classification, and quantitative estimates of risk from oral exposure and from inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen. 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. Background Document 2 (Service Code 5) provides details on the rationale and methods used to derive the carcinogenicity values found in IRIS. Users are referred to Section I for information on long-term toxic effects other than carcinogenicity.

<<< Acetone >>>

II.A. EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

II.A.1. WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification -- D; not classifiable as to human carcinogenicity

Basis -- Based on lack of data concerning carcinogenicity in humans or animals.

<<< Acetone >>>

II.A.2. HUMAN CARCINOGENICITY DATA

None.

<<< Acetone >>>

II.A.3. ANIMAL CARCINOGENICITY DATA

None.

<<< Acetone >>>

II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Acetone did not show mutagenic activity when tested in Salmonella typhimurium strains TA98 and TA100 or in Schizosaccharomyces pombe strain P1 both in the presence and absence of liver homogenates (McCann et al., 1975; Abbondandolo et al., 1980; Maron et al., 1981; Hallstrom et al., 1981) or in cell transformation systems (Freeman et al., 1973; Rhim et al., 1974; Quarles et al., 1979a,b). Furthermore, acetone gave negative results in assays that

tested for chromosomal aberrations and sister chromatid exchange (Norppa et al., 1981; Norppa, 1981; Tates and Kriek, 1981), DNA binding (Kubinski et al., 1981), point mutation in mouse lymphoma cells (Amacher et al., 1980), and transfection of E. coli CR63 cells (Vasavada and Padayatty, 1981). In one study, however, acetone was reported to produce chromosomal aberrations but not sister chromatid exchanges (Kawachi et al., 1980).

---------<<< Acetone >>>---------

__II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

None.

---------<<< Acetone >>>---------

__II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

None.

---------<<< Acetone >>>---------

__II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

___II.D.1. EPA DOCUMENTATION

U.S. EPA. 1988. Updated Health Effects Assessment for Acetone. 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.

<<< Acetone >>>

___II.D.2. REVIEW (CARCINOGENICITY ASSESSMENT)

The 1988 updated Health Effects Document for Acetone has received Agency review and is approved for publication.

Agency Work Group Review: 12/06/89

Verification Date: 12/06/89

___II.D.3. U.S. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

Charles Ris / ORD -- (202)382-5895 / FTS 382-5898

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_III. HEALTH HAZARD ASSESSMENTS FOR VARIED EXPOSURE DURATIONS

__III.A. DRINKING WATER HEALTH ADVISORIES

Substance Name -- Acetone
CASRN -- 67-64-1

Not available at this time.

__III.B. OTHER ASSESSMENTS

Substance Name -- Acetone
CASRN -- 67-64-1

Content to be determined.

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_IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- Acetone
CASRN -- 67-64-1
Last Revised -- 07/01/90

EPA risk assessments may be updated as new data are published and as assessment methodologies evolve. Regulatory actions are frequently not updated at the same time. Compare the dates for the regulatory actions in this section with the verification dates for the risk assessments in sections I and II, as this may explain inconsistencies. Also note that some regulatory actions consider factors not related to health risk, such as technical or economic feasibility. Such considerations are indicated for each action. In addition, not all of the regulatory actions listed in this section involve enforceable federal standards. Please direct any questions you may have concerning these regulatory actions to the U.S. EPA contact listed for that particular action. Users are strongly urged to read the background information on each regulatory action in Background Document 4 in Service Code 5.

<<< Acetone >>>

__IV.A. CLEAN AIR ACT (CAA)

No data available

---------<<< Acetone >>>---------

__IV.B. SAFE DRINKING WATER ACT (SDWA)

No data available

---------<<< Acetone >>>---------

__IV.C. CLEAN WATER ACT (CWA)

No data available

---------<<< Acetone >>>---------

__IV.D. FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT (FIFRA)

No data available

---------<<< Acetone >>>---------

__IV.E. TOXIC SUBSTANCES CONTROL ACT (TSCA)

No data available

---------<<< Acetone >>>---------

__IV.F. RESOURCE CONSERVATION AND RECOVERY ACT (RCRA)

___IV.F.1. RCRA APPENDIX IX, for Ground Water Monitoring

Status -- Listed

Reference -- 52 FR 25942 (07/09/87)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)382-3000 / FTS 382-3000

---------<<< Acetone >>>---------

__IV.G. SUPERFUND (CERCLA)

___IV.G.1. REPORTABLE QUANTITY (RQ) for Release into the Environment

Value (status) -- 5000 pounds (Final, 1985)

Considers technological or economic feasibility? -- NO

Discussion -- The final adjusted RQ for acetone is 5000 pounds, based on the application of the secondary criterion of biodegradation to the primary criteria RQ of 1000 pounds, determined by ignitability. Available data indicate a flash point of -4F and a boiling point of 133F, which corresponds to an RQ of 1000 pounds. The final RQ takes biodegradation into account, since acetone biodegrades when released into the environment. The biological oxygen deman for 5 days (BOD5) is 46-55%.

Reference -- 50 FR 13456 (04/04/85)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)382-3000 / FTS 382-3000

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_V. SUPPLEMENTARY DATA

Substance Name -- Acetone
CASRN -- 67-64-1

Not available at this time.

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_VI. BIBLIOGRAPHY

Substance Name -- Acetone
CASRN -- 67-64-1
Last Revised -- 07/01/90

__VI.A. ORAL RfD REFERENCES

U.S. EPA. 1986. Ninety-day gavage study in albino rats using acetone. Office of Solid Waste, Washington, DC.

---------<<< Acetone >>>---------

__VI.B. INHALATION RfD REFERENCES

None

---------<<< Acetone >>>---------

__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

Abbondandolo, A., S. Bonatti, C. Corsi, et al. 1980. The use of organic solvents in mutagenicity testing. Mutat. Res. 79: 141-150.

Amacher, D.E., S.C. Paillet, G.N. Turner, V.A. Ray and D.S. Salsburg. 1980. Point mutations at the thymidine kinase locus in L5178Y mouse lymphoma cells. 2. Test validation and interpretation. Mutat. Res. 72: 447-474.

Freeman, A.E., E.K. Weisburger, J.H. Weisburger, R.G. Wolford, J.M. Maryak and R.J. Huebner. 1973. Transformation of cell cultures as an indication of the carcinogenic potential of chemicals. J. Natl. Cancer Inst. 51(3): 799-808.

Hallstrom, I., A. Sundvall, U. Rannug, R. Grafstrom and C. Ramel. 1981. The metabolism of drugs and carcinogens in isolated subcellular fractions of Drosophila melangaster. I. Activation of vinyl chloride, 2-amnioanthrecene and benzo(a)pyrene as measured by mutagenic effects in Salmonella typhimurium. Chem. Biol. Inter. 34: 129-143.

Kawachi, T., T. Yahagi, T. Kada et al. 1980. Cooperative programme on short-term assays for carcinogenicity in Japan. In: Molecular and Cellular Aspects of Carcinogen Screening Tests. R. Montesano, ed. WHO, IARC, Lyon, France. p. 323-330.

Kubinski, H., G.E. Gutzke and Z.O. Kubinski. 1981. DNA-cell-binding (DCB) assay for suspected carcinogens and mutagens. Mutat. Res. 89: 95-136.

Maron, D., J. Katzenellenbogen and B.N. Ames. 1981. Compatability of organic solvents with the Salmonella/microsome test. Mutat. Res. 88: 343-350.

McCann, J., E. Choi, E. Yamasaki and B.N. Ames. 1975. Detection of carcinogens as mutagens in the Salmonella/microsome test: Assay of 300 chemicals. Proc. Natl. Acad. Sci. 72(12): 5135-5139.

Norppa, H. 1981. The in vitro induction of sister chromatid exchanges and chromosome aberrations in human lymphocytes by styrene derivatives. Carcinogenesis. 2(3): 237-242.

Norppa, H., K. Hemminki, M. Sorsa and H. Vainio. 1981. Effect of monosubstituted epoxides on chromosome aberrations and SCE in cultured human lymphocytes. Mutat. Res. 91: 243-250.

Quarles, J.M., M.W. Sega, C.K. Schenley and W. Lijinsky. 1979a.

Transformation of hamster fetal cells by nitrosated pesticides in a transplacental assay. Cancer Res. 39: 4525-4533.

Quarles, J.M., M.W. Sega, C.K Schenley and R.W. Tennant. 1979b. Rapid screening for chemical carcinogens: Transforming activity of selected nitroso compounds detected in a transplacental host-mediated culture system. Natl. Cancer Inst. Monogr. 51: 257-263.

Rhim, J.S., D.K. Park, E.K. Weisburger and J.H. Weisburger. 1974. Evaluation of an in vitro assay system for carcinogens based on prior infection of rodent cells with nontransforming RNA tumor virus. J. Natl. Cancer Inst. 52(4): 1167-1173.

Tates, A.D. and E. Kriek. 1981. Induction of chromosomal aberrations and sister-chromatid exchanges in Chinese hamster cells in vitro by some proximate and ultimate carcinogenic arylamide derivatives. Mutat. Res. 88: 397-410.

Vasavada, H.A. and J.D. Padayatty. 1981. Rapid transfection assay for screening mutagens and carcinogens. Mutat. Res. 91: 9-14.

U.S. EPA. 1988. Updated Health Effects Assessment for Acetone. 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.

---------<<< Acetone >>>---------

__VI.D. DRINKING WATER HA REFERENCES

None

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SYNONYMS

Substance Name -- Acetone
CASRN -- 67-64-1
Last Revised -- / /

67-64-1
ACETON
Acetone
DIMETHYLFORMALDEHYDE
DIMETHYLKETAL
DIMETHYL KETONE
KETONE, DIMETHYL
KETONE PROPANE
beta-KETOPROPANE

STATUS OF DATA FOR Anthracene

File On-Line 09/01/90

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	09/01/90
Inhalation RfC Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	pending	
Drinking Water Health Advisories (III.A.)	no data	
U.S. EPA Regulatory Actions (IV.)	no data	
Supplementary Data (V.)	no data	

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_I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

__I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name -- Anthracene
CASRN -- 120-12-7
Last Revised -- 09/01/90

The Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. 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 Background Document 1 in Service Code 5 for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of compounds which 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 when a review of that evaluation is completed.

<<< Anthracene >>>

___I.A.1. ORAL RfD SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfD
No observed effects	NOEL: 1000 mg/kg/day	3000	1	3E-1

mg/kg/day

Subchronic Toxicity LOAEL: none
Study in Mice

U.S. EPA, 1989

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*Conversion Factors: none

<<< Anthracene >>>

___I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

U.S. EPA. 1989. Subchronic toxicity in mice with anthracene. Final Report. Hazelton Laboratories America, Inc. Prepared for the Office of Solid Waste, Washington, DC.

Anthracene was administered to groups of 20 male and female CD-1 (ICR)BR mice by oral gavage at doses of 0, 250, 500, and 1000 mg/kg/day for at least 90 days. Mortality, clinical signs, body weights, food consumption, opthalmology findings, hematology and clinical chemistry results, organ weights, organ-to-body weight ratios, gross pathology, and histopathology findings were evaluated. No treatment-related effects were noted. The no-observed-effect level (NOEL) is the highest dose tested (1000 mg/kg/day).

<<< Anthracene >>>

___I.A.3. UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

UF = 3000. An uncertainty factor of 3000 was used: 10 to account for interspecies extrapolation, 10 for intraspecies variability and 30 for both the use of a subchronic study for chronic RfD derivation and for lack of reproductive/developmental data and adequate toxicity data in a second species.

MF = 1.

<<< Anthracene >>>

___I.A.4. ADDITIONAL COMMENTS (ORAL RfD)

In a chronic bioassay (Schmahl, 1955), a group of 28 BD I and BD III rats received anthracene in the diet, starting when the rats were approximately 100 days old. The daily dosage was 5 to 15 mg/rat, and the experiment was terminated when a total dose of 4.5 g/rat was achieved, on the 550th experimental day. The rats were observed until they died, with some living more than 1000 days. No treatment-related effects on lifespan or gross and histological appearance of tissues were observed. Body weights were not mentioned, and hematological parameters were not measured. No chronic LOAEL could be determined from this study.

<<< Anthracene >>>

___I.A.5. CONFIDENCE IN THE ORAL RfD

Study: Low
Data Base: Low
RfD: Low

Confidence in the study is low. It was a well-designed experiment examining a variety of toxicological endpoints; however, failure to identify a LOAEL precludes a higher level of confidence. Confidence in the data base is low, because of the lack of adequate toxicity data in a second species and developmental/reproductive studies. Low confidence in the RfD follows.

<<< Anthracene >>>

___I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

U.S. EPA. 1987. Health and Environmental Effects Profile for Anthracene. 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. 1989. Subchronic toxicity in mice with anthracene. Final Report. Hazelton Laboratories America, Inc. Prepared for the Office of Solid Waste, Washington, DC.

ECAO-CIN Internal Review and Limited Agency Review.

Agency RfD Work Group Review: 10/19/89, 11/15/89

Verification Date: 11/15/89

___I.A.7. EPA CONTACTS (ORAL RfD)

John Risher / ORD -- (513)569-7633 / FTS 684-7633

Harlal Choudhury / ORD -- (513)569-7536 / FTS 684-7536

__I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

Substance Name -- Anthracene
CASRN -- 120-12-7

Not available at this time.

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_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Anthracene
CASRN -- 120-12-7

This substance/agent has been evaluated by the U.S. EPA for evidence of human carcinogenic potential. This does not imply that this chemical is necessarily a carcinogen. The evaluation for this chemical is under review by an inter-office Agency work group. A risk assessment summary will be included on IRIS when the review has been completed.

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_III. HEALTH HAZARD ASSESSMENTS FOR VARIED EXPOSURE DURATIONS

__III.A. DRINKING WATER HEALTH ADVISORIES

Substance Name -- Anthracene
CASRN -- 120-12-7

Not available at this time.

__III.B. OTHER ASSESSMENTS

Substance Name -- Anthracene
CASRN -- 120-12-7

Content to be determined.

==========

_IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- Anthracene
CASRN -- 120-12-7

Not available at this time.

==========

_V. SUPPLEMENTARY DATA

Substance Name -- Anthracene
CASRN -- 120-12-7

Not available at this time.

==========

_VI. BIBLIOGRAPHY

Substance Name -- Anthracene
CASRN -- 120-12-7
Last Revised -- 09/01/90

__VI.A. ORAL RfD REFERENCES

Schmahl, D. 1955. Testing of naphthalene and anthracene as carcinogenic agents in the rat. Krebsforsch. 60: 697-710. (Ger.)

U.S. EPA. 1987. Health and Environmental Effects Profile for Anthracene. 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. 1989. Subchronic toxicity in mice with anthracene. Final Report. Hazelton Laboratories America, Inc. Prepared for the Office of Solid Waste, Washington, DC.

---------<<< Anthracene >>>---------

__VI.B. INHALATION RfD REFERENCES

None

---------<<< Anthracene >>>---------

__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

None

---------<<< Anthracene >>>---------

__VI.D. DRINKING WATER HA REFERENCES

None

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SYNONYMS

Substance Name -- Anthracene
CASRN -- 120-12-7
Last Revised -- 09/01/90

120-12-7
ANTHRACEN [GERMAN]
ANTHRACENE
ANTHRACIN
GREEN OIL
HSDB 702
NSC 7958
PARANAPHTHALENE
TETRA OLIVE N2G

Enter keywords or Read or Scan or Mail
--50-32-8
Searching - Please wait...
1 Occurrences...

Enter keywords or Read or Scan or Mail
--read

Sullivan's Ridge
3.9.2 (mx)
OUT

STATUS OF DATA FOR Benzo[a]pyrene (BaP)

File On-Line 03/31/87

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	no data	
Inhalation RfD Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	on-line	03/31/87
Drinking Water Health Advisories (III.A.)	no data	
U.S. EPA Regulatory Actions (IV.)	on-line	03/01/88

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_I. CHRONIC HEALTH HAZARD ASSESSMENT FOR NONCARCINOGENIC EFFECTS

Substance Name -- Benzo[a]pyrene (BaP)
CASRN -- 50-32-8

Not available at this time

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_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Benzo[a]pyrene (BaP)
CASRN -- 50-32-8
Last Revised -- 03/31/87

Section II provides information on three aspects of the carcinogenic risk assessment for the agent in question; the U.S. EPA classification, and quantitative estimates of risk from oral exposure and from inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen. 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. Background Document 2 (Service Code 5) provides details on the rationale and methods used to derive the carcinogenicity values found in IRIS. Users are referred to Section I for information on long-term toxic effects other than carcinogenicity.

<<< BaP >>>

II.A. EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

II.A.1. WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification -- B2; probable human carcinogen

Basis -- Human data specifically linking BaP to a carcinogenic effect are lacking. There are, however, multiple animal studies in rodent and nonrodent species demonstrating BaP to be carcinogenic following administration by oral, intratracheal, inhalation and dermal routes. BaP has produced positive results in several in vitro bacterial and mammalian genetic toxicology assays.

II.A.2. HUMAN CARCINOGENICITY DATA

Inadequate. Lung cancer has been shown to be induced in humans by various mixtures of polycyclic aromatic hydrocarbons known to contain BaP, including cigarette smoke, roofing tar and coke oven emissions. It is not possible, however, to conclude from this information that BaP is the responsible agent.

<<< BaP >>>

II.A.3. ANIMAL CARCINOGENICITY DATA

BaP is well known as a complete carcinogen when applied to the skin of mice, rats, and rabbits (IARC, 1973). Subcutaneous or intramuscular BaP injection has been shown to result in local tumors in mice, rats, guinea pigs, monkeys and hamsters (IARC, 1973). Intratracheal instillation of BaP produced increased incidences of respiratory tract neoplasms in both male and female Syrian hamsters (Feron et al., 1973; Kobayashi, 1975).

BaP administered orally to rats and hamsters produces stomach tumors. Neal and Rigdon (1967) administered dietary BaP at concentrations of 0, 1, 10, 20, 30, 40, 45, 50, 100, and 250 ppm to male and female CFW-Swiss mice. The control group numbered 289; treatment groups varied in number from 9 to 73 animals and treatment time from 1 to 197 days. Stomach tumors were observed in mice consuming 20 or more ppm BaP. Incidence was apparently related both to the dose and the number of administered doses. Apparent increased incidences of leukemia and lung adenomas were reported in the mice on high BaP diets (250 and 1000 ppm) (Rigdon and Neal, 1966, 1969).

Thyssen et al. (1981) exposed groups of 24 hamsters by inhalation of BaP at concentrations of 2.2, 9.5, or 45 mg/cu.m for 4.5 hours/day for 10 weeks followed by 3 hours/day (7 days/week) for up to 675 days. No animals in the lowest treatment group developed respiratory tumors. Those hamsters exposed to 9.5 mg/cu.m developed tumors of the nasal cavity, larynx, trachea, and pharynx. In addition to respiratory tract tumors, animals in the highest dose group were seen to have neoplasms of the upper digestive tract.

<<< BaP >>>

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

BaP is among the best-studied agents producing genetic toxicological effects. It is metabolized to reactive electrophiles capable of binding to DNA. In vitro assays in which BaP has produced positive results include the following: bacterial DNA repair, bacteriophage induction, point mutations at multiple loci in several bacterial species and strains, mutations in Drosophila melanogaster, sister-chromatid-exchange, chromosomal aberrations and mutation and transformation of cultured mammalian cells. In vivo exposure of mammalian species to BaP has produced the following results: sister-chromatid-exchange, chromosomal aberrations, sperm abnormalities, and positive results in the mouse specific locus (spot) test (IARC, 1973, 1983; Santodonato et al., 1981).

------<<< BaP >>>------

__II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

Not available.

------<<< BaP >>>------

__II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

Not available.

------<<< BaP >>>------

__II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

___II.D.1. EPA DOCUMENTATION

U.S. EPA. 1980. Ambient Water Quality Criteria Document for Polynuclear Aromatic Hydrocarbons. 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 440/5-80-069. NTIS PB 81 117806.

U.S. EPA. 1984. Health Effects Assessment for Benzo[a]pyrene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC. EPA 540/1-86-022.

___II.D.2. REVIEW (CARCINOGENICITY ASSESSMENT)

The risk assessment in the 1984 Health Effects Assessment for Benzo[a]-pyrene has received an Agency review. The 1980 Ambient Water Quality Criteria Document for Polynuclear Aromatic Hydrocarbons has received both Agency and public review.

Agency Work Group Review: 01/07/87

Verification Date: 01/07/87

___II.D.3. U.S. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

Robert E. McGaughy / ORD -- (202)382-5898 / FTS 382-5898

Herman J. Gibb / ORD -- (202)382-5720 / FTS 382-5720

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_III. HEALTH HAZARD ASSESSMENTS FOR VARIED EXPOSURE DURATIONS

Substance Name -- Benzo[a]pyrene (BaP)
CASRN -- 50-32-8

Not available at this time

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_IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- Benzo[a]pyrene (BaP)
CASRN -- 50-32-8
Last Revised -- 03/01/88

EPA risk assessments may be updated as new data are published and as assessment methodologies evolve. Regulatory actions are frequently not updated at the same time. Compare the dates for the regulatory actions in this section with the verification dates for the risk assessments in sections I and II, as this may explain inconsistencies. Also note that some regulatory actions consider factors not related to health risk, such as technical or economic feasibility. Such considerations are indicated for each action. In addition, not all of the regulatory actions listed in this section involve enforceable federal standards. Please direct any questions you may have concerning these regulatory actions to the U.S. EPA contact listed for that particular action. Users are strongly urged to read the background information on each regulatory action in Background Document 4 in Service Code 5.

__IV.A. CLEAN AIR ACT (CAA)

No data available

------<<< BaP >>>------

__IV.B. SAFE DRINKING WATER ACT (SDWA)

No data available

------<<< BaP >>>------

__IV.C. CLEAN WATER ACT (CWA)

No data available

------<<< BaP >>>------

__IV.D. FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT (FIFRA)

No data available

------<<< BaP >>>------

__IV.E. TOXIC SUBSTANCES CONTROL ACT (TSCA)

No data available

------<<< BaP >>>------

__IV.F. RESOURCE CONSERVATION AND RECOVERY ACT (RCRA)

___IV.F.1. RCRA APPENDIX IX, for Ground Water Monitoring

Status -- Listed

Reference -- 52 FR 25942 (07/09/87)

EPA Contact -- Jerry Garman / OSW / (202)382-4658 / FTS 382-4658

------<<< BaP >>>------

__IV.G. SUPERFUND (CERCLA)

No data available

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_V. SUPPLEMENTARY DATA

Substance Name -- Benzo[a]pyrene (BaP)
CASRN -- 50-32-8

Not available at this time

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_VI. BIBLIOGRAPHY

Substance Name -- Benzo[a]pyrene (BaP)
CASRN -- 50-32-8
Last Revised -- 08/01/89

__VI.A. ORAL RfD REFERENCES

None

------<<< BaP >>>------

__VI.B. INHALATION RfD REFERENCES

None

------<<< BaP >>>------

__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

Feron, V.J., D. Jong and P. Emmelot. 1973. Dose-response correlation for the induction of respiratory-tract tumors in Syrian golden hamsters by intratracheal instillations of benzo(a)pyrene. Eur. J. Cancer. 9: 387.

IARC (International Agency for Research on Cancer). 1973. Certain polycyclic aromatic hydrocarbons and heterocyclic compounds. In: IARC Monographs on the

Evaluation of the Carcinogenic Risk of Chemicals to Man. WHO, IARC, Lyon, France. Vol. 3.

IARC (International Agency for Research on Cancer). 1983. Polynuclear Aromatic Compounds, Part 1, Chemical, Environmental and Experimental Data. In: IARC Monographs of the Carcinogenic Risk of Chemicals to Humans. WHO, IARC, Lyon, France. Vol. 32.

Kobayashi, N. 1975. Production of respiratory tract tumors in hamsters by benzo(a)pyrene. Gann. 66: 311.

Neal, J. and R.H. Rigdon. 1967. Gastric tumors in mice fed benzo(a)pyrene: A quantitative study. Texas Rep. Biol. Med. 25: 553.

Rigdon, R.H. and J. Neal. 1966. Gastric carcinomas and pulmonary adenomas in mice fed benzo(a)pyrene. Tex. Rep. Biol. Med. 24: 195.

Rigdon, R.H. and J. Neal. 1969. Relationship of leukemia to lung and stomach tumors in mice fed benzo(a)pyrene. Proc. Soc. Exp. Biol. 130: 146.

Santodonato, J., P. Howard and D. Basu. 1981. Health and Ecological Assessment of Polynuclear Aromatic Hydrocarbons. Pathotox Publishers, Inc., Park Forest South, IL.

Thyssen, J., J. Althoff, G. Kimmerle and U. Mohr. 1981. Inhalation studies with benzo(a)pyrene in Syrian golden hamsters. J. Natl. Cancer Inst. 66(3): 575-577.

U.S. EPA. 1980. Ambient Water Quality Criteria Document for Polynuclear Aromatic Hydrocarbons. 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 440/5-80-069. NTIS PB 81 117806.

U.S. EPA. 1984. Health Effects Assessment for Benzo(a)pyrene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC. EPA 540/1-86-022.

------<<< BaP >>>------

__VI.D. DRINKING WATER HA REFERENCES

None

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SYNONYMS

Sullivan's Ledge
3.9.2 (AK)
OUT

STATUS OF DATA FOR Benzo[k]fluoranthene

File On-Line 11/01/90

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	no data	
Inhalation RfC Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	on-line	11/01/90
Drinking Water Health Advisories (III.A.)	no data	
U.S. EPA Regulatory Actions (IV.)	no data	
Supplementary Data (V.)	no data	

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_I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

__I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name -- Benzo[k]fluoranthene
CASRN -- 207-08-9

Not available at this time.

__I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

Substance Name -- Benzo[k]fluoranthene
CASRN -- 207-08-9

Not available at this time.

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_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Benzo[k]fluoranthene
CASRN -- 207-08-9

Last Revised -- 11/01/90

Section II provides information on three aspects of the carcinogenic risk assessment for the agent in question; the U.S. EPA classification, and quantitative estimates of risk from oral exposure and from inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen. 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. Background Document 2 (Service Code 5) provides details on the rationale and methods used to derive the carcinogenicity values found in IRIS. Users are referred to Section I for information on long-term toxic effects other than carcinogenicity.

<<< Benzo[k]fluoranthene >>>

II.A. EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

II.A.1. WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification -- B2; probable human carcinogen

Basis -- Based on no human data and sufficient data from animal bioassays. Benzo[k]fluoranthene produced tumors after lung implantation in mice and when administered with a promoting agent in skin-painting studies. Equivocal results have been found in a lung adenoma assay in mice. Benzo[k]fluoranthene is mutagenic in bacteria.

<<< Benzo[k]fluoranthene >>>

II.A.2. HUMAN CARCINOGENICITY DATA

None. Although there are no human data that specifically link exposure to benzo[k]fluoranthene to human cancers, benzo[k]fluoranthene is a component of mixtures that have been associated with human cancer. These include coal tar, soots, coke oven emissions and cigarette smoke (U.S. EPA, 1984, 1990; IARC, 1984).

<<< Benzo[k]fluoranthene >>>

II.A.3. ANIMAL CARCINOGENICITY DATA

Sufficient. In a lifetime implant study, female Osborne-Mendel rats (27-35/group) received lung implants of 0.16 mg (0.65 mg/kg), 0.83 mg (3.4 mg/kg) or 4.15 mg (17 mg/kg) benzo[k]fluoranthene in 0.05 mL of a 1:1 (v:v) mixture of beeswax and trioctanoin (Deutsch-Wenzel et al., 1983). Controls consisted of an untreated group and a group receiving an implant of the vehicle. Median survival times (weeks) were: 118 (untreated controls), 104 (vehicle controls); 114 (0.16 mg dose); 95 (0.83 mg dose); 98 (4.15 mg

dose). The incidences of epidermoid carcinomas in the lung and thorax (combined) showed a statistically significant dose-related increase. The observed incidences were: untreated controls, 0/35; vehicle controls, 0/35; low-dose, 0/35; mid-dose, 3/31; high-dose, 12/27.

Groups of 16-17 male and 18 female newborn CD-1 mice received intraperitoneal injections of benzo[k]fluoranthene in DMSO on days 1, 8 and 15 after birth (total dose approximately 126 ug/mouse) and were sacrificed at 52 weeks of age (LaVoie et al., 1987). The incidence of hepatic adenomas and hepatomas was increased in treated male mice (3/16) relative to vehicle controls (1/17), although this increase was not statistically significant. No liver tumors were found in females. Lung adenomas were found in treated male (1/16) and female (3/18) mice, whereas none were reported for the controls. This assay is considered to be a short-term, in vivo, lung tumor assay.

Benzo[k]fluoranthene has yielded positive results for initiating activity in several mouse skin-painting assays. A single dermal application of 11 mg benzo[k]fluoranthene to 20 Swiss mice in a 63-week study did not induce tumors (Van Duuren et al., 1966). However, when the same dose was followed by promoting treatments with croton resin, 18/20 animals developed papillomas and 5/20 developed carcinomas. LaVoie et al. (1982) applied doses of 0, 30, 100 or 1000 ug benzo[k]fluoranthene (10 doses each, every other day, in 0.1 mL acetone) to the skin of groups of 20 Crl:CD-1 mice. This regimen was followed by treatment with 2.5 ug 12-O-tetradecanoyl phorbol-13-acetate (TPA) (a tumor promoter), 3 times/week for 20 weeks. Increases in the percentage of tumor-bearing animals (0, 5, 25, 75), as well as the number of tumors per animal (0, 0.1, 0.4, 2.8), appeared to be dose-related. These results were corroborated by reports of Amin et al. (1985a,b).

<<< Benzo[k]fluoranthene >>>

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Tests for mutagenicity in prokaryotic cells have produced positive results. Tests for reverse mutation in Salmonella typhimurium strain TA100 and TA98 yielded positive results for benzo[k]fluoranthene in the presence of a metabolic activation system (rat liver S9) (LaVoie et al., 1980; Hermann et al., 1980).

---------<<< Benzo[k]fluoranthene >>>---------

__II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

Not available.

---------<<< Benzo[k]fluoranthene >>>---------

__II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

Not available.

---------<<< Benzo[k]fluoranthene >>>---------

__II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

___II.D.1. EPA DOCUMENTATION

U.S. EPA. 1984. Carcinogen Assessment of Coke Oven Emissions. Office of Health and Environmental Assessment, Washington, DC. EPA 600/6-82-003F. NTIS PB84-170181.

U.S. EPA. 1990. Drinking Water Criteria Document for Polycyclic Aromatic Hydrocarbons (PAHs). Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. Final Draft. ECAO-CIN-D010, September, 1990.

<<< Benzo[k]fluoranthene >>>

___II.D.2. REVIEW (CARCINOGENICITY ASSESSMENT)

The 1990 Drinking Water Criteria Document for Polycyclic Aromatic Hydrocarbons has received Agency and external review.

Agency Work Group Review: 02/07/90

Verification Date: 02/07/90

___II.D.3. U.S. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

Rita S. Schoeny / ORD -- (513)569-7544 / FTS 684-7544

Robert E. McGaughy / ORD -- (202)382-5898 / FTS 382-5898

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_III. HEALTH HAZARD ASSESSMENTS FOR VARIED EXPOSURE DURATIONS

__III.A. DRINKING WATER HEALTH ADVISORIES

Substance Name -- Benzo[k]fluoranthene
CASRN -- 207-08-9

Not available at this time.

__III.B. OTHER ASSESSMENTS

Substance Name -- Benzo[k]fluoranthene
CASRN -- 207-08-9

Content to be determined.

==========

_IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- Benzo[k]fluoranthene
CASRN -- 207-08-9

Not available at this time.

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_V. SUPPLEMENTARY DATA

Substance Name -- Benzo[k]fluoranthene
CASRN -- 207-08-9

Not available at this time.

==========

_VI. BIBLIOGRAPHY

Substance Name -- Benzo[k]fluoranthene
CASRN -- 207-08-9
Last Revised -- 11/01/90

__VI.A. ORAL RfD REFERENCES

None

---------<<< Benzo[k]fluoranthene >>>---------

__VI.B. INHALATION RfC REFERENCES

None

---------<<< Benzo[k]fluoranthene >>>---------

__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

Amin, S., K. Huie and S.S. Hecht. 1985a. Mutagenicity and tumor initiating activity of methylated benzo[b]fluoranthenes. Carcinogenesis. 6(7): 1023-1025.

Amin, S., N. Hussain, G. Balanikas, K. Huie and S.S. Hecht. 1985b. Mutagenicity and tumor initiating activity of methylated benzo[k]fluoranthenes. Cancer Lett. 26: 343-347.

Deutsch-Wenzel, R., H. Brune, G. Grimmer, G. Dettbarn and J. Misfeld. 1983. Experimental studies in rat lungs on the carcinogenicity and dose-response relationships of eight frequently occurring environmental polycyclic aromatic hydrocarbons. J. Natl. Cancer Inst. 71(3): 539-543.

Hermann, M., J.P. Durand, J.M. Charpentier, et al. 1980. Correlations of mutagenic activity with polynuclear aromatic hydrocarbon content of various mineral oils. In: Polynuclear Aromatic Hydrocarbons: Chemistry and Biological Effects, 4th Int. Symp., A. Bjorseth and A.J. Dennis, Ed. Battelle Press, Columbus, OH. p. 899-916.

IARC (International Agency for Research on Cancer). 1984. Monographs on the Evaluation of the Carcinogenic Risk of the Chemical to Man. Polynuclear Aromaitc Hydrocarbons. Part 3. Industrial Exposures in Aluminum Production, Coal Gasification, Coke Production, and Iron and Steel Founding. Vol. 34. World Health Organization.

LaVoie, E.J., S.S. Hecht, S. Amin, V. Bedenko and D. Hoffmann. 1980. Identification of mutagenic dihydrodiols as metabolites of benzo(j)fluoranthene and benzo(k)fluoranthene. Cancer Res. 40: 4528-4532.

LaVoie, E.J., S. Amin., S.S. Hecht, K. Furuya and D. Hoffmann. 1982. Tumor initiating activity of dihydrodiols of benzo[b]fluoranthene, benzo[j]fluoranthene and benzo[k]fluoranthene. Carcinogenesis. 3(1): 49-52.

LaVoie, E.J., J. Braley, J.E. Rice and A. Rivenson. 1987. Tumorigenic activity for non-alternant polynuclear aromatic hydrocarbons in newborn mice. Cancer Lett. 34: 15-20.

U.S. EPA. 1984. Carcinogen Assessment of Coke Oven Emissions. Office of Health and Environmental Assessment, Washington, DC. EPA 600/6-82-003F.

NTIS PB84-170181.

U.S. EPA. 1990. Drinking Water Criteria Document for Polycyclic Aromatic Hydrocarbons (PAHs). Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. Final Draft. ECAO-CIN-D010, September, 1990.

Van Duuren, B.L., A. Sivak, A. Segal, L. Orris and L. Langseth. 1966. The tumor-promoting agents of tobacco leaf and tobacco smoke condensate. J. Natl. Cancer Inst. 37(4): 519-526.

---------<<< Benzo[k]fluoranthene >>>---------

__VI.D. DRINKING WATER HA REFERENCES

None

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SYNONYMS

Substance Name -- Benzo[k]fluoranthene
CASRN -- 207-08-9
Last Revised -- 11/01/90

207-08-9
Benzo(k)fluoranthene
Dibenzo(b,jk)fluorene
HSDB 6012
11,12-BENZO(k)FLUORANTHENE
11,12-Benzofluoranthene
2,3,1',8'-Binaphthylene
8,9-BENZOFLUORANTHENE

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--65-85-0
Searching - Please wait...
1 Occurrences...

Enter keywords or Read or Scan or Mail
--read

3.7.2 (AIR)
JUL

STATUS OF DATA FOR Benzoic acid

File On-Line 09/07/88

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	07/01/89
Inhalation RfD Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	on-line	08/01/89
Drinking Water Health Advisories (III.A.)	no data	
U.S. EPA Regulatory Actions (IV.)	no data	

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_I. CHRONIC HEALTH HAZARD ASSESSMENT FOR NONCARCINOGENIC EFFECTS

Substance Name -- Benzoic acid
CASRN -- 65-85-0
Last Revised -- 07/01/89

The Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. 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 Background Document 1 in Service Code 5 for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of compounds which 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 when a review of that evaluation is completed.

<<< Benzoic acid >>>

__I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfDo)

___I.A.1. ORAL RfD SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfD
Human daily per capita intakes	NOAEL: 34 mg/day benzoic acid and 328	1	1	4E+0 mg/kg/day

	mg/day for sodium
FDA, 1973;	benzoate (converted
Selected Committee	to 312 mg/day
on Review of the	benzoic acid)
GRAS List	
	LOAEL: none

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*Conversion Factors: 328 mg/day sodium benzoate x [122.12 (MW benzoic acid)/144.11 (MW sodium benzoate)] = 278 mg/day benzoic acid. 278 mg/day benzoic acid from sodium benzoate + 34 mg/day benzoic acid = 312 mg/day

<<< Benzoic acid >>>

___I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

FDA (Food and Drug Administration). 1973. Evaluation of the Health Aspects of Benzoic Acid and Sodium Benzoate as Food Ingredients. DHEW, Washington, DC. Report No. SCOGS-7. NTIS PB-223837/6.

Early studies using humans indicate that laboratory animals are inappropriate models for the toxicity of benzoic acid in humans (see Additional Comments). Based on data regarding the amounts of benzoic acid and sodium benzoate produced for addition to food as a preservative, FDA (1973) estimated daily per capita intakes of 0.9-34 mg for benzoic acid and 34-328 mg for sodium benzoate. At these levels, there are no reports of toxic effects in humans, and these compounds have GRAS status by FDA. Therefore, the upper ranges can be considered NOELs for benzoic acid and sodium benzoate. In the stomach, both benzoic acid and sodium benzoate exist in the ionized form as benzoate. Both benzoic acid and sodium benzoate are absorbed rapidly and completely by the GI tract. Therefore, exposure to sodium benzoate is essentially equivalent to exposure to benzoic acid. Correcting for molecular weight differences, 328 mg sodium benzoate is equivalent to 278 mg benzoic acid. Adding 278 to the daily intake for benzoic acid of 34 mg yields a total of 312 mg benzoic acid (see Conversion Factors). If no uncertainty factor is used, the RfD is 312 mg/day for a 70 kg human or 4 mg/kg/day.

<<< Benzoic acid >>>

___I.A.3. UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

UF = 1. An uncertainty factor of 10 for the protection of sensitive subgroups was considered unnecessary because although reactions to benzoate and structurally related compounds do occur, an uncertainty factor of 10 would be of little value to the sensitive individuals.

MF = 1.

___I.A.4. ADDITIONAL COMMENTS (ORAL RfD)

Sodium benzoate appeared to have no maternal toxicity, fetal toxicity or teratogenic potency in mice, rats, hamsters or rabbits when given orally

(FDRL, 1972). The highest dosages tested were 175.0, 175.0, 300.0, and 250.0 mg/kg/day in these species, respectively.

The only chronic oral data available involve administration of benzoic acid to rats and mice (Shtenberg and Ignat'ev, 1970; Ignat'ev, 1965; Marquardt, 1960). A dose of 40 mg/kg/day for 17 months was associated with decreased resistance to stress in mice and possibly with reduced food and water intake in rats after 18 months (Shtenberg and Ignat'ev, 1970), although in another report from this laboratory (Ignat'ev, 1965) 80 mg/kg/day in rats for 18 months was not associated with adverse effects on body weight, survival or gross or microscopic pathology.

In other long-term dietary studies using rats, 1.5% in the diet (750 mg/kg/day) for 18 months was associated with decreased food intakes and growth (Marquardt, 1960) but 1.0% of the diet (500 mg/kg/day) for lifetime resulted in no signs of toxicity and no adverse reproductive effects over 4 generations. If 40 mg/kg/day in mice in the study by Shtenberg and Ignat'ev (1970) is considered to be the LOAEL, application of an uncertainty factor of 1000 would result in an RfD of 0.04 mg/kg/day or 2.8 mg/day, which is near the lower end of the range of the estimated daily human exposure. The lower RfD based on animal data is not unexpected, however, since application of uncertainty factors is meant to be conservative in the absence of human data. Since human data are available in this case, it is not appropriate to use the animal data for the RfD.

Gerlach (1909) reported no externally visible effects in humans ingesting benzoic acid at 0.5-1.0 g/day for 44 consecutive days or for 82/86 or 88/92 days. Assuming a human body weight of 70 kg, this level corresponds to a dosage of 14 mg/kg/day. Wiley and Bigelow (1908), however, observed irritation, discomfort, weakness and malaise in humans given oral bolus doses of less than or equal to 1.75 g/day over a 20-day period (25 mg/kg/day). The RfD is well below these doses.

<<< Benzoic acid >>>

___I.A.5. CONFIDENCE IN THE ORAL RfD

Study: Medium
Data Base: Medium
RfD: Medium

Medium confidence is placed in the FDA (1973) estimate of per capita intake. Medium confidence in the data base reflects the inappropriateness of using animal data as the basis of the RfD for humans and the lack of reported effects in humans at the estimated intakes. Thus, confidence in the RfD is medium.

___I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

U.S. EPA. 1986. Health and Environmental Effects Document on Benzoic Acid. 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.

Limited peer review and extensive Agency-wide review 1987.

Agency RfD Work Group Review: 09/17/87

Verification Date: 09/17/87

___I.A.7. EPA CONTACTS (ORAL RfD)

Harlal Choudhury / ORD -- (513)569-7536 / FTS 684-7536

Christopher T. DeRosa / ORD -- (513)569-7534 / FTS 684-7534

------<<< Benzoic acid >>>------

__I.B. REFERENCE DOSE FOR CHRONIC INHALATION EXPOSURE (RfDi)

Not available at this time

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_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Benzoic acid
CASRN -- 65-85-0
Last Revised -- 08/01/89

Section II provides information on three aspects of the carcinogenic risk assessment for the agent in question; the U.S. EPA classification, and quantitative estimates of risk from oral exposure and from inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen. 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. Background Document 2 (Service Code 5) provides details on the rationale and methods used to derive the carcinogenicity values found in IRIS. Users are referred to Section I for information on long-term toxic effects other than carcinogenicity.

<<< Benzoic acid >>>

__II.A. EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

___II.A.1. WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification -- D; not classifiable as to human carcinogenicity

Basis -- No human data and inadequate data from animal bioassays.

___II.A.2. HUMAN CARCINOGENICITY DATA

None.

<<< Benzoic acid >>>

___II.A.3. ANIMAL CARCINOGENICITY DATA

Inadequate. In a lifetime study, Toth (1984) administered sodium benzoate (of 99% purity) to groups of 50 male and 50 female 5 week-old albino Swiss mice at a level of 2% in the drinking water. Control groups consisted of 100 mice/sex. The dose level was selected based on results of a subchronic study in which levels of 4 and 8% were considered to be too toxic. The 2% level was equivalent to sodium benzoate doses of 4133 and 3973 mg/kg/day for males and females, respectively. This was based on average measured daily water consumptions of 6.2 mL for males and 5.9 mL for females and an assumed average body weight of 0.03 kg. The equivalent benzoic acid doses, adjusted for moleculer weight differences between sodium benzoate and benzoic acid, are 3502 mg/kg/day and 3367 mg/kg/day for males and females, respectively. Histopathologic examinations of all mice included 11 organs and all gross lesions. The treatment had no apparent effect on survival or tumor incidence.

Shtenberg and Ignat'ev (1970) administered daily doses of 40 mg/kg benzoic acid combined with 80 mg/kg sodium bisulfite to a group of 50 white cross-bred mice of each sex for 17 months. The test compounds were administered in a paste before feeding. An unspecified number of control animals received only basic diet. Malignant tumors (not otherwise specified) occurred in 8/100 treated mice and 1/8 mice in the third generation of the treated group. Tumor incidences were not reported for untreated mice or for mice treated with benzoic acid only.

<<< Benzoic acid >>>

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Dinerman and Ignat'ev (1966) reported that a 3-month exposure to 0.2% benzoic acid in the diet increased the susceptibility of mice to carcinoma development following intraperitoneal inoculation with Erlich ascites carcinoma cells. Tumors developed in 62/90 (68.8%) of benzoic acid treated mice and in 16/49 (32.6%) of control mice.

Benzoic acid and sodium benzoate have been tested for mutagenicity or genotoxicity in prokaryotes (McCann et al., 1975), eukaryotes (Litton Bionetics, Inc., 1974), and several mammalian test systems (Litton Bionetics, Inc., 1974, 1975; Oikawa et al., 1980). No positive results have been

reported.

__II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

Not available.

__II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

Not available.

__II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)
<<< Benzoic acid >>>

___II.D.1. EPA DOCUMENTATION

U.S. EPA. 1987. Health and Environmental Effects Document for Benzoic Acid. 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.

___II.D.2. REVIEW (CARCINOGENICITY ASSESSMENT)

The 1987 Health and Environmental Effects Document has received OHEA review.

Agency Work Group Review: 03/01/89

Verification Date: 03/01/89

___II.D.3. U.S. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

Dharm V. Singh / ORD -- (202)382-5958 / FTS 382-5958

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_III. HEALTH HAZARD ASSESSMENTS FOR VARIED EXPOSURE DURATIONS

Substance Name -- Benzoic acid
CASRN -- 65-85-0

Not available at this time

_IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- Benzoic acid
CASRN -- 65-85-0

Not available at this time

_V. SUPPLEMENTARY DATA

Substance Name -- Benzoic acid
CASRN -- 65-85-0

Not available at this time

_VI. BIBLIOGRAPHY

Substance Name -- Benzoic acid
CASRN -- 65-85-0
Last Revised -- 08/01/89

__VI.A. ORAL RfD REFERENCES

FDA (Food and Drug Administration). 1973. Evaluation of the Health Aspects of Benzoic Acid and Sodium Benzoate as Food Ingredients. DHEW, Washington, DC. Report No. SCOGS-7. NTIS PB-223 837/6.

FDRL (Food and Drug Research Labs., Inc.). 1972. Teratologic Evaluation of FDA 71-37 (Sodium Benzoate). p. 75-79.

Gerlach, V. 1909. VII. Summary of the results. In: Physiological Activity of Benzoic Acid and Sodium Benzoate, V. Gerlach, Ed. Verlag von Heinrich Staadt, Wiesbaden. p. 90-92. (Cited in Informatics, Inc., 1972)

Ignat'ev, A.D. 1965. Experimental information contributing to a hygienic characterization of the combined effect produced by some food presentations. Vop. Pitan. 24(3): 61-68. (Cited in Informatics, Inc., 1972)

Informatics, Inc. 1972. GRAS (Generally Recognized as Safe) Food Ingredients: Benzoic Acid and Sodium Benzoate. p. 75-79.

Shtenberg, A.J. and A.D. Ignat'ev. 1970. Toxicological evaluation of some combinations of food preservatives. Food Cosmet. Toxicol. 8(4): 369-380.

U.S. EPA. 1987. Health and Environmental Effects Document for Benzoic Acid. 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.

Wiley, H.M. and W.D. Bigelow. 1908. Influence of benzoic acid and benzoates on digestion and health. Bulletin 84, pt. IV, Bureau of Chemistry, U.S. Dept. Agriculture. (Cited in Informatics, Inc., 1972)

------<<< Benzoic acid >>>------

__VI.B. INHALATION RfD REFERENCES

None

------<<< Benzoic acid >>>------

__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

Dinerman, A.A and A.D. Ignat'ev. 1966. Effect of certain food preservatives on the development of tumors in mice. Gig. Sanit. 31(9): 38-42. (Eng. trans.)

Litton Bionetics, Inc. 1974. Mutagenic Evaluation of Compound FDA 71-37, Sodium Benzoate. Report No. LBI 2446-297, FDA, Washington, DC, PB-245-453/6.

Litton Bionetics, Inc. 1975. Mutagenic Evaluation of Compound FDA 73-70, Benzoic Acid Certified A.C.S. Report No. LBI-2468-376; FDABF-GRAS-376 PB-245-500/4.

McCann, J., E. Choi, E. Yamasaki and B.N. Ames. 1975. Detection of carcinogens as mutagens in the Salmonella/microsome test: Assay of 300 chemicals. Proc. Natl. Acad. Sci. 72: 5135-5139.

Oikawa, A., H. Tohda, M. Kanai, M. Miwa and T. Sugimura. 1980. Inhibitors of poly(adenosine diphosphate ribose) induced sister chromatid exchanges. Biochem. Biophys. Res. Commun. 97(4): 1311-1316.

Shtenberg, A.J. and A.D. Ignat'ev. 1970. Toxicological evaluation of some combinations of food preservatives. Food Cosmet. Toxicol. 8(4): 369-380.

Toth, B. 1984. Lack of tumorigenicity of sodium benzoate in mice. Fund. Appl. Toxicol. 4(3): 494-496.

U.S. EPA. 1987. Health and Environmental Effects Document for Benzoic Acid. 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.

------<<< Benzoic acid >>>------

__VI.D. DRINKING WATER HA REFERENCES

None

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SYNONYMS

65-85-0
benzenecarboxylic acid
Benzoic acid
carboxybenzene
dracylic acid
phenyl carboxylic acid
phenylformic acid

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--117-81-7
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Soil Screening
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DOT

STATUS OF DATA FOR Bis(2-ethylhexyl)phthalate (BEHP)

File On-Line 01/31/87

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	08/01/89
Inhalation RfD Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	on-line	05/01/90
Drinking Water Health Advisories (III.A.)	no data	
U.S. EPA Regulatory Actions (IV.)	on-line	03/01/88

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_I. CHRONIC HEALTH HAZARD ASSESSMENT FOR NONCARCINOGENIC EFFECTS

Substance Name -- Bis(2-ethylhexyl)phthalate (BEHP)
Primary Synonym -- Di(2-ethylhexyl)phthalate
CASRN -- 117-81-7
Last Revised -- 08/01/89

The Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. 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 Background Document 1 in Service Code 5 for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of compounds which 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 when a review of that evaluation is completed.

<<< BEHP >>>

__I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfDo)

___I.A.1. ORAL RfD SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfD
Increased relative liver weight	NOAEL: none	1000	1	2E-2 mg/kg/day

	LOAEL: 0.04% of diet
Guinea Pig Sub-chronic-to-Chronic Oral Bioassay	(19 mg/kg bw/day)
Carpenter et al., 1953	

*Conversion Factors: none

<<< BEHP >>>

___I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

Carpenter, C.P., C.S. Weil and H.F. Smyth. 1953. Chronic oral toxicity of di(2-ethylhexyl)phthalate for rats, guinea pigs and dogs. Arch. Indust. Hyg. Occup. Med. 8: 219-226.

The following numbers of guinea pigs were fed diets containing BEHP for a period of 1 year: 24 males and 23 females consumed feed containing 0.13% BEHP; 23 males and 23 females consumed feed containing 0.04% BEHP; and 24 males and 22 females were fed the control diet. These dietary levels corresponded to 64 or 19 mg/kg bw/day based on measured food consumption. No treatment-related effects were observed on mortality, body weight, kidney weight, or gross pathology and histopathology of kidney, liver, lung, spleen, or testes. Statistically significant increases in relative liver weights were observed in both groups of treated females (64 and 19 mg/kg bw/day).

Groups of 32 male and 32 female Sherman rats were maintained for 2 years on diets containing either 0.04, 0.13 or 0.4% BEHP (equivalent to 20, 60, and about 195 g/kg bw/day based on measured food consumption). An F1 group of 80 animals was fed the 0.04% diet for 1 year. Mortality in the F1 treated and control groups was high; 46.2 and 42.7%, respectively, survived to 1 year. There was, however, no effect of treatment on either parental or F1 group mortality, life expectancy, hematology, or histopathology of organs. Both parental and F1 rats receiving the 0.4% BEHP diet were retarded in growth and had increased kidney and liver weights.

It appears that guinea pigs offer the more sensitive animal model for BEHP toxicity. A LOAEL in this species is determined to be 19 mg/kg/day.

<<< BEHP >>>

___I.A.3. UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

UF = 1000. Factors of 10 each were used for interspecies variation and for protection of sensitive human subpopulations. An additional factor of 10 was used since the guinea pig exposure was longer than subchronic but less than lifetime, and because, while the RfD is set on a LOAEL, the effect observed was considered to be minimally adverse.

MF = 1.

___I.A.4. ADDITIONAL COMMENTS (ORAL RfD)

Dietary levels of 0, 0.01, 0.1, and 0.3% BEHP (greater than 99% pure) were administered to male and female CD-1 mice that were examined for adverse fertility and reproductive effects using a continuous breeding protocol. BEHP was a reproductive toxicant in both sexes significantly decreasing fertility and the proportion of pups born alive per litter at the 0.3% level, and inducing damage to the seminiferous tubules. BEHP has been observed to be both fetotoxic and teratogenic (Singhe, 1972; Shiot and Nishimura, 1982).

<<< BEHP >>>

___I.A.5. CONFIDENCE IN THE ORAL RfD

Study: Medium
Data Base: Medium
RfD: Medium

The study by Carpenter et al. (1953) utilized sufficient numbers of guinea pigs and measured multiple endpoints. The fact that there were only two concentrations of BEHP tested precludes a rating higher than medium. Since there are corroboratin^Vhronic animal bioassays, the data base is likewise rated medium. Medium confidence in the RfD follows.

___I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

The RfD has been reviewed by the RfD Work Group. Documentation may be found in the meeting notes of 01/22/86.

Agency RfD Work Group Review: 01/22/86

Verification Date: 01/22/86

___I.A.7. EPA CONTACTS (ORAL RfD)

Michael L. Dourson / ORD -- (513)569-7544 / FTS 684-7544

Christopher T. DeRosa / ORD -- (513)569-7534 / FTS 684-7534

------<<< BEHP >>>------

__I.B. REFERENCE DOSE FOR CHRONIC INHALATION EXPOSURE (RfDi)

Not available at this time

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_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Bis(2-ethylhexyl)phthalate (BEHP)
Primary Synonym -- Di(2-ethylhexyl)phthalate
CASRN -- 117-81-7
Last Revised -- 05/01/90

Section II provides information on three aspects of the carcinogenic risk assessment for the agent in question; the U.S. EPA classification, and quantitative estimates of risk from oral exposure and from inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen. 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. Background Document 2 (Service Code 5) provides details on the rationale and methods used to derive the carcinogenicity values found in IRIS. Users are referred to Section I for information on long-term toxic effects other than carcinogenicity.

<<< BEHP >>>

__II.A. EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

___II.A.1. WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification -- B2; probable human carcinogen.

Basis -- Orally administered DEHP produced significant dose-related increases in liver tumor responses in rats and mice of both sexes.

___II.A.2. HUMAN CARCINOGENICITY DATA

Inadequate. Thiess et al. (1978) conducted a mortality study of 221 DEHP production workers exposed to unknown concentrations of DEHP for 3 months to 24 years. Workers were followed for a minimum of 5 to 10 years (mean follow-up time was 11.5 years). Eight deaths were reported in the exposed population. Deaths attributable to pancreatic carcinoma (1 case) and uremia (1 case in which the workers also had urethral and bladder papillomas) were significantly elevated in workers exposed for >15 years when compared to the corresponding age groups in the general population. The study is limited by a short follow-up period and unquantified worker exposure. Results are considered inadequate for evidence of a causal association.

<<< BEHP >>>

___II.A.3. ANIMAL CARCINOGENICITY DATA

Sufficient. In an NTP (1982) study, 50 male and 50 female fisher 344 rats per group were fed diets containing 0, 6000 or 12,000 ppm DEHP for 103 weeks. Similarly, groups of 50 male and 50 female B6C3F1 mice were given 0, 3000 or 6000 ppm DEHP in the diet for 103 weeks. Animals were killed and examined histologically when morbund or after 105 weeks. No clinical signs of toxicity were observed in either rats or mice. A statistically significant increase in the incidence of hepatocellular carcinomas and combined incidence of carcinomas and adenoma were observed in female rats and both sexes of mice. The combined incidence of neoplastic nodules and hepatocellular carcinomas was statistically significantly increased in the high-dose male rats. A positive dose response trend was also noted.

Carpenter et al. (1953) found no malignant tumors in treated groups of 32 male and 32 female Sherman rats. Animals were given 400, 1300 or 4000 ppm DEHP in the diet for 1 year and reduced to a maximum of 8 males and 8 females and treated for another year. Controls, F1 and 4000 ppm groups were sacrificed after being maintained on control or 4000 ppm diets for 1 year. Only 40 to 47% of the animals in each group, including F1 animals, survived 1 year. Thus, an insufficient number of animals were available for a lifetime evaluation.

Carpenter et al. (1953) did not find a carcinogenic effect in guinea pigs and dogs exposed to 1300 or 4000 ppm DEHP. Both guinea pigs and dogs were terminated after 1 year of exposure. The treatment and survival periods for these animals were considerably below their lifetimes.

<<< BEHP >>>

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Studies indicate that DEHP is not a direct acting mutagen in either a forward mutation assay in Salmonella typhimurium (Seed, 1982) or the rec assay in Bacillus subtilis (Tomita et al., 1982). DEHP did not induce mutations in a modified reverse mutation plate incorporation assay in Salmonella strains TA100 and TA98 at concentrations up to 1000 ug/plate in the presence or absence of S9 hepatic homogenate (Kozumbo et al., 1982). MEHP, the monoester form of DEHP and a metabolite is positive in the rec assay and in the reverse mutation assay in Salmonella. In the absence of exogenous metabolism MEHP produced chromosomal aberrations and sister chromatid exchanges in V79 cells. Both DEHP and MEHP induced chromosomal aberrations and morphological transformation in cultured fetal Syrian hamster cells exposed in utero (Tomita et al., 1982). Chromosomal effects were not found in CHO mammalian cells (Phillips et al., 1982) exposed to DEHP. DEHP was weakly positive with metabolic activation in only one of several studies testing for mutagenic activity at the thymidine kinase locus in L5178Y mouse lymphoma cells (Ashby et al., 1985). DEHP is a potent inducer of hepatic peroxisomal enzyme activity (Ganning et al., 1984).

__II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE
<<< BEHP >>>

___II.B.1. SUMMARY OF RISK ESTIMATES

Oral Slope Factor -- 1.4E-2/mg/kg/day

Drinking Water Unit Risk -- 4.0E-7/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)	3E+2 ug/L
E-5 (1 in 100,000)	3E+1 ug/L
E-6 (1 in 1,000,000)	3 ug/L

<<< BEHP >>>

___II.B.2. DOSE-RESPONSE DATA (CARCINOGENICITY, ORAL EXPOSURE)

Tumor Type -- Mouse/B6C3Fl, male
Test Animals -- hepatocellular carcinoma and adenoma
Route -- oral, diet
Reference -- NTP, 1982

---- Dose ----- Administered (ppm)	Human Equivalent (mg/kg/day)	Tumor Incidence
0	0	14/50
3000	32	25/48
6000	65	29/50

<<< BEHP >>>

___II.B.3. ADDITIONAL COMMENTS (CARCINOGENICITY, ORAL EXPOSURE)

In this study powdered rodent meal was provided in such a way that measured food consumption could include significant waste and spillage rather than true food intake. For this reason a standard food consumption rate of 13% mouse body weight was used in the dose conversion.

DEHP is hydrolyzed to monoesters including MEHP (Pollack et al., 1985; Lhuguenot et al., 1985; Kluwe, 1982). Although several species of animals have been determined to excrete glucuronide conjugates of monoethylhexyl phthalate (MEHP) upon exposure to DEHP, rats do not (Tanaka et al., 1975; Williams and Blanchfield, 1975; Albro et al., 1982).

Slope factors based on combined hepatocellular carcinoma and neoplastic nodule incidences were 4.5E-3/mg/kg/day for female rats, 3.2E-3/mg/kg/day for

male rats. A slope factor based on hepatocellular adenomas or carcinomas in female mice is 1.0E-2/mg/kg/day.

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

<<< BEHP >>>

___II.B.4. DISCUSSION OF CONFIDENCE (CARCINOGENICITY, ORAL EXPOSURE)

An adequate number of animals was observed and a statistically significant increase in incidence of liver tumors was seen in both sexes and were dose dependent in both sexes of mice and female rats. A potential source of variability in the NTP study is the possibility of feed scattering. The above calculations are based on standard food consumption rates for mice (13% of body weight) and rats (5% of body weight).

__II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

Not available.

__II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)
<<< BEHP >>>

___II.D.1. EPA DOCUMENTATION

U.S. EPA. 1988. Drinking Water Criteria Document for Phthalic Acid Esters. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. (External Review Draft).

___II.D.2. REVIEW (CARCINOGENICITY ASSESSMENT)

The values in the 1988 Drinking Water Criteria Document for Phthalic Acid Esters (External Review Draft) have received Agency review.

Agency Work Group Review: 08/26/87; 10/07/87

Verification Date: 10/07/87

___II.D.3. U.S. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

Robert Vanderslice / ODW -- (202)475-6711 / FTS 475-6711

Annette Gatchett / ORD -- (513)569-7813 / FTS 684-7813

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_III. HEALTH HAZARD ASSESSMENTS FOR VARIED EXPOSURE DURATIONS

Substance Name -- Bis(2-ethylhexyl)phthalate (BEHP)
Primary Synonym -- Di(2-ethylhexyl)phthalate
CASRN -- 117-81-7

Not available at this time

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_IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- Bis(2-ethylhexyl)phthalate (BEHP)
Primary Synonym -- Di(2-ethylhexyl)phthalate
CASRN -- 117-81-7
Last Revised -- 03/01/88

EPA risk assessments may be updated as new data are published and as assessment methodologies evolve. Regulatory actions are frequently not updated at the same time. Compare the dates for the regulatory actions in this section with the verification dates for the risk assessments in sections I and II, as this may explain inconsistencies. Also note that some regulatory actions consider factors not related to health risk, such as technical or economic feasibility. Such considerations are indicated for each action. In addition, not all of the regulatory actions listed in this section involve enforceable federal standards. Please direct any questions you may have concerning these regulatory actions to the U.S. EPA contact listed for that particular action. Users are strongly urged to read the background information on each regulatory action in Background Document 4 in Service Code 5.

__IV.A. CLEAN AIR ACT (CAA)

No data available

------<<< BEHP >>>------

__IV.B. SAFE DRINKING WATER ACT (SDWA)

No data available

------<<< BEHP >>>------

__IV.C. CLEAN WATER ACT (CWA)

___IV.C.1. AMBIENT WATER QUALITY CRITERIA, Human Health

Water and Fish Consumption: 1.5E+4 ug/L

Fish Consumption Only: 5E+4 ug/L

Considers technological or economic feasibility? -- NO

Discussion --

Reference -- 45 FR 79318 (11/28/80)

EPA Contact -- Criteria and Standards Division, OWRS
(202)475-7315 / FTS 475-7315

<<< BEHP >>>

___IV.C.2. AMBIENT WATER QUALITY CRITERIA, Aquatic Organisms

Freshwater:

Acute LEC -- 9.4E+2 ug/L
Chronic LEC -- 3E+0 ug/L

Marine:

Acute LEC -- 2.944E+3 ug/L
Chronic LEC -- 3.4E+0 ug/L

Considers technological or economic feasibility? -- NO

Discussion -- The values that are indicated as "LEC" are not criteria, but are the lowest effect levels found in the literature. LECs are given when the minimum data required to derive water quality criteria are not available.

Reference -- 45 FR 79318 (11/28/80)

EPA Contact -- Criteria and Standards Division, OWRS
(202)475-7315 / FTS 475-7315

------<<< BEHP >>>------

__IV.D. FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT (FIFRA)

No data available

------<<< BEHP >>>------

__IV.E. TOXIC SUBSTANCES CONTROL ACT (TSCA)

No data available

------<<< BEHP >>>------

__IV.F. RESOURCE CONSERVATION AND RECOVERY ACT (RCRA)

___IV.F.1. RCRA APPENDIX IX, for Ground Water Monitoring

Status -- Listed

Reference -- 52 FR 25942 (07/09/87)

EPA Contact -- Jerry Garman / OSW / (202)382-4658 / FTS 382-4658

------<<< BEHP >>>------

__IV.G. SUPERFUND (CERCLA)

___IV.G.1. REPORTABLE QUANTITY (RQ) for Release into the Environment

Value (status) -- 100 pounds (Proposed, 1987)

Considers technological or economic feasibility? -- NO

Discissuion -- The 100-pound RQ is based on assessment for potential carcinogenicity. Available data indicate a hazard ranking of low based on a potency factor of 0.015/mg/kg/day and weight-of-evidence group B2, which corresponds to an RQ of 100 pounds.

Reference -- 52 FR 8140 (03/16/87)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)382-3000 / FTS 382-3000

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_V. SUPPLEMENTARY DATA

Substance Name -- Bis(2-ethylhexyl)phthalate (BEHP)
Primary Synonym -- Di(2-ethylhexyl)phthalate
CASRN -- 117-81-7

Not available at this time

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_VI. BIBLIOGRAPHY

Substance Name -- Bis(2-ethylhexyl)phthalate (BEHP)
Primary Synonym -- Di(2-ethylhexyl)phthalate
CASRN -- 117-81-7
Last Revised -- 05/01/90

__VI.A. ORAL RfD REFERENCES

Carpenter, C.P., C.S. Weil and H.F. Smyth. 1953. Chronic oral toxicity of di(2-ethylhexyl)phthalate for rats,and guinea pigs and dogs. Arch. Indust. Hyg. Occup. Med. 8: 219-226.

NTP (National Toxicology Program). 1984. Di(2-ethylhexyl)phthalate: Reproduction and fertility assessment in CD-1 mice when administered by gavage. Final Report. NTP-84-079. NTP, Research Triangle Park, NC.

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Singhe, A.R., W.H. Lawrence and J. Autian. 1972. Teratogenicity of phthalate esters in rats. J. Pharmacol. Sci. 61: 51.

------<<< BEHP >>>------

__VI.B. INHALATION RfD REFERENCES

None

------<<< BEHP >>>------

__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

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interactions with macromolecules and species differences in metabolism of DEHP. Environ. Health Perspect. 45: 19-25.

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Kluwe, W.M. 1982. Overview of phthalate ester pharmacokinetics in mammalian species. Environ. Health Perspect. 45: 3-10.

Kozumbo, W.J., R. Kroll and R.J. Rubin. 1982. Assessment of the mutagenicity of phthalate esters. Environ. Health Perspect. 45: 103-109.

Lhuguenot, J.C., A.M. Mitchell, G. Milner, E.A. Lock and C.R. Elcombe. 1985. The metabolism of di-(2-ethylhexyl)phthalate (DEHP) and mono-(2-ethylhexyl)phthalate (MEHP) in rats: In vivo and in vitro dose and time dependency of metabolism. Toxicol. Appl. Pharmacol. 80: 11-22.

NTP (National Toxicology Program). 1982. Carcinogenesis bioassay of di-(2-ethylhexyl)phthalate (CAS No. 117-81-7) in F344 rats and B6C3F, mice (feed study). NTP Tech. Rep. Ser. TR No. 217, NTP, Research Triangle Park, NC.

Phillips, B.J., T.E.B. James and S.D. Gangolli. 1982. Genotoxicity studies of di-(2-ethylhexyl)phthalate and its metabolites in CHO cells. Mutat. Res. 102: 297-304.

Pollack, G.M., R.C. Li, J.C. Ermer and D.D. Shen. 1985. Effects of route of administration and repetitive dosing on the disposition kinetics of di-(2-ethylhexyl)phthalate and its mono-de-esterified metabolite in rats. Toxicol. Appl. Pharmacol. 79: 246-256.

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Tanaka, A., T. Adachi, T. Takahashi and T. Yamaha. 1975. Biochemical studies on phthalic esters. I. Elimination, distribution and metabolism of di-(2-ethylhexyl)phthalate in rats. Toxicology. 4: 253-264.

Thiess, A.M., R. Frentzel-Beyme and R. Wieland. 1978. Mortality study in workers exposed to di-(2-ethylhexyl)phthalate (DOP). In: Moglichkerten und Grenzen des Biological Monitoring. Arbeitsmedizinische Probleme des Dienstleistungsqewerbes. Arbeitsmedizinische kolloquium [Possibilities and Limits of Biological Monitoring. Problems of Occupational Medicine in Small Industries. Colloquim in Occupational Medicine], Frankfurt/M., May 1978. Stuttgart, A.W. Gentner, p. 155-164. (Ger.)

Tomita, I., Y. Nakamura, N. Aoki and N. Inui. 1982. Mutagenic/carcinogenic potential of DEHP and MEHP. Environ. Health Perspect. 45: 119-125.

Williams, D.T. and B.J. Blanchfield. 1975. The retention, distribution, excretion and metabolism of dibutylphthalate-7-14C in the rat. J. Agric. Food Chem. 23: 854-857.

U.S. EPA. 1988. Drinking Water Criteria Document for Phthalic Acid Esters. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. (External Review Draft).

------<<< BEHP >>>------

__VI.D. DRINKING WATER HA REFERENCES

None

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SYNONYMS

117-81-7
BEHP
Bis(2-ethylhexyl)-1,2-benzene-dicarboxylate
Bis(2-ethylhexyl)phthalate
Bisoflex 81
Bisoflex DOP
Compound 889
DAF 68
DEHP
Di(2-ethylhexyl)orthophthalate
Di(2-ethylhexyl)phthalate
Dioctyl phthalate
Di-sec-octyl phthalate
DOP
Ergoplast FDO
Ethylhexyl phthalate
2-Ethylhexyl phthalate
Eviplast 80
Eviplast 81
Fleximel
Flexol DOP
Flexol plasticizer DOP
Good-Rite GP 264
Hatcol DOP
Hercoflex 260
Kodaflex DOP
Mollan O

Sullivan's Ledge
3.9.2 (nr)
0 0 II

STATUS OF DATA FOR Butyl benzyl phthalate

File On-Line 08/22/88

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	09/01/89
Inhalation RfD Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	on-line	02/01/89
Drinking Water Health Advisories (III.A.)	no data	
U.S. EPA Regulatory Actions (IV.)	no data	

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_I. CHRONIC HEALTH HAZARD ASSESSMENT FOR NONCARCINOGENIC EFFECTS

Substance Name -- Butyl benzyl phthalate
CASRN -- 85-68-7
Last Revised -- 09/01/89

The Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. 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 Background Document 1 in Service Code 5 for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of compounds which 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 when a review of that evaluation is completed.

<<< Butyl benzyl phthalate >>>

__I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfDo)

___I.A.1. ORAL RfD SUMMARY

Critical Effect	Experimental Doses	UF	MF	RfD
Significantly increased liver-	NOAEL: 2800 ppm (159 mg/kg/day)	1000	1	2E-1 mg/kg/day

to-body weight and liver-to-brain weight ratios	LOAEL: 8300 ppm (470 mg/kg/day)

6-Month Rat Study
Oral Exposure (diet)

NTP, 1985

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*Conversion Factors: approximately 300 g bw and 17 g of food consumption/day from data presented in the report

I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

NTP (National Toxicology Program). 1985. Twenty-six week subchronic study and modified mating trial in F344 rats. Butyl benzyl phthalate. Final Report. Project No. 12307-02, -03. Hazelton Laboratories America, Inc. Unpublished study.

NTP (1985) conducted a toxicity study in F344 rats in which 15 males/group were administered concentrations of either 0, 0.03, 0.09, 0.28, 0.83, or 2.5% BBP in the diet for 26 weeks. Using body weight and food consumption data presented in the report these dietary levels correspond to 0, 17, 51, 159, 470, and 1417 mg/kg/day, respectively. In this study powdered rodent meal was provided in such a way that measured food consumption at the highest dose level could include significant waste and spillage rather than true food intake. For this reason a standard food consumption rate of 5% rat body weight was used in the 2.5% dose conversion. Throughout the study body weight gain was significantly depressed at the 2.5% BBP level when compared with the controls. There were no deaths attributed to BBP toxicity. All the rats given 2.5% BBP had small testes upon gross necropsy; 5/11 had soft testes and 1/11 had a small prostate and seminal vesicle. In the 0.03, 0.09, 0.28, and 0.83% dose groups there were no grossly observable effects on male reproductive organs. Terminal mean organ weight values were significantly decreased ($p<0.05$) for the heart, kidney, lungs, seminal vesicles and testes in the 2.5% group. Hematological effects at 2.5% BBP included decreased red cell mass (which the authors state is indicative of deficient hemoglobin synthesis), reduced values for hemoglobin, total RBC and hematocrit. The kidneys of six animals in the 2.5% group contained focal cortical areas of infarct-like atrophy. In addition, testicular lesions were also observed at the 2.5% dose level. Lesions were characterized by atrophy of seminiferous tubules and aspermia. At 0.83% the effects noted were significantly ($p<0.05$) increased absolute liver weight, increased liver-to-body weight and liver-to-brain weight ratios and increases in mean corpuscular hemoglobin. The 0.03, 0.09, 0.28, and 0.83% treatment groups showed no evidence of abnormal morphology in any organ. No adverse effects were observed at the 0.28% treatment level or below.

The only other information on subchronic effects is reported by Krauskopf (1973) from an unpublished study by Monsanto (1972). Rats fed diets containing 0.25% (125 mg/kg/day) and 0.5% (250 mg/kg/day) for 90 days showed no toxic effects. Liver weights were increased in animals fed diets

containing 1.0, 1.5, or 2.0% (500, 750, or 1000 mg/kg/day, respectively) for 90 days, and a mild decrease in growth rate was reported for the 1.5 and 2.0% groups. No other hematologic, histopathologic or urinalysis effects were observed. When dogs were administered gelatin capsules containing doses equivalent to 1.0, 2.0, or 5.0% of the daily diet (10,000 20,000 and 50,000 ppm) for 90 days, no effect on hematological parameters, urinalysis or liver and kidney functions were observed. No further details of this study were available for review.

Similar LOAELs of 470 and 500 mg/kg/day for increased liver weight were identified in both the NTP (1985) and Monsanto (1972) studies, respectively. NOAELs differ slightly: 159 (NTP, 1985) versus 250 mg/kg/day (Monsanto, 1972). It is recommended that the NOAEL of 159 mg/kg/day from the NTP (1985) study be used to derive the RfD for two reasons: 1) the NTP (1985) study is of longer duration, and 2) The Monsanto (1972) study provides an incomplete description of methods comparing study design and clinical analysis. Treatment-related effects across similar dose ranges including liver effects in both studies support the use of 159 mg/kg/day as a NOAEL.

<<< Butyl benzyl phthalate >>>

___I.A.3. UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

UF = 1000. 10 for intraspecies sensitivity, 10 for interspecies variability and 10 for extrapolating from subchronic to chronic NOAELs.

MF = 1.

___I.A.4. ADDITIONAL COMMENTS (ORAL RfD)

Two 14-day studies support the selection of the NTP (1985) bioassay for deriving the oral RfD. Agarwal et al. (1985) administered BBP to male F344 rats in the diet for 14 consecutive days at dose levels of 0.625, 1.25, 2.5, and 5.0%. Significant increases in liver and kidney weights and kidney pathology (proximal tubular regeneration) was observed at 0.625% (375 mg/kg/day), which represents a LOAEL.

In male Sprague-Dawley rats administered 160, 480, or 1600 mg/kg/day BBP for 14 days by gastric intubation, biochemical or morphological changes in the liver as well as effects on testes weights were not observed in the 160 mg/kg/day dose group (Lake et al., 1978). However, at 480 mg/kg/day activities of ethyl morphine N-demethylase and cytochrome oxidase were significantly increased and testicular atrophy was observed in one-third Sprague-Dawley rats in the first portion of this experiment. In the second position, the 480 mg/kg/day dose induced testicular atrophy in one-sixth Sprague-Dawley rats, whereas the Wistar albino strain revealed no such effects. A NOAEL for this study would be 160 mg/kg/day based on the absence of liver and testicular effects.

In an addendum to the NTP (1985) final report, evaluation of the data revealed a significantly reduced total marrow cell count in the 2.5% dose group (NTP, 1986). The change in total cell count was comprised primarily of

significant decreases in neutrophil, metamyelocytes, bands, segmeters, lymphocytes and leasophilic rubricytes. The total marrow cell counts, metamyelocyte, and leasophilic rubricyte counts were also significantly decreased in the lowest dose group, 0.03%. No statistically significant differences were noted in the middle dose groups (0.09, 0.28, or 0.83%) when compared with controls. The addendum states that decreased total marrow cell count in the 0.03 and 2.5% dose group represent change of uncertain meaning in light of the systemic effects noted in the middle dose groups. Trend analysis by the Terpstra-Jonckheere test revealed significantly ($p<0.05\%$) decreasing trends in all of the previously mentioned parameters as well as an increasing trend for monocytes at 0.03 and 2.5%.

NTP (1985) also conducted a male mating trial study concomitantly with the toxicity study. Testicular atrophy was observed in male F344 rats after 10 weeks of exposure to 2.5% (2875 mg/kg/day) BBP. Throughout the study, body weight gain was significantly depressed at the 2.5% BBP level when compared with the controls.

<<< Butyl benzyl phthalate >>>

___I.A.5. CONFIDENCE IN THE ORAL RfD

Study: Medium
Data Base: Low
RfD: Low

The critical study is of adequate quality and is given a medium confidence rating. Since the critical study used only male rats and there are no adequate supporting studies of chronic duration, the data base is given a low confidence rating. Low confidence in the RfD follows.

<<< Butyl benzyl phthalate >>>

___I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

U.S. EPA. 1987a. Health and Environmental Profile for Phthalic Acid Alkyl, Aryl and Alkyl/Aryl Esters. 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. 1987b. Health Effects Assessment for Selected Phthalic Acid Esters. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC.

U.S. EPA. 1988. Drinking Water Criteria Document for Phthalic Acid Esters (PAEs). Prepared by the Office of Health and Environmental Assessment Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. Final Draft.

U.S. EPA (1987a, 1988) have been both OHEA reviewed and Agency reviewed. U.S. EPA (1987b) has been OHEA reviewed.

Agency RfD Work Group Review: 06/15/89

Verification Date: 06/15/89

___I.A.7. EPA CONTACTS (ORAL RfD)

Robert Vanderslice / ODW -- (202)475-6711 / FTS 475-6711

Annette Gatchett / ORD -- (513)569-7813 / FTS 684-7813

------<<< Butyl benzyl phthalate >>>------

__I.B. REFERENCE DOSE FOR CHRONIC INHALATION EXPOSURE (RfDi)

Not available at this time

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_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Butyl benzyl phthalate
CASRN -- 85-68-7
Last Revised -- 02/01/89

Section II provides information on three aspects of the carcinogenic risk assessment for the agent in question; the U.S. EPA classification, and quantitative estimates of risk from oral exposure and from inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen. 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. Background Document 2 (Service Code 5) provides details on the rationale and methods used to derive the carcinogenicity values found in IRIS. Users are referred to Section I for information on long-term toxic effects other than carcinogenicity.

<<< Butyl benzyl phthalate >>>

__II.A. EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

___II.A.1. WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification -- C; possible human carcinogen.

Basis -- Based on statistically significant increase in mononuclear cell leukemia in female rats; the response in male rats was inconclusive and there was no such response in mice.

___II.A.2. HUMAN CARCINOGENICITY DATA

None.

<<< Butyl benzyl phthalate >>>

___II.A.3. ANIMAL CARCINOGENICITY DATA

Limited. A bioassay was performed by the NTP (1982) to evaluate the carcinogenic potential of orally administered butyl benzyl phthalate (BBP) to both rats and mice. Dietary levels of 0, 6000, and 12,000 ppm BBP were fed to groups of 50 male and 50 female F344 rats and 50 male and 50 female B6C3F1 mice for 103 weeks. The male rats at both dose levels experienced high mortality within the first 30 weeks of the study due to apparent internal hemorrhaging; all male rats were, thus, terminated at 30 weeks. No chronic toxicity or carcinogenic effects were observed in male or female mice. Among female rats a statistically significant increase in mononuclear cell leukemia (MCL) or lymphoma ($p=0.007$) was observed at the high dose level compared with controls with an increasing trend at $p=0.006$. The time to first tumor was 83 weeks in control as well as in the high-dose group. NTP indicated that BBP was "probably" carcinogenic in female rats. The tumor incidence was 7/49 (14%) for controls, 7/49 (14%) in low dose and 19/50 (38%) in the high dose as compared with historical control incidence in the laboratory of 19% (12-24% range).

Given the similarity of the MCL pathology in the control and the dosed female rats as well as the absence of a reduction in time to first tumor, the response is judged to be an acceleration of an old age tumor in the F344 rats. This weakens somewhat the interpretive value of the MCL response. The NTP has initiated a retest in the rats.

BBP did not induce lung adenomas in strain A mice administered 24 intraperitoneal injections of 160, 400 or 800 mg/kg (Theiss et al., 1977).

<<< Butyl benzyl phthalate >>>

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Studies indicate that BBP is not a direct acting mutagen in the reverse mutation assay in Salmonella typhimurium (Rubin et al., 1979; Kozumbo et al., 1982; Zeiger et al., 1982) or in E. coli (NTP, 1982). Mammalian cytogenicity studies using chinese hamster ovary cells were also negative (NTP, 1982). NTP (1982) noted that additional studies on metabolites, benzyl alcohol and n-butanol was important.

------<<< Butyl benzyl phthalate >>>------

__II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

Not available. The qualitative weaknesses of the MCL response does not provide a compelling basis to model the dose-response data.

------<<< Butyl benzyl phthalate >>>------

__II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

Not available.

------<<< Butyl benzyl phthalate >>>------

__II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

___II.D.1. EPA DOCUMENTATION

U.S. EPA. 1987. Drinking Water Criteria Document for Phthalic Acid Esters. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. External Review Draft.

___II.D.2. REVIEW (CARCINOGENICITY ASSESSMENT)

The 1987 Draft Drinking Water Quality Criteria Document received Agency review.

Agency Work Group Review: 08/26/87

Verification Date: 08/26/87

___II.D.3. U.S. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

Robert Vanderslice / ODW -- (202)475-6711 / FTS 475-6711

Annette M. Gatchett / ORD -- (513)569-7813 / FTS 684-7813

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_III. HEALTH HAZARD ASSESSMENTS FOR VARIED EXPOSURE DURATIONS

Substance Name -- Butyl benzyl phthalate
CASRN -- 85-68-7

Not available at this time

_IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- Butyl benzyl phthalate
CASRN -- 85-68-7

Not available at this time

_V. SUPPLEMENTARY DATA

Substance Name -- Butyl benzyl phthalate
CASRN -- 85-68-7

Not available at this time

_VI. BIBLIOGRAPHY

Substance Name -- Butyl benzyl phthalate
CASRN -- 85-68-7
Last Revised -- 09/01/89

__VI.A. ORAL RfD REFERENCES

Agarwal, D.K., R.R. Maronpot, J.C. Lamb, IV and W.M. Kluwe. 1985. Adverse effects of butylbenzyl phthalate on the reproductive and hematopoietic systems of male rats. Toxicology. 35: 189-206.

Krauskopf, L.G. 1973. Studies on the toxicity of phthalates via ingestion. Environ. Health Perspect. 3: 61-72.

Lake, B.G., R.A. Harris, P. Grasso and S.D. Gangollia. 1978. Studies on the metabolism and biological effects of n-butyl benzyl phthalate in the rat. Prepared by British Industrial Biological Research Association for Monsanto,

Report No. 232/78, June.

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NTP (National Toxicology Program). 1985. Twenty-six week subchronic study and modified mating trial in F344 rats. Butyl benzyl phthalate. Final Report. Project No. 12307-02, -03. Hazelton Laboratories America, Inc. Unpublished study.

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U.S. EPA. 1987a. Health and Environmental Profile for Phthalic Acid Alkyl, Aryl and Alkyl/Aryl Esters. 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. 1987b. Health Effects Assessment for Selected Phthalic Acid Esters. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC.

U.S. EPA. 1988. Drinking Water Criteria Document for Phthalic Acid Esters (PAEs). Prepared by the Office of Health and Environmental Assessment Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. Final Draft.

------<<< Butyl benzyl phthalate >>>------

__VI.B. INHALATION RfD REFERENCES

None

------<<< Butyl benzyl phthalate >>>------

__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

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NTP (National Toxicology Program). 1982. Carcinogenesis Bioassay of Butyl Benzyl Phthalate (CAS No. 85-68-7) in F344 Rats and B6C3F1 Mice (Feed Study). NTP Tech. Rep. Ser. TR No. 213, NTP, Research Triangle Park, NC. p. 98

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of phthalic acid esters: Positive response of the dimethyl and diethyl esters in TA100. Soc. Toxicol. Ann. Meet., New Orleans, March 11-15. p. 11. (Abstract)

Theiss, J.C., G.D. Stoner, M.B. Shimkin and E.K. Weisburger. 1977. Test for carcinogenicity of organic contaminants of United States drinking waters by pulmonary tumor response in strain A mice. Cancer Res. 37: 2717-2720.

U.S. EPA. 1987. Drinking Water Criteria Document for Phthalic Acid Esters. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. External Review Draft.

Zeiger, E., S. Haworth, W. Speck and V. Mortlemans. 1982. Phthalate ester testing in the National Toxicology Program's environmental mutagenesis test development program. Environ. Health Perspect. 45: 99-101.

------<<< Butyl benzyl phthalate >>>------

__VI.D. DRINKING WATER HA REFERENCES

None

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SYNONYMS

85-68-7
BBP
1,2-BENZENEDICARBOXYLIC ACID, BUTYL PHENYLMETHYL ESTER
BENZYL-BUTYLESTER KYSELINY FTALOVE
BENZYL BUTYL PHTHALATE
BENZYL n-BUTYL PHTHALATE
Butyl benzyl phthalate
n-BUTYL BENZYL PHTHALATE
BUTYL PHENYLMETHYL 1,2-BENZENEDICARBOXYLATE
NCI-C54375
PALATINOL BB
PHTHALIC ACID, BENZYL BUTYL ESTER
SANTICIZER 160
SICOL 160
UNIMOLL BB

Enter keywords or Read or Scan or Mail
--84-74-2
Searching - Please wait...
1 Occurrences...

Cadmium; CASRN 7440-43-9 (08/01/90)

Health risk assessment information on a chemical is included in IRIS only after a comprehensive review of chronic toxicity data by work groups composed of U.S. EPA scientists from several Program Offices. The summaries presented in Sections I and II represent a consensus reached in the review process. The other sections contain U.S. EPA information which is specific to a particular EPA program and has been subject to review procedures prescribed by that Program Office. The regulatory actions in Section IV may not be based on the most current risk assessment, or may be based on a current, but unreviewed, risk assessment, and may take into account factors other than health effects (e.g., treatment technology). When considering the use of regulatory action data for a particular situation, note the date of the regulatory action, the date of the most recent risk assessment relating to that action, and whether technological factors were considered. Background information and explanations of the methods used to derive the values given in IRIS are provided in the five Background Documents in Service Code 5, which correspond to Sections I through V of the chemical files.

STATUS OF DATA FOR Cadmium

File On-Line 03/31/87

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	10/01/89
Inhalation RfC Assessment (I.B.)	pending	
Carcinogenicity Assessment (II.)	on-line	08/01/90
Drinking Water Health Advisories (III.A.)	no data	
U.S. EPA Regulatory Actions (IV.)	on-line	01/01/89
Supplementary Data (V.)	no data	

_I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

__I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name -- Cadmium
CASRN -- 7440-43-9
Last Revised -- 10/01/89

The Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. 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 Background Document 1 in Service Code 5 for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of compounds which 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 when a review of that evaluation is completed.

<<< Cadmium >>>

___I.A.1. ORAL RfD SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfD
Significant proteinuria	NOAEL (water): 0.005 mg/kg/day	10	1	5E-4 mg/kg/day (water)
Human studies involving chronic exposures	NOAEL (food): 0.01 mg/kg/day	10	1	1E-3 mg/kg/day (food)
U.S. EPA, 1985				

*Conversion Factors: See text for discussion

<<< Cadmium >>>

___I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

U.S. EPA. 1985. Drinking Water Criteria Document on Cadmium. Office of Drinking Water, Washington, DC. (Final draft)

A concentration of 200 ug cadmium (Cd)/gm wet human renal cortex is the highest renal level not associated with significant proteinuria (U.S. EPA, 1985). A toxicokinetic model is available to determine the level of chronic human oral exposure (NOAEL) which results in 200 ug Cd/gm wet human renal cortex; the model assumes that 0.01% day of the Cd body burden is eliminated per day (U.S. EPA, 1985). Assuming 2.5% absorption of Cd from food or 5% from water, the toxicokinetic model predicts that the NOAEL for chronic Cd exposure is 0.005 and 0.01 mg Cd/kg/day from water and food, respectively (i.e., levels which would result in 200 ug Cd/gm wet weight human renal cortex). Thus, based on an estimated NOAEL of 0.005 mg Cd/kg/day for Cd in drinking water and an UF of 10, an RfD of 0.0005 mg Cd/kg/day (water) was calculated; an equivalent RfD for Cd in food is 0.001 mg Cd/kg/day (see Section VI.A. for references).

<<< Cadmium >>>

___I.A.3. UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

UF = 10. This uncertainty factor is used to account for intrahuman variability to the toxicity of this chemical in the absence of specific data on sensitive individuals.

MF = 1.

<<< Cadmium >>>

___I.A.4. ADDITIONAL COMMENTS (ORAL RfD)

Cd is unusual in relation to most, if not all, of the substances for which an oral RfD has been determined in that a vast quantity of both human and animal toxicity data are available. The RfD is based on the highest level of Cd in the human renal cortex (i.e., the critical level) not associated with significant proteinuria (i.e., the critical effect). A toxicokinetic model has been used to determine the highest level of exposure associated with the lack of a critical effect. Since the fraction of ingested Cd that is absorbed appears to vary with the source (e.g., food vs. drinking water), it is necessary to allow for this difference in absorption when using the toxicokinetic model to determine an RfD.

<<< Cadmium >>>

___I.A.5. CONFIDENCE IN THE ORAL RfD

Study: Not applicable
Data Base: High
RfD: High

The choice of NOAEL does not reflect the information from any single study. Rather, it reflects the data obtained from many studies on the toxicity of cadmium in both humans and animals. These data also permit calculation of pharmacokinetic parameters of cadmium absorption, distribution, metabolism and elimination. All of this information considered together gives high confidence in the data base. High confidence in either RfD follows as well.

<<< Cadmium >>>

___I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

U.S. EPA. 1985. Drinking Water Criteria Document on Cadmium. Office of Drinking Water, Washington, DC. (Final draft)

Agency RfD Work Group Review: 05/15/86, 08/19/86, 09/17/87, 12/15/87, 01/20/88, 05/25/88

Verification Date: 05/25/88

___I.A.7. EPA CONTACTS (ORAL RfD)

Ken Bailey / ODW -- (202)382-5535 / FTS 382-5535

Warren Banks / OWRS -- (202)382-7893 / FTS 382-7893

__I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

Substance Name -- Cadmium
CASRN -- 7440-43-9

A risk assessment for this substance/agent is under review by an EPA work group.

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_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Cadmium
CASRN -- 7440-43-9
Last Revised -- 08/01/90

Section II provides information on three aspects of the carcinogenic risk assessment for the agent in question; the U.S. EPA classification, and quantitative estimates of risk from oral exposure and from inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen. 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. Background Document 2 (Service Code 5) provides details on the rationale and methods used to derive the carcinogenicity values found in IRIS. Users are referred to Section I for information on long-term toxic effects other than carcinogenicity.

<<< Cadmium >>>

__II.A. EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

___II.A.1. WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification -- B1; probable human carcinogen by inhalation

Basis -- Limited evidence from epidemiologic studies of occupationally-exposed workers; sufficient evidence of carcinogenicity in rats and mice by inhalation and intramuscular and subcutaneous injection. Seven studies in rats and mice wherein cadmium salts (acetate, sulfate, chloride) were administered orally have shown no evidence of carcinogenic response.

<<< Cadmium >>>

___II.A.2. HUMAN CARCINOGENICITY DATA

Limited. A 2-fold excess risk of lung cancer was observed in cadmium smelter workers. The cohort consisted of 602 white males who had been employed in production work a minimum of 6 months during the years 1940-1969. The population was followed to the end of 1978. Urine cadmium data available for 261 workers employed after 1960 suggested a highly exposed population. The authors were able to ascertain that the increased lung cancer risk was probably not due to the presence of arsenic or to smoking (Thun et al., 1985). An evaluation by the Carcinogen Assessment Group of these possible confounding factors has indicated that the assumptions and methods used in accounting for them may not be valid. As the SMRs observed were low and there is a lack of clear cut evidence of a causal relationship of the cadmium exposure only, this study is considered to supply only limited evidence of human carcinogenicity.

An excess lung cancer risk was also observed in three other studies which were, however, compromised by the presence of other carcinogens (arsenic, smoking) in the exposure or by a small population (Varner, 1983; Sorahan and Waterhouse, 1983; Armstrong and Kazantzis, 1983).

Four studies of workers exposed to cadmium dust or fumes provided evidence of a statistically significant positive association with prostate cancer (Kipling and Waterhouse, 1967; Lemen et al., 1976; Holden, 1980; Sorahan and Waterhouse, 1983), but the total number of cases was small in each study. The Thun et al. (1985) study is an update of an earlier study (Lemen et al., 1976) and does not show excess prostate cancer risk in these workers. Studies of human ingestion of cadmium are inadequate to assess carcinogenicity.

<<< Cadmium >>>

___II.A.3. ANIMAL CARCINOGENICITY DATA

Exposure of Wistar rats to cadmium as cadmium chloride at concentrations of 12.5, 25 and 50 ug/cu.m for 18 months, with an additional 13-month observation period, resulted in significant increases in lung tumors (Takenaka et al., 1983). Intratracheal instillation of cadmium oxide did not produce lung tumors in Fischer 344 rats but rather mammary tumors in females and tumors at multiple sites in males (Sanders and Mahaffey, 1984). Injection site tumors and distant site tumors (for example, testicular) have been reported by a number of authors as a consequence of intramuscular or subcutaneous administration of cadmium metal and chloride, sulfate, oxide and sulfide compounds of cadmium to rats and mice (U.S. EPA, 1985). Seven studies in rats and mice where cadmium salts (acetate, sulfate, chloride) were administered orally have shown no evidence of a carcinogenic response.

<<< Cadmium >>>

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Results of mutagenicity tests in bacteria and yeast have been inconclusive. Positive responses have been obtained in mutation assays in Chinese hamster cells (Dom and V79 lines) and in mouse lymphoma cells (Casto, 1976; Ochi and Ohsawa, 1983; Oberly et al., 1982).

Conflicting results have been obtained in assays of chromosomal aberrations in human lymphocytes treated in vitro or obtained from exposed workers. Cadmium treatment in vivo or in vitro appears to interfere with spindle formation and to result in aneuploidy in germ cells of mice and hamsters (Shimada et al., 1976; Watanabe et al., 1979; Gilliavod and Leonard, 1975).

---------<<< Cadmium >>>---------

__II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

Not available. There are no positive studies suitable for quantitation.

---------<<< Cadmium >>>---------

__II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

___II.C.1. SUMMARY OF RISK ESTIMATES

Inhalation Slope Factor -- 6.1E+0/mg/kg/day

Inhalation Unit Risk -- 1.8E-3/ug/cu.m

Extrapolation Method -- Two stage; only first affected by exposure; extra risk

Air Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	6E-2 ug/cu.m
E-5 (1 in 100,000)	6E-3 ug/cu.m
E-6 (1 in 1,000,000)	6E-4 ug/cu.m

<<< Cadmium >>>

___II.C.2. DOSE-RESPONSE DATA FOR CARCINOGENICITY, INHALATION EXPOSURE

Tumor Type -- lung, trachea, bronchus cancer deaths
Test Animals -- human/white male
Route -- inhalation, exposure in the workplace
Reference -- Thun et al., 1985

Cumulative Exposure (mg/day/cu.m)	Median Observation	24 hour/ ug/cu.m Equivalent	No. of Expected Lung, Trachea and Bronchus Cancers Assuming No Cadmium Effect	Observed No. of Deaths (lung, trachea, bronchus cancers)
less than or equal to 584	280	168	3.77	2
585-2920	1210	727	4.61	7
greater than or equal to 2921	4200	2522	2.50	7

The 24-hour equivalent = median observation x 10E-3 x 8/24 x 1/365 x 240/365.

<<< Cadmium >>>

___II.C.3. ADDITIONAL COMMENTS (CARCINOGENICITY, INHALATION EXPOSURE)

The unit risk should not be used if the air concentration exceeds 6 ug/cu.m, since above this concentration the slope factor may differ from that stated.

<<< Cadmium >>>

___II.C.4. DISCUSSION OF CONFIDENCE (CARCINOGENICITY, INHALATION EXPOSURE)

The data were derived from a relatively large cohort. Effects of arsenic and smoking were accounted for in the quantitative analysis for cadmium effects.

A slope factor derived from cadmium chloride inhalation assay data in rats (Takenaka et al., 1983) equals 3.4E-1/ug/kg/day for elemental cadmium or 2.1E-1/ug/kg/day for cadmium chloride. An inhalation unit risk for cadmium based on this analysis is 9.2E-2/ug/cu.m. While this estimate is higher than that derived from human data (1.8E-3/ug/cu.m) and thus more conservative, it was felt that the use of available human data was more reliable because of species variations in response and the type of exposure (cadmium salt vs. cadmium fume and cadmium oxide).

---------<<< Cadmium >>>---------

__II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

___II.D.1. EPA DOCUMENTATION

U.S. EPA. 1985. Updated Mutagenicity and Carcinogenicity Assessment of Cadmium: Addendum to the Health Assessment Document for Cadmium (May 1981,

EPA 600/B-B1-023). EPA 600/B-83-025F.

<<< Cadmium >>>

___II.D.2. REVIEW (CARCINOGENICITY ASSESSMENT)

The Addendum to the Cadmium Health Assessment has received both Agency and external review.

Agency Work Group Review: 11/12/86

Verification Date: 11/12/86

___II.D.3. U.S. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

William E. Pepelko / ORD -- (202)382-5904 / FTS 382-5904

David Bayliss / ORD -- (202)382-5726 / FTS 382-5726

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_III. HEALTH HAZARD ASSESSMENTS FOR VARIED EXPOSURE DURATIONS

__III.A. DRINKING WATER HEALTH ADVISORIES

Substance Name -- Cadmium
CASRN -- 7440-43-9

Not available at this time.

__III.B. OTHER ASSESSMENTS

Substance Name -- Cadmium
CASRN -- 7440-43-9

Content to be determined.

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_IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- Cadmium
CASRN -- 7440-43-9
Last Revised -- 01/01/89

EPA risk assessments may be updated as new data are published and as assessment methodologies evolve. Regulatory actions are frequently not updated at the same time. Compare the dates for the regulatory actions in this section with the verification dates for the risk assessments in sections I and II, as this may explain inconsistencies. Also note that some regulatory actions consider factors not related to health risk, such as technical or economic feasibility. Such considerations are indicated for each action. In addition, not all of the regulatory actions listed in this section involve enforceable federal standards. Please direct any questions you may have concerning these regulatory actions to the U.S. EPA contact listed for that particular action. Users are strongly urged to read the background information on each regulatory action in Background Document 4 in Service Code 5.

<<< Cadmium >>>

__IV.A. CLEAN AIR ACT (CAA)

___IV.A.1. CAA REGULATORY DECISION

Action -- Intent to list under Section 112

Considers technological or economic feasibility? -- NO

Discussion -- Cadmium is a probable human caracinogen (IARC category 2A) and according to EPA's preliminary risk assessment from ambient air exposures, public health risks are significant (3-7 cancer cases/year and maximum lifetime individual risks of 0.003. Thus, EPA indicated that it intends to add cadmium to the list of hazardous air pollutants for which it intends to establish emission standards under section 112(b)(1)(A) of the Clean Air Act. The EPA will decide whether to add cadmium to the list only after studying possible techniques that might be used to control emissions and further assessing the public health risks. The EPA will add cadmium to the list if emission standards are warranted.

Reference -- 50 FR 42000 (10/16/85)

EPA Contact -- Emissions Standards Division, OAQPS
(919)541-5571 / FTS 629-5571

---------<<< Cadmium >>>---------

__IV.B. SAFE DRINKING WATER ACT (SDWA)

___IV.B.1. MAXIMUM CONTAMINANT LEVEL GOAL (MCLG) for Drinking Water

Value (status) -- 0.005 mg/L (Proposed, 1985)

Considers technological or economic feasibility? -- NO

Discussion -- An MCLG of 0.005 mg/L for cadmium is proposed based on a provisional DWEL of 0.018 mg/L and drinking water contribution (plus aquatic organism) of 25%. A DWEL of 0.018 mg/L was calculated from a LOAEL of 0.352 mg/day for renal toxicity in humans (calculated), with an uncertainty factor of 10 applied and consumption of 2 L of water/day assumed.

Reference -- 50 FR 46936 Part IV (11/13/85)

EPA Contact -- Criteria and Standards Division, ODW /
(202)382-7571 / FTS 382-7571; or Drinking Water Hotline / (800)426-4791

<<< Cadmium >>>

___IV.B.2. MAXIMUM CONTAMINANT LEVEL (MCL) for Drinking Water

Value (status) -- 0.01 mg/L (Interim, 1980)

Considers technological or economic feasibility? -- YES

Discussion --

Reference -- 45 FR 57332

EPA Contact -- Kenneth Bailey / Criteria and Standards Division, ODW /
(202)382-7571 / FTS 382-7571; or Drinking Water Hotline / (800)426-4791

---------<<< Cadmium >>>---------

__IV.C. CLEAN WATER ACT (CWA)

___IV.C.1. AMBIENT WATER QUALITY CRITERIA, Human Health

Water and Fish Consumption: 1E+1 ug/L

Fish Consumption Only: None

Considers technological or economic feasibility? -- NO

Discussion -- The criteria is the same as the existing standard for drinking water.

Reference -- 45 FR 79318 (11/28/80)

EPA Contact -- Criteria and Standards Division, OWRS
(202)475-7315 / FTS 475-7315

<<< Cadmium >>>

___IV.C.2. AMBIENT WATER QUALITY CRITERIA, Aquatic Organisms

Freshwater:

Acute -- 3.9E+0 ug/L (1-hour average)
Chronic -- 1.1E+0 ug/L (4-day average)

Marine:

Acute -- 4.3E+1 ug/L (1-hour average)
Chronic -- 9.3E+0 ug/L (4-day average)

Considers technological or economic feasibility? -- NO

Discussion -- The freshwater criteria are hardness dependent. Values given here are calculated at a hardness of 100 mg/L CaCO3. A complete discussion can be found in the referenced notice.

Reference -- 50 FR 30784 (07/29/85)

EPA Contact -- Criteria and Standards Division, OWRS
(202)475-7315 / FTS 475-7315

---------<<< Cadmium >>>---------

__IV.D. FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT (FIFRA)

___IV.D.1. PESTICIDE ACTIVE INGREDIENT, Registration Standard

None

<<< Cadmium >>>

___IV.D.2. PESTICIDE ACTIVE INGREDIENT, Special Review

Action -- Final regulatory action - PD4 (1987)

Considers technological or economic feasibility? -- YES

Summary of regulatory action -- The basis for selection of the final regulatory option is presented in Position Document 4.

Reference -- 52 FR 31076 (08/19/87)

EPA Contact -- Special Review Branch, OPP / (703)557-7400 / FTS 557-7400

---------<<< Cadmium >>>---------

__IV.E. TOXIC SUBSTANCES CONTROL ACT (TSCA)

No data available

---------<<< Cadmium >>>---------

__IV.F. RESOURCE CONSERVATION AND RECOVERY ACT (RCRA)

___IV.F.1. RCRA APPENDIX IX, for Ground Water Monitoring

Status -- Listed

Reference -- 52 FR 25942 (07/09/87)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)382-3000 / FTS 382-3000

---------<<< Cadmium >>>---------

__IV.G. SUPERFUND (CERCLA)

___IV.G.1. REPORTABLE QUANTITY (RQ) for Release into the Environment

Value (status) -- 10 pounds (Proposed, 1987)

Considers technological or economic feasibility? -- NO

Discussion -- The proposed RQ for cadmium is 10 pounds, based on potential carcinogenicity. Available data indicate a hazard ranking of medium, based on a potency factor of 57.87/mg/kg/day and weight-of-evidence group B1, which corresponds to an RQ of 10 pounds. Cadmium has also been found to bioaccumulate in the tissues of aquatic and marine organisms, and has the potential to concentrate in the food chain.

Reference -- 52 FR 8140 (03/16/87)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)382-3000 / FTS 382-3000

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_V. SUPPLEMENTARY DATA

Substance Name -- Cadmium
CASRN -- 7440-43-9

Not available at this time.

_VI. BIBLIOGRAPHY

Substance Name -- Cadmium
CASRN -- 7440-43-9
Last Revised -- 10/01/89

__VI.A. ORAL RfD REFERENCES

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WHO (World Health Organization). 1984. Guidelines for drinking water quality -- recommendations. Vol. 1. Geneva, Switzerland.

---------<<< Cadmium >>>---------

__VI.B. INHALATION RfD REFERENCES

None

---------<<< Cadmium >>>---------

__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

Armstrong, B.G. and G. Kazantzis. 1983. The mortality of cadmium workers. Lancet. June 25, 1983: 1425-1427.

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Oberly, T., C.E. Piper and D.S. McDonald. 1982. Mutagenicty of metal salts in the L5178 Y mouse lymphoma assay. J. Toxicol. Environ. Health. 9: 367-376.

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Shimada, T., T. Watanabe and A. Endo. 1976. Potential mutagenicity of cadmium in mammalian oocytes. Mutat. Res. 40: 389-396.

Sorahan, T. and J.A.H. Waterhouse. 1983. Mortality study of nickel-cadmium battery workers by the method of regression models in life tables. Br. J. Ind. Med. 40: 293-300.

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Thun, M.J., T.M. Schnorr, A.B. Smith and W.E. Halperin. 1985. Mortality among a cohort of U.S. cadmium production workers: An update. J. Natl. Cancer Inst. 74(2): 325-333.

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---------<<< Cadmium >>>---------

__VI.D. DRINKING WATER HA REFERENCES

None

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SYNONYMS

Substance Name -- Cadmium
CASRN -- 7440-43-9
Last Revised -- / /

7440-43-9
C.I. 77180
Cadmium
KADMIUM

Enter keywords or Read or Scan or Mail
--7439-97-6
Searching - Please wait...
1 Occurrences...

Enter keywords or Read or Scan or Mail
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3.9.2 (ne)
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STATUS OF DATA FOR Carbon tetrachloride

File On-Line 01/31/87

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	12/01/89
Inhalation RfC Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	on-line	03/01/88
Drinking Water Health Advisories (III.A.)	on-line	08/01/90
U.S. EPA Regulatory Actions (IV.)	on-line	03/01/88
Supplementary Data (V.)	no data	

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I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name -- Carbon tetrachloride
CASRN -- 56-23-5
Last Revised -- 12/01/89

The Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. 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 Background Document 1 in Service Code 5 for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of compounds which 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 when a review of that evaluation is completed.

<<< Carbon tetrachloride >>>

I.A.1. ORAL RfD SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfD
Liver lesions	NOAEL: 1 mg/kg/day	1000	1	7E-4

	(converted to 0.71 mg/kg/day)	mg/kg/day
Subchronic Rat Gavage Study		
	LOAEL: 10 mg/kg/day	
Bruckner et al., 1986	(converted to 7.1 mg/kg/day)	

*Conversion Factors: 1 mg/kg/day (NOAEL) x 5/7 = 0.71 mg/kg/day (5 day/week dosing regimen)

<<< Carbon tetrachloride >>>

___I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

Bruckner, J.V., W.F. MacKenzie, S. Muralidhara, R. Luthra, G.M. Kyle and D. Acosta. 1986. Oral toxicity of carbon tetrachloride: Acute, subacute and subchronic studies in rats. Fund. Appl. Toxicol. 6(1): 16-34.

Male Sprague-Dawley rats were given 1, 10, or 33 mg CCl4/kg/day by corn oil gavage, 5 days/week for 12 weeks. Liver lesions, as evidenced by mild centrilobular vacuolization and statistically significant increases in serum sorbitol dehydrogenase activity, were observed at the 10 and 33 mg/kg/day doses.

<<< Carbon tetrachloride >>>

___I.A.3. UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

UF = 1000. UF allows for interspecies and intrahuman variability and extrapolation from subchronic to chronic duration of exposure.

MF = 1.

<<< Carbon tetrachloride >>>

___I.A.4. ADDITIONAL COMMENTS (ORAL RfD)

The draft Bruckner et al. (1983) study was used as the basis for the RfD in the 05/20/85 verification meeting. This study was subsequently published (Bruckner et al., 1986). No change to the verified value was required.

Subchronic studies in mice gavaged with carbon tetrachloride in corn oil support the critical effect and the magnitude of the NOAEL and LOAEL found in the rat studies (Condie et al., 1986; Hayes et al., 1985). Additional studies (Alumot et al., 1976; NCI, 1976) in rats lend moderate support to the choice of a NOAEL in the chosen rat study.

<<< Carbon tetrachloride >>>

___I.A.5. CONFIDENCE IN THE ORAL RfD

Study: High
Data Base: Medium
RfD: Medium

The principal study was well conducted and good dose-response was observed in the liver, which is the target organ for CCl4 toxicity; thus, high confidence was assigned. Four additional subchronic studies support the RfD, but reproductive and teratology endpoints are not well investigated; thus, the data base rates a medium confidence. Medium confidence in the RfD follows.

<<< Carbon tetrachloride >>>

___I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

U.S. EPA. 1985. Drinking Water Criteria Document for Carbon Tetrachloride. Office of Drinking Water, Washington, DC.

Public review of RfD following ODW proposal of RMCL in June 1984.

Science Advisory Board review of RfD on January 14, 1986.

Agency RfD Work Group Review: 05/20/85

Verification Date: 05/20/85

___I.A.7. EPA CONTACTS (ORAL RfD)

Larry Anderson / ODW -- (202)382-7587 / FTS 382-7587

Michael L. Dourson / ORD -- (513)569-7544 / FTS 684-7544

__I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

Substance Name -- Carbon tetrachloride
CASRN -- 56-23-5

Not available at this time.

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_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Carbon tetrachloride
CASRN -- 56-23-5
Last Revised -- 03/01/88

Section II provides information on three aspects of the carcinogenic risk assessment for the agent in question; the U.S. EPA classification, and quant-

itative estimates of risk from oral exposure and from inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen. 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. Background Document 2 (Service Code 5) provides details on the rationale and methods used to derive the carcinogenicity values found in IRIS. Users are referred to Section I for information on long-term toxic effects other than carcinogenicity.

<<< Carbon tetrachloride >>>

II.A. EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

II.A.1. WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification -- B2; probable human carcinogen

Basis -- Carcinogenicity in rats, mice, and hamsters

<<< Carbon tetrachloride >>>

II.A.2. HUMAN CARCINOGENICITY DATA

Inadequate. There have been three case reports of liver tumors developing after carbon tetrachloride exposure. Several studies of workers who may have used carbon tetrachloride have suggested that these workers may have an excess risk of cancer.

<<< Carbon tetrachloride >>>

II.A.3. ANIMAL CARCINOGENICITY DATA

Sufficient. Carbon tetrachloride has proved carcinogenic to all species evaluated (rats, mice, and hamsters), producing hepatocellular carcinomas in all of these species.

Hepatocellular carcinomas developed in Osborne-Mendel, Japanese, and Wistar rats, but not Sprague-Dawley or Black rats, following s.c. injection of carbon tetrachloride. Hyperplastic nodules were noted in Buffalo rats treated s.c. (Reuber and Glover, 1967a,b, 1970). Sensitivity varied among strains, and trends in incidence appeared inversely related to severity of cirrhosis.

Fifty Osborne-Mendel rats/sex were administered carbon tetrachloride in corn oil by gavage 5 times/week for 78 weeks at 47 and 94 mg/kg bw for males and 80 and 159 mg/kg bw for females. At 110 weeks, only 7/50 males and 14/50 females survived the high-dose treatment. Similarly, 14/50 males and 20/50 females survived the low-dose treatment. The incidence of hepatocellular carcinomas was increased in animals exposed to CCl4 as compared with pooled

colony controls. The apparent decrease (1/14) in the incidence of hepatocellular carcinomas in female rats at the high dose in comparison with the low-dose (4/20) treatment was attributed by the authors to increased lethality before tumors could be expressed (NCI, 1976a,b, 1977).

In this same study, B6C3F1 mice of both sexes received 250 or 2500 mg/kg CCl4. Hepatocellular carcinomas were found in 49/49, 47/48 (low- and high-dose males); 40/40, 43/45 (low- and high-dose females) in comparison with the control males (5/77) and females (1/80).

Carbon tetrachloride administered by gavage has also been shown to produce neoplastic changes in livers of five additional strains (C3H, A, Y, C, and L) (Andervont, 1958; Edwards, 1941; Eschenbrenner and Miller 1943; Edwards and Dalton, 1942; Edwards et al., 1942). In the last study, L mice, which have a low incidence of spontaneous hepatomas, were treated 2 or 3 times/week over a period of 4 months for a total of 46 treatments with 0.1 mL of a 40% solution of carbon tetrachloride. Animals were killed 3-3.5 months after the last treatment. The combined hepatoma incidence of treated male mice was 47% (7/15) and of treated females 38% (3/8) in comparison with 2/71 (untreated male controls) and 0/81 (untreated female controls).

As part of a larger study of liver carcinogens, Della Porta et al. (1961) gave weekly gavage treatments to Syrian golden hamsters for 30 weeks. For the first 7 weeks, 0.25 mL of a corn oil solution containing 12.5 uL carbon tetrachloride was given; this dose was halved for the remainder of the exposure period. All animals were observed for an additional 25 weeks. Each of 10 hamsters killed or dying between weeks 43 and 55 had liver cell carcinomas, in comparison with 0 in controls.

<<< Carbon tetrachloride >>>

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Carbon tetrachloride was not mutagenic either for S. typhimurium or E. coli (McCann et al., 1975; Simmon et al., 1977; Uehleke et al., 1976). Carbon tetrachloride at low concentrations did not produce chromatid or chromosomal aberrations in an epithelial cell line derived from rat liver (Dean and Hodson-Walker, 1979). In vivo unscheduled DNA synthesis assays have likewise been negative (Mirsalis and Butterworth, 1980; Mirsalis et al., 1982). Carbon tetrachloride produced mitotic recombination and gene conversion in S. cerevisiae, but only at concentrations which reduced viability to 10% (Callen et al., 1980). Carbon tetrachloride may be metabolized to reactive intermediates capable of binding to cellular nucleophilic macromolecules. Negative responses in bacterial mutagenicity assays may have been due to inadequate metabolic activation in the test systems.

---------<<< Carbon tetrachloride >>>---------

__II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

___II.B.1. SUMMARY OF RISK ESTIMATES

Oral Slope Factor -- 1.3E-1/mg/kg/day

Drinking Water Unit Risk -- 3.7E-6/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)	3E+1 ug/L
E-5 (1 in 100,000)	3E+0 ug/L
E-6 (1 in 1,000,000)	3E-1 ug/L

<<< Carbon tetrachloride >>>

___II.B.2. DOSE-RESPONSE DATA (CARCINOGENICITY, ORAL EXPOSURE)

Species/Strain Tumor Type		Dose Administered mg/day	Dose Human Equivalent mg/kg/day	Tumor Incidence	Unit Risk (/ug/L)	Reference
Hepatocellular carcinomas/ hepatomas	Route: Oral, gavage					
Hamster/Syrian, male and female		0	0	0/80	3.4E-5	Della Porta et al., 1961
		0.95	1.02	10/19		
Mouse/L, male and female		0	0	2/52	9.4E-6	Edwards et al., 1942
		15	2.3	34/73		
Mouse/B6C3F1, male and female		0	0	6/157	1.8E-6	NCI, 1976a,b, 1977
		21	55.4	89/89		
		42	110.8	90/93		
Rat/Osborne-Mendel						NCI, 1976a,b, 1977
	M, F	0	0	0/37	3.1E-7	
	M	11	4.5	2/45		
	F	18	7.4	4/46		
	M	21	8.7	2/47		
	F	36	14.9	1/30		

<<< Carbon tetrachloride >>>

___II.B.3. ADDITIONAL COMMENTS (CARCINOGENICITY, ORAL EXPOSURE)

A geometric mean was calculated from the unit risks derived from the

four data sets above. Della Porta et al. (1961) did not report controls in this study, but did give incidence rate for vehicle controls in an earlier study. Animal doses are TWA.

The unit risk should not be used if the water concentration exceeds 3E+3 ug/L, since above this concentration the slope factor may differ from that stated.

<<< Carbon tetrachloride >>>

___II.B.4. DISCUSSION OF CONFIDENCE (CARCINOGENICITY, ORAL EXPOSURE)

The studies used were all deficient in some respect, precluding the choice of any one study as most appropriate. In the first and second studies only one dose was tested. Della Porta et al. (1961) did not report concurrent control incidence. Tumor incidence in the NCI (1976a,b) studies of mice was virtually 100%. For the NCI (1976a,b) mouse data, the goodness-of-fit criteria were not satisfied for the multistage model. For all studies, data from males and females were combined because of the small sample sizes. Tumor incidence in rats in these studies was higher at low doses, presumably because early mortality at higher doses precluded tumor formation. The studies lacked pharmacokinetic data. However, a common biological mechanism, cell death and regeneration, leading to development of the same tumor type, was suggested by observations in all the studies. Since the risk estimates from these data (across 3-4 species and strains) are relatively close, varying by 2 orders of magnitude, a geometric mean was derived as the risk estimate to accommodate the several study deficiencies.

---------<<< Carbon tetrachloride >>>---------

__II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

___II.C.1. SUMMARY OF RISK ESTIMATES

Inhalation Slope Factor -- 1.3E-1/mg/kg/day

Inhalation Unit Risk -- 1.5E-5/ug/cu.m

Extrapolation Method -- Linearized multistage procedure^V extra risk

Air Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	7E+0 ug/cu.m
E-5 (1 in 100,000)	7E-1 ug/cu.m
E-6 (1 in 1,000,000)	7E-2 ug/cu.m

<<< Carbon tetrachloride >>>

___II.C.2. DOSE-RESPONSE DATA FOR CARCINOGENICITY, INHALATION EXPOSURE

The inhalation risk estimates were calculated from the oral exposure data in Section II.B.2.

<<< Carbon tetrachloride >>>

___II.C.3. ADDITIONAL COMMENTS (CARCINOGENICITY, INHALATION EXPOSURE)

Inhalation risk was calculated assuming an air intake of 20 cu.m/day and 40% absorption rate by humans (U.S. EPA, 1984). This absorption coefficient was based on 30% inhalation in monkeys, and 30% and 57-65% inhalation in humans. A range of estimates of unit risk for inhalation exposures for the four studies cited above was determined, with 1.5E-5/ug/cu.m calculated as the geometric mean for the unit risk.

The unit risk should not be used if the air concentration exceeds 7E+2 ug/cu.m, since above this concentration the slope factor may differ from that stated.

<<< Carbon tetrachloride >>>

___II.C.4. DISCUSSION OF CONFIDENCE (CARCINOGENICITY, INHALATION EXPOSURE)

See II.B.4.

---------<<< Carbon tetrachloride >>>---------

__II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

___II.D.1. EPA DOCUMENTATION

U.S. EPA. 1984. Health Assessment Document for Carbon Tetrachloride. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 600/8/82-001F.

<<< Carbon tetrachloride >>>

___II.D.2. REVIEW (CARCINOGENICITY ASSESSMENT)

The 1984 Health Assessment Document for Carbon Tetrachloride received Agency and external review.

Agency Work Group Review: 11/12/86, 12/04/86

Verification Date: 12/04/86

___II.D.3. U.S. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

Jean C. Parker / ORD -- (202)382-5898 / FTS 382-5898

Arthur Chiu / ORD -- (202)382-5898 / FTS 382-5898

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_III. HEALTH HAZARD ASSESSMENTS FOR VARIED EXPOSURE DURATIONS

__III.A. DRINKING WATER HEALTH ADVISORIES

Substance Name -- Carbon tetrachloride
CASRN -- 56-23-5
Last Revised -- 08/01/90

The Office of Drinking Water provides Drinking Water Health Advisories (HAs) as technical guidance for the protection of public health. HAs are not enforceable Federal standards. HAs are concentrations of a substance in drinking water estimated to have negligible deleterious effects in humans, when ingested, for a specified period of time. Exposure to the substance from other media is considered only in the derivation of the lifetime HA. Given the absence of chemical-specific data, the assumed fraction of total intake from drinking water is 20%. The lifetime HA is calculated from the Drinking Water Equivalent Level (DWEL) which, in turn, is based on the Oral Chronic Reference Dose. Lifetime HAs are not derived for compounds which are potentially carcinogenic for humans because of the difference in assumptions concerning toxic threshold for carcinogenic and noncarcinogenic effects. A more detailed description of the assumptions and methods used in the derivation of HAs is provided in Background Document 3 in Service Code 5.

<<< Carbon tetrachloride >>>

___III.A.1. ONE-DAY HEALTH ADVISORY FOR A CHILD

One-day HA -- 4E+0 mg/L

NOAEL -- 40 mg/kg/day
UF -- 100 (allows for interspecies and intrahuman variability with the use of a NOAEL from an animal study)
Assumptions -- 1 L/day water consumption for a 10-kg child

Principal Study -- Bruckner et al., 1986

Rats were administered single oral doses of carbon tetrachloride. Doses of 80 mg/kg and higher caused changes in liver enzymes (BUN, GPT, SDH, OCT) and histopathologic liver and kidney changes. A dose of 40 mg/kg produced no effects and is identified as the NOAEL.

<<< Carbon tetrachloride >>>

___III.A.2. TEN-DAY HEALTH ADVISORY FOR A CHILD

Ten-day HA -- 1.6E-1 mg/L

LOAEL -- 16 mg/kg/day
UF -- 1000 (allows for interspecies and intrahuman variability with the use of a LOAEL from an animal study)
Assumptions -- 1 L/day water consumption for a 10-kg child

Principal Study -- Bruckner et al., 1986

Rats were administered nine doses of carbon tetrachloride by gavage over an 11-day period. The lowest dose tested (20 mg/kg/day) produced significant changes in serum enzyme levels and hepatic midzonal vacuolation. Higher doses caused more extensive liver damage. A LOAEL of 16 mg/kg/day is established after adjustment for the treatment schedule.

<<< Carbon tetrachloride >>>

___III.A.3. LONGER-TERM HEALTH ADVISORY FOR A CHILD

LONGER-TERM HEALTH ADVISORY FOR A CHILD

Longer-term (Child) HA -- 7.1E-2 mg/L

NOAEL -- 0.71 mg/kg/day
UF -- 100 (allows for interspecies and intrahuman variability with the use of a NOAEL from an animal study)
Assumptions -- 1 L/day water consumption for a 10-kg child

Principal Study -- Bruckner et al., 1986

Rats were administered carbon tetrachloride by gavage, 5 times weekly for 12 weeks, at doses of 1, 10, or 33 mg/kg/day. Doses of 10 and 33 mg/kg/day were hepatotoxic (changes in serum enzyme levels, centrilobular vacuolation, and necrosis). The NOAEL of 1 mg/kg/day, based on a 7 days/week dosing regimen, is equivalent to 0.71 mg/kg/day.

<<< Carbon tetrachloride >>>

___III.A.4. LONGER-TERM HEALTH ADVISORY FOR AN ADULT

Longer-term (Adult) HA -- 2.5E-1 mg/L

NOAEL -- 0.71 mg/kg/day
UF -- 100 (allows for interspecies and intrahuman variability with the use of a NOAEL from an animal study)
Assumptions -- 2 L/day water consumption for a 70-kg adult

Principal Study -- Bruckner et al., 1986 (study described in III.A.3.)

<<< Carbon tetrachloride >>>

___III.A.5. DRINKING WATER EQUIVALENT LEVEL / LIFETIME HEALTH ADVISORY

DWEL -- 2.5E-2 mg/L
Basis -- Derived from an oral chronic RfD of 7.1E-4 (unrounded); verification date - 07/08/85; Refer to Section I.A. for a discussion of the RfD.
Assumptions -- 2 L/day water consumption for a 70-kg adult

Lifetime HA -- None
NOTE: Carbon tetrachloride is considered to be a probable human carcinogen. Refer to Section II of this file for information on the carcinogenicity of this substance.

Principal Study (DWEL) -- Bruckner et al., 1986 (This study was used in the derivation of the oral chronic RfD; see Section I.A.2.)

<<< Carbon tetrachloride >>>

___III.A.6. ORGANOLEPTIC PROPERTIES

Odor perception threshold -- 0.52 mg/L.

<<< Carbon tetrachloride >>>

___III.A.7. ANALYTICAL METHODS FOR DETECTION IN DRINKING WATER

Analysis of carbon tetrachloride is by a purge-and-trap gas chromatographic procedure used for the determination of volatile organohalides in drinking water. Confirmatory analysis is by mass spectrometry.

<<< Carbon tetrachloride >>>

___III.A.8. WATER TREATMENT

Treatment techniques which will remove carbon tetrachloride from drinking water include granular activated carbon adsorption, boiling, and air stripping. Conventional treatment processes (coagulation, sedimentation, filtration), even when augmented by the addition of powdered activated carbon, provide little removal of carbon tetrachloride.

<<< Carbon tetrachloride >>>

___III.A.9. DOCUMENTATION AND REVIEW OF HAs

Bruckner, J.V., W.F. MacKenzie, S. Muralidhara, R. Luthra, G.M. Kyle and D. Acosta. 1986. Oral toxicity of carbon tetrachloride: Acute, subacute and subchronic studies in rats. Fund. Appl. Toxicol. 6(1): 16-34.

U.S. EPA. 1985. Final Draft of the Drinking Water Criteria Document on Carbon Tetrachloride. Office of Drinking Water, Washington, DC.

EPA review of HAs in 1985.

Public review of HAs following notification of availability in October, 1985.

Scientific Advisory Panel review of HAs in January, 1986.

Preparation date of this IRIS summary -- 06/22/87

___III.A.10. EPA CONTACTS

Jennifer Orme / ODW -- (202)382-7586 / FTS 382-7586

Edward V. Ohanian / ODW -- (202)382-7571 / FTS 382-7571

__III.B. OTHER ASSESSMENTS

Substance Name -- Carbon tetrachloride
CASRN -- 56-23-5

Content to be determined.

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_IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- Carbon tetrachloride
CASRN -- 56-23-5
Last Revised -- 03/01/88

EPA risk assessments may be updated as new data are published and as assessment methodologies evolve. Regulatory actions are frequently not updated at the same time. Compare the dates for the regulatory actions in this section with the verification dates for the risk assessments in sections I and II, as this may explain inconsistencies. Also note that some regulatory actions consider factors not related to health risk, such as technical or economic feasibility. Such considerations are indicated for each action. In addition, not all of the regulatory actions listed in this section involve enforceable federal standards. Please direct any questions you may have concerning these regulatory actions to the U.S. EPA contact listed for that particular action. Users are strongly urged to read the background information on each regulatory action in Background Document 4 in Service Code 5.

<<< Carbon tetrachloride >>>

__IV.A. CLEAN AIR ACT (CAA)

___IV.A.1. CAA REGULATORY DECISION

Action -- Intent to list under Section 112

Considers technological or economic feasibility? -- NO

Discussion -- EPA's preliminary risk assessment from ambient air exposures indicates that public health risks are significant (about 70 cases/year in the U.S.). Because carbon tetrachloride is extremely stable in the atmosphere, these risks are due to a worldwide buildup of carbon tetrachloride caused by emissions from the U.S. as well as other countries. Since these risks were considered significant, EPA indicated that it intends to add carbon tetrachloride to the list of hazardous air pollutants for which it intends to establish emission standards under section 112(b)(1)(A) of the Clean Air Act. The EPA will decide whether to add carbon tetrachloride to the list only after studying possible techniques that might be used to control emissions, and further assessing the public health risks. The EPA will add carbon tetrachloride to the list if emission standards are warranted. This decision did not consider the role of carbon tetrachloride in reducing stratospheric ozone. This issue is being evaluated separately and will consider the effect of a number of trace gases on stratospheric ozone.

Reference -- 50 FR 32621 (08/13/85)

EPA Contact -- Emissions Standards Division, OAQPS
(919)541-5571 / FTS 629-5571

---------<<< Carbon tetrachloride >>>---------

__IV.B. SAFE DRINKING WATER ACT (SDWA)

___IV.B.1. MAXIMUM CONTAMINANT LEVEL GOAL (MCLG) for Drinking Water

Value (status) -- 0 mg/L (Final, 1985)

Considers technological or economic feasibility? -- NO

Discussion -- An MCLG of 0 mg/L for carbon tetrachloride is proposed based on carcinogenic effects. Carbon tetrachloride has been shown to be carcinogenic in rats, mice, and hamsters through oral exposure. Hepatocellular carcinomas in several studies have been observed. EPA has classified carbon tetrachloride in Group B2: sufficient evidence in animals and inadequate evidence in humans.

Reference -- 50 FR 46880 Part III (11/13/85)

EPA Contact -- Larry Anderson / Criteria and Standards Division, ODW / (202)382-7571 / FTS 382-7571; or Drinking Water Hotline / (800)426-4791

<<< Carbon tetrachloride >>>

___IV.B.2. MAXIMUM CONTAMINANT LEVEL (MCL) for Drinking Water

Value (status) -- 5 ppb (Final, 1987)

Considers technological or economic feasibility? -- YES

Discussion --

Reference -- 52 FR 25690 (07/08/87)

EPA Contact -- Larry Anderson / Criteria and Standards Division, ODW / (202)382-7571 / FTS 382-7571; or Drinking Water Hotline / (800)426-4791

---------<<< Carbon tetrachloride >>>---------

__IV.C. CLEAN WATER ACT (CWA)

___IV.C.1. AMBIENT WATER QUALITY CRITERIA, Human Health

Water and Fish Consumption: 4.0E-1 ug/L

Fish Consumption Only: 6.94E+0 ug/L

Considers technological or economic feasibility? -- NO

Discussion -- For maximum protection from the potential carcinogenic properties of this chemical, the ambient concentration should be zero. However, zero may not be attainable at this time so the recommended criteria represents a E-6 estimated incremental increase in cancer risk over a lifetime.

Reference -- 45 FR 791318 (11/28/80)

EPA Contact -- Criteria and Standards Division, OWRS (202)475-7315 / FTS 475-7315

<<< Carbon tetrachloride >>>

___IV.C.2. AMBIENT WATER QUALITY CRITERIA, Aquatic Organisms

Freshwater:

Acute LEC -- 3.52E+4 ug/L
Chronic -- None

Marine:

Acute LEC -- 5.0E+4 ug/L
Chronic -- None

Considers technological or economic feasibility? -- NO

Discussion -- The values that are indicated as "LEC" are not criteria, but are the lowest effect levels found in the literature. LECs are given when the minimum data required to derive water quality criteria are not available.

Reference -- 45 FR 791318 (11/28/80)

EPA Contact -- Criteria and Standards Division, OWRS
(202)475-7315 / FTS 475-7315

---------<<< Carbon tetrachloride >>>---------

__IV.D. FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT (FIFRA)

___IV.D.1. PESTICIDE ACTIVE INGREDIENT, Registration Standard

None

<<< Carbon tetrachloride >>>

___IV.D.2. PESTICIDE ACTIVE INGREDIENT, Special Review

Action -- Registration voluntarily canceled

Considers technological or economic feasibility? -- Not applicable

Summary of regulatory action -- For specific details on the Special Review process for this active ingredient please call the EPA Contact.

Reference -- None

EPA Contact -- Special Review Branch, OPP / (703)557-7400 / FTS 557-7400

---------<<< Carbon tetrachloride >>>---------

__IV.E. TOXIC SUBSTANCES CONTROL ACT (TSCA)

No data available

---------<<< Carbon tetrachloride >>>---------

__IV.F. RESOURCE CONSERVATION AND RECOVERY ACT (RCRA)

___IV.F.1. RCRA APPENDIX IX, for Ground Water Monitoring

Status -- Listed

Reference -- 52 FR 25942 (07/09/87)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)382-3000 / FTS 382-3000

---------<<< Carbon tetrachloride >>>---------

__IV.G. SUPERFUND (CERCLA)

___IV.G.1. REPORTABLE QUANTITY (RQ) for Release into the Environment

Value (status) --10 pounds (Proposed, 1987)

Considers technological or economic feasibility? -- NO

Discussion -- The final RQ for carbon tetrachloride is based on potential carcinogenicity. Available data indicate a hazard ranking of medium based upon a potency factor of 59.9/mg/kg/day and assignment to weight-of-evidence group B2. This corresponds to an RQ of 10 pounds.

Reference -- 52 FR 8140 (03/16//87)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)382-3000 / FTS 382-3000

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_V. SUPPLEMENTARY DATA

Substance Name -- Carbon tetrachloride
CASRN -- 56-23-5

Not available at this time.

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_VI. BIBLIOGRAPHY

Substance Name -- Carbon tetrachloride
CASRN -- 56-23-5
Last Revised -- 12/01/89

__VI.A. ORAL RfD REFERENCES

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Acosta. 1983. Oral toxicity of carbon tetrachloride: Acute, subacute and subchronic studies in rats. University of Georgia, Athens, GA. (Draft)

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U.S. EPA. 1985. Drinking Water Criteria Document for Carbon Tetrachloride. Office of Drinking Water, Washington, DC.

---------<<< Carbon tetrachloride >>>---------

__VI.B. INHALATION RfD REFERENCES

None

---------<<< Carbon tetrachloride >>>---------

__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

Andervont, H.B. 1958. Induction of hepatomas in strain C3H mice with 4-o-tolylazo-o-toluidine and carbon tetrachloride. J. Natl. Cancer Inst. 20(2): 431-438.

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Simmon, V.F., K. Kauhanen and R.G. Tardiff. 1977. Mutagenic activity of chemicals identified in drinking water. In: Progress in Genetic Toxicology, D. Scott, B.A Bridges and F.H. Sobels, Ed. Elsevier/North-Holland Biomedical Press, New York. p. 249-258.

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---------<<< Carbon tetrachloride >>>---------

__VI.D. DRINKING WATER HA REFERENCES

Bruckner, J.V., W.F. MacKenzie, S. Muralidhara, R. Luthra, G.M. Kyle and D. Acosta. 1986. Oral toxicity of carbon tetrachloride: Acute, subacute and subchronic studies in rats. Fund. Appl. Toxicol. 6(1): 16-34.

U.S. EPA. 1985. Drinking Water Criteria Document for Carbon Tetrachloride. Office of Drinking Water, Washington, DC. (Final draft)

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SYNONYMS

Substance Name -- Carbon tetrachloride
CASRN -- 56-23-5
Last Revised -- / /

56-23-5
Acritet
Benzinoform
Carbona
Carbon chloride
Carbon tet
Carbon tetrachloride
Carbo tetrachloride
Czterochlorek wegla
ENT 4,705
Fasciolin
Flukoids
Freon 10
Halon 104
Mecatorina
Methane tetrachloride
Methane, tetrachloro-
Necatorina
Necatorine
Perchloromethane
R 10
Tetrachloorkoolstof
Tetrachloormetaan
Tetrachlorkohlenstoff, tetra
Tetrachlormethan
Tetrachlorocarbon
Tetrachloromethane
Tetrachlorure de carbone
Tetrachorkohlenstoff uvasol
Tetraclorometano

Tetracloruro di carbonio
Tetrafinol
Tetraform
Tetrasol
Univerm
Ventox
Vermoestricid
WLN: GXGGG.

3.9.2 (ARC)
OOII

STATUS OF DATA FOR Chloroform

File On-Line 01/31/87

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	06/30/88
Inhalation RfD Assessment (I.B.)	pending	
Carcinogenicity Assessment (II.)	on-line	06/30/88
Drinking Water Health Advisories (III.A.)	no data	
U.S. EPA Regulatory Actions (IV.)	on-line	06/01/90

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_I. CHRONIC HEALTH HAZARD ASSESSMENT FOR NONCARCINOGENIC EFFECTS

Substance Name -- Chloroform
Primary Synonym -- Trichloromethane
CASRN -- 67-66-3
Last Revised -- 06/30/88

The Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. 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 Background Document 1 in Service Code 5 for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of compounds which 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 when a review of that evaluation is completed.

<<< Chloroform >>>

__I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfDo)

___I.A.1. ORAL RfD SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfD
Fatty cyst formation in liver	NOEL: none	1000	1	1E-2 mg/kg/day

Dog, Chronic Oral Bioassay	LOAEL: 15 mg/kg/day (converted to 12.9 mg/kg/day)

Heywood et al., 1979

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*Conversion Factors: 15 mg/kg/day x 6 days/7 days = 12.9 mg/kg/day

<<< Chloroform >>>

___I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

Heywood, R., R.J. Sortwell, P.R.B. Noel, et al. 1979. Safety evaluation of toothpaste containing chloroform. III. Long-term study in beagle dogs. J. Environ. Pathol. Toxicol. 2: 835-851.

In this study beagle dogs were administered chloroform in a toothpaste base (0.5 mL of toothpaste base/kg/day) in gelatin capsules. A control group composed of 16 males and 16 females received the vehicle, and additional control groups of eight animals/sex were administered an alternative toothpaste or were left untreated. Experimental groups of eight male and eight female dogs received 15 or 30 mg chloroform/kg/day for 6 days/week. Treatment was continued for 7.5 years. Fatty cysts, considered to be treatment-related, were observed in livers of some dogs in both treatment groups. Nodules of altered hepatocytes were considered treatment-related but not dose-dependent. A dose-related increase in SGPT levels was noted and a less marked increase in SGOT was noted in the high-dose animals. The LOAEL was determined to be 12.9 mg/kg/day, and an RfD was set at 0.01 mg/kg/day.

___I.A.3. UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

UF = 1000. Uncertainty factors of 10 each were applied to the LOAEL of 12.9 mg/kg/day to account for the interspecies conversion, protection of sensitive human subpopulations, and concern that the effect seen was a LOAEL and not a NOEL.

MF = 1.

<<< Chloroform >>>

___I.A.4. ADDITIONAL COMMENTS (ORAL RfD)

Chloroform is considered to be highly fetotoxic, but not teratogenic (Schwetz, 1974; Thompson et al., 1974).

A study in rats, using only one treatment dose (Palmer et al., 1979), identified 60 mg/kg/day by gavage as a LOAEL for decreased weight gain, plasma cholinesterase and relative liver weight. Other data in the literature (Jorgenson et al., 1982) also indicate changes in liver fat to be treatment-related.

___I.A.5. CONFIDENCE IN THE ORAL RfD

Study: Medium
Data Base: Medium
RfD: Medium

The critical study (Heywood et al., 1979) was of chronic duration, used a fairly large number of dogs, and measured multiple endpoints; however, only two treatment doses were used and no NOEL was determined. Therefore, confidence in the study is rated medium. Confidence in the data base is considered medium to low; several studies support the choice of a LOAEL, but a NOEL was not found. Confidence in the RfD is also considered medium to low.

<<< Chloroform >>>

___I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

U.S. EPA. 1985. Drinking Water Criteria Document for Trihalomethanes. Office of Drinking Water, Washington, DC. External Review Draft.

The 1985 Drinking Water Criteria Document for Trihalomethanes is currently undergoing Agency review.

Agency RfD Work Group Review: 12/02/85, 05/15/86

Verification Date: 12/02/85

___I.A.7. EPA CONTACTS (ORAL RfD)

James Murphy / ODW -- (202)382-7591 / FTS 382-7591

M.L. Dourson / ORD -- (513)569-7534 / FTS 684-7534

------<<< Chloroform >>>------

__I.B. REFERENCE DOSE FOR CHRONIC INHALATION EXPOSURE (RfDi)

A risk assessment for this chemical is under review by an EPA work group.

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_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Chloroform
Primary Synonym -- Trichloromethane
CASRN -- 67-66-3
Last Revised -- 06/30/88

Section II provides information on three aspects of the carcinogenic risk assessment for the agent in question; the U.S. EPA classification, and quantitative estimates of risk from oral exposure and from inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen. 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. Background Document 2 (Service Code 5) provides details on the rationale and methods used to derive the carcinogenicity values found in IRIS. Users are referred to Section I for information on long-term toxic effects other than carcinogenicity.

<<< Chloroform >>>

II.A. EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

II.A.1. WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification -- B2; probable human carcinogen

Basis -- Based on increased incidence of several tumor types in rats and three strains of mice

II.A.2. HUMAN CARCINOGENICITY DATA

Inadequate. There are no epidemiologic studies of chloroform itself. Chloroform and other trihalomethanes are formed from the interaction of chlorine with organic material found in water. Several ecological and case-control studies of populations consuming chlorinated drinking water in which chloroform was the major chlorinated organic show small significant increases in the risk of rectal bladder or colon cancer on an intermittent basis. Many other suspected carcinogens were also present in these water supplies.

<<< Chloroform >>>

II.A.3. ANIMAL CARCINOGENICITY DATA

Sufficient. Chloroform has been tested for carcinogenicity in eight strains of mice, two strains of rats and in beagle dogs.

In a gavage bioassay (NCI, 1976), Osborne-Mendel rats and B6C3F1 mice were treated with chloroform in corn oil 5 times/week for 78 weeks. Fifty male rats received 90 or 125 mg/kg/day; females initially were treated with 125 or 250 mg/kg/day for 22 weeks and 90 or 180 mg/kg/day thereafter. Male mice received 100 or 200, raised to 150 or 300 mg/kg/day at 18 weeks; females were dosed with 200 or 400, raised to 250 or 500 mg/kg/day. A significant increase in kidney epithelial tumors was observed in male rats and highly significant

increases in hepatocellular carcinomas in mice of both sexes. Liver nodular hyperplasia was observed in low-dose male mice not developing hepatocellular carcinoma. Hepatomas have also developed in female strain A mice and NLC mice gavaged with chloroform (Eschenbrenner and Miller, 1945; Rudali, 1967).

Jorgenson et al. (1985) administered chloroform (pesticide quality and distilled) in drinking water to male Osborne-Mendel rats and female B6C3F1 mice at concentrations of 200, 400, 900, and 1800 mg/L for 104 weeks. These concentrations were reported by the author to correspond to 19, 38, 81, and 160 mg/kg/day for rats and 34, 65, 130, and 263 mg/kg/day for mice. A significant increase in renal tumors in rats was observed in the highest dose group. The increase was dose related. The liver tumor incidence in female mice was not significantly increased. This study was specifically designed to measure the effects of low doses of chloroform.

Chloroform administered in toothpaste was not carcinogenic to male C57B1, CBA, CF-1 or female ICI mice or to beagle dogs. Male ICI mice administered 60 mg/kg/day were found to have an increased incidence of kidney epithelial tumors (Roe et al., 1979; Heywood et al., 1979). A pulmonary tumor bioassay in strain A/St mice was negative as was one in which newborn C57X DBA2/F1 mice were treated s.c. on days 1 to 8 of life (Theiss et al., 1977; Roe et al., 1968).

<<< Chloroform >>>

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

The majority of tests for genotoxicity of chloroform have been negative. These negative findings include covalent binding to DNA, mutation in Salmonella, a Drosophila sex-linked recessive, tests for DNA damage a micronucleus test, and transformation of BHK cells. By contrast one study demonstrated binding of radiolabeled chloroform to calf thymus DNA following metabolism by rat liver microsomes (DiRenzo, 1982). Chloroform caused mitotic recombination in Saccharomyces (Callen et al., 1980) and sister chromatid exchange in cultured human lymphocytes and in mouse bone marrow cells exposed in vivo (Morimoto and Koizumi, 1983).

The carcinogenicity of chloroform may be a function of its metabolism to phosgene, which is known to cross-link DNA. A host-mediated assay using mice indicated that chloroform was metabolized in vivo to a form mutagenic to Salmonella strain TA1537. Likewise urine extracts from chloroform-treated mice were mutagenic (Agustin and Lim-Sylianco, 1978).

Chloroform administered to mice in drinking water promoted growth and metastasis of Ehrlich ascites cells injected i.p. (Capel et al., 1979).

------<<< Chloroform >>>------

__II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

___II.B.1. SUMMARY OF RISK ESTIMATES

Oral Slope Factor -- 6.1E-3/mg/kg/day

Drinking Water Unit Risk -- 1.7E-7/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)	600 ug/L
E-5 (1 in 100,000)	60 ug/L
E-6 (1 in 1,000,000)	6 ug/L

<<< Chloroform >>>

___II.B.2. DOSE-RESPONSE DATA (CARCINOGENICITY, ORAL EXPOSURE)

Tumor Type -- all kidney tumors
Test Animals -- rat/Osborne-Mendel, male
Route -- oral, drinking water
Reference -- Jorgensen et al., 1985

Dose		Tumor
Administered (mg/L)	Human Equivalent (mg/kg/day)	Incidence
0	0	1/50
200	3.4	6/313
400	6.9	7/148
900	14.8	3/48
1800	28.9	7/50

___II.B.3. ADDITIONAL COMMENTS (CARCINOGENICITY, ORAL EXPOSURE)

Historical control kidney tumor incidence was 5/301.

The unit risk should not be used if the water concentration exceeds 6E+4 ug/L, since above this concentration the slope factor may differ from that stated.

___II.B.4. DISCUSSION OF CONFIDENCE (CARCINOGENICITY, ORAL EXPOSURE)

This assay was designed for detection and quantitation of effects at low dose; thus, large numbers of animals were treated and observed for their lifetime. Exposure route and vehicle is relevant to the medium for which the risk estimate was developed.

------<<< Chloroform >>>------

__II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

___II.C.1. SUMMARY OF RISK ESTIMATES

Inhalation Slope Factor -- 8.1E-2/mg/kg/day

Inhalation Unit Risk -- 2.3E-5/ug/cu.m

Extrapolation Method -- Linearized multistage procedure, extra risk

Air Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	4 ug/cu.m
E-5 (1 in 100,000)	4E-1 ug/cu.m
E-6 (1 in 1,000,000)	4E-2 ug/cu.m

<<< Chloroform >>>

___II.C.2. DOSE-RESPONSE DATA FOR CARCINOGENICITY, INHALATION EXPOSURE

Tumor Type -- hepatocellular carcinoma
Test Animals -- mouse, B6C3F1, female
Route -- oral, gavage
Reference -- NCI, 1976

Dose		Tumor
Administered (mg/kg/day)	Human Equivalent (mg/kg/day)	Incidence
Female		
0	0	0/20
238	9.9	36/45
477	19.9	39/41
Male		
0	0	1/18
138	6.2	18/50
277	12.5	44/45

<<< Chloroform >>>

___II.C.3. ADDITIONAL COMMENTS (CARCINOGENICITY, INHALATION EXPOSURE)

This inhalation quantitative risk estimate is based on oral data. Above

doses are TWA; body weights at the end of the assay were 35 g, males and 28 g, females. Vehicle control animals were run concurrently and housed with test animals. All treated animals experienced decreased body weight gain. Survival was reduced in high-dose males and in all treated females.

Experimental data for this compound support complete absorption of orally administered chloroform under conditions of this assay. There are no apparent species differences in this regard. Extrapolation of metabolism-dependent carcinogenic responses from mice to humans on the basis of body surface area is supported by experimental data. The slope factor is the geometric mean calculated from male (3.3E-2) and female (2.0E-1) data.

The unit risk should not be used if the air concentration exceeds 400 ug/cu.m, since above this concentration the slope factor may differ from that stated.

___II.C.4. DISCUSSION OF CONFIDENCE (CARCINOGENICITY, INHALATION EXPOSURE)

Adequate numbers of animals were treated and observed.

Slope factors derived from male rat kidney tumor data (2.4E-2) (NCI, 1976) and studies by Roe et al. (1979) (1.0E-1) are generally supportive of the risk estimate.

------<<< Chloroform >>>------

__II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

___II.D.1. EPA DOCUMENTATION

U.S. EPA. 1985. Health Assessment Document for Chloroform. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Research Triangle Park, NC for the Office of Air Quality Planning and Standards. EPA 600/8-84-004F.

U.S. EPA. 1987. Drinking Water Criteria Document for Trihalomethanes. Office of Drinking Water, Washington, DC. Draft.

NCI (National Cancer Institute). 1976. Report on Carcinogenesis Bioassay of Chloroform. National Cancer Institute, Washington, DC. NTIS PB 264018.

___II.D.2. REVIEW (CARCINOGENICITY ASSESSMENT)

The Health Assessment Document for Chloroform received extensive Agency and external review.

The Draft Drinking Water Criteria Document for Trihalomethanes has

received external peer review.

Agency Work Group Review: 10/29/86, 08/26/87

Verification Date: 08/26/87

___II.D.3. U.S. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

James Murphy / ODW -- (202)382-7591 / FTS 382-7591

David L. Bayliss / ORD -- (202)382-5726 / FTS 382-5726

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_III. HEALTH HAZARD ASSESSMENTS FOR VARIED EXPOSURE DURATIONS

Substance Name -- Chloroform
Primary Synonym -- Trichloromethane
CASRN -- 67-66-3

Not available at this time

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_IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- Chloroform
Primary Synonym -- Trichloromethane
CASRN -- 67-66-3
Last Revised -- 06/01/90

EPA risk assessments may be updated as new data are published and as assessment methodologies evolve. Regulatory actions are frequently not updated at the same time. Compare the dates for the regulatory actions in this section with the verification dates for the risk assessments in sections I and II, as this may explain inconsistencies. Also note that some regulatory actions consider factors not related to health risk, such as technical or economic feasibility. Such considerations are indicated for each action. In addition, not all of the regulatory actions listed in this section involve enforceable federal standards. Please direct any questions you may have concerning these regulatory actions to the U.S. EPA contact listed for that particular action. Users are strongly urged to read the background information on each regulatory action in Background Document 4 in Service Code 5.

__IV.A. CLEAN AIR ACT (CAA)

___IV.A.1. CAA REGULATORY DECISION

Action -- Intent to list under Section 112

Considers technological or economic feasibility? -- NO

Discussion -- Chloroform is a probable human carcinogen (EPA Group B2) and according to EPA's preliminary risk assessment from ambient air exposures, public health risks are significant (13 cancer cases/year and maximum lifetime individual risks of 7.1E-4). Thus, EPA indicated that it intends to add chloroform to the list of hazardous air pollutants for which it intends to establish emission standards under section 112(b)(1)(A) of the Clean Air Act. The EPA will decide whether to add chloroform to the list only after studying possible techniques that might be used to control emissions of chloroform and further assessing the public health risks. The EPA will add chloroform to the list if emission standards are warranted.

Reference -- 50 FR 39626 (09/27/85)

EPA Contact -- Emissions Standards Division, OAQPS
(919)541-5571 / FTS 629-5571

------<<< Chloroform >>>------

__IV.B. SAFE DRINKING WATER ACT (SDWA)

___IV.B.1. MAXIMUM CONTAMINANT LEVEL (MCL) for Drinking Water

Value (status) -- 0.10 mg/L [total trihalomethanes*] (Interim, 1979)

Considers technological or economic feasibility? -- YES

Discussion -- An interim MCL of 0.10 mg/L for total trihalomethanes* is proposed based on chronic toxicity data for chloroform and existing technology and treatment methods. Chloroform produced central nervous system depression, hepatic, renal, teratogenic and carcinogenic effects at dose levels from 30 to 350 mg/kg.
*Chloroform (67-66-3), dibromochloromethane (124-48-1), bromodichloromethane (75-27-4) and bromoform (75-25-2).

Reference -- 44 FR 68624 (11/29/79)

EPA Contact -- James Murphy / Criteria and Standards Division, ODW / (202)382-7571 / FTS 382-7571; or Drinking Water Hotline / (800)426-4791

------<<< Chloroform >>>------

__IV.C. CLEAN WATER ACT (CWA)

___IV.C.1. AMBIENT WATER QUALITY CRITERIA, Human Health

Water and Fish Consumption: 1.9E-1 ug/L

Fish Consumption Only: 1.57E+1 ug/L

Considers technological or economic feasibility? -- NO

Discussion -- The WQC of 0.19 ug/L represents a cancer risk level of 1E-6, based on consumption of contaminated organisms and water. A WQC of 15.7 ug/L (cancer risk level of 1E-6) has also been established based on consumption of contaminated organisms alone.

Reference -- 45 FR 79318 (11/28/80)

EPA Contact -- Criteria and Standards Division, OWRS
(202)475-7315 / FTS 475-7315

<<< Chloroform >>>

___IV.C.2. AMBIENT WATER QUALITY CRITERIA, Aquatic Organisms

Freshwater:

Acute LEC -- 2.89E+4 ug/L
Chronic LEC -- 1.24E+3 ug/L

Marine: None

Considers technological or economic feasibility? -- NO

Discussion -- The values that are indicated as "LEC" are not criteria, but are the lowest effect levels found in the literature. LECs are given when the minimum data required to derive water quality criteria are not available.

Reference -- 45 FR 79318 (11/28/80)

EPA Contact -- Criteria and Standards Division, OWRS
(202)475-7315 / FTS 475-7315

------<<< Chloroform >>>------

__IV.D. FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT (FIFRA)

___IV.D.1. PESTICIDE ACTIVE INGREDIENT, Registration Standard

None

___IV.D.2. PESTICIDE ACTIVE INGREDIENT, Special Review

Action -- Risk benefit analysis - PD2/3 (1976)

Considers technological or economic feasibility? -- YES

Summary of regulatory action -- An outline of regulatory options based on risk-benefit considerations is presented in Position Document 2/3.

Reference -- 48 FR 498 (01/05/82)

EPA Contact -- Special Review Branch, OPP / (703)557-7400 / FTS 557-7400

------<<< Chloroform >>>------

__IV.E. TOXIC SUBSTANCES CONTROL ACT (TSCA)

No data available

------<<< Chloroform >>>------

__IV.F. RESOURCE CONSERVATION AND RECOVERY ACT (RCRA)

___IV.F.1. RCRA APPENDIX IX, for Ground Water Monitoring

Status -- Listed

Reference -- 52 FR 25942 (07/09/87)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)382-3000 / FTS 382-3000

------<<< Chloroform >>>------

__IV.G. SUPERFUND (CERCLA)

___IV.G.1. REPORTABLE QUANTITY (RQ) for Release into the Environment

Value (status) -- 10 pounds (Proposed, 1987)

Considers technological or economic feasibility? -- NO

Discussion -- The RQ for chloroform is based on potential carcinogenicity. Available data indicate a hazard ranking of medium based on a potency factor of 1.97/mg/kg/day and assignment to weight-of-evidence group B2. These

correspond to an RQ of 10 pounds.

Reference -- 52 FR 8140 (03/16/87)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)382-3000 / FTS 382-3000

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_V. SUPPLEMENTARY DATA

Substance Name -- Chloroform
Primary Synonym -- Trichloromethane
CASRN -- 67-66-3
Last Revised -- 01/31/87

The information contained in this section (subsections A and B) has been extracted from the EPA Chemical Profiles Database, which has been compiled from a number of secondary sources and has not undergone formal Agency review. The complete reference listings for the citations in this section are provided in Service Code 5. The user is urged to read Background Document 5 in Service Code 5 for further information on the sources and limitations of the data presented here.

<<< Chloroform >>>

__V.A. ACUTE HEALTH HAZARD INFORMATION

Toxicity -- Chloroform is classified as moderately toxic. A probable oral lethal dose for humans is 0.5 to 5 g/kg (between 1 ounce and 1 pint) for a 150-lb. person. The mean lethal dose is probably near 1 fluid ounce (44 g) (Gosselin et al., 1976). Also, it is a central nervous system depressant and a gastrointestinal irritant (Challen et al., 1958). Chloroform has caused rapid death attributable to cardiac arrest.

Medical Conditions Generally Aggravated by Exposure -- Not Found

Signs and Symptoms of Exposure -- Symptoms of acute exposure include fainting sensation, vomiting, dizziness, salivation, nausea, fatigue, and headache (ACGIH, 1971-1979). Other symptoms are respiratory depression, coma, kidney damage, and liver damage (IARC, 1972-1985). Liquid in the eye causes tearing and conjunctivitis (Grant, 1974). Symptoms of chronic exposure include loss of appetite, hallucinations, moodiness, and physical and mental sluggishness (NIOSH, 1974).

------<<< Chloroform >>>------

__V.B. PHYSICAL-CHEMICAL PROPERTIES

Chemical Formula -- CHCl3

Molecular Weight -- 119.39

Boiling Point -- 143F, 61.7C

Specific Gravity (H2O=1) -- 1.4832 at 20C/4C

Vapor Pressure (mmHg) -- 100 at 10.4C

Melting Point -- -82.3F, -63.5C

Vapor Density (AIR=1) -- 4.12

Evaporation Rate (Butyl acetate=1) -- (Carbon Tetrachloride = 1) 1.18

Solubility in Water -- 1 mL/200 mL at 25C

Flash Point [Method Used] -- None

Flammable Limits -- None

Appearance and Odor -- Chloroform is a clear, colorless and mobile liquid with a characteristic odor.

Conditions or Materials to Avoid -- Chloroform develops acidity from prolonged exposure to air and light (General Electric Co., 1979, MSDS #315). Chloroform explodes when in contact with aluminum powder or magnesium powder or with alkali metals (e.g., lithium, sodium, and potassium) (NFPA, 1978) and dinitrogen tetroxide. Chloroform reacts vigorously with acetone in the presence of potassium hydroxide or calcium hydroxide (Bretherick, 1979). It is oxidized by strong oxidizers such as chromic acid, forming phosgene and chlorine (IARC, 1972-1985). Chloroform reacts vigorously with triisopropylphosphine (Bretherick, 1979).

Hazardous Decomposition or Byproducts -- When heated, chloroform emits hydrogen chloride, chlorine, and toxic and corrosive oxides of carbon and chlorine (General Electric Co., 1979, MSDS #315) and phosgene (ITI, 1982).

Use -- Chloroform is used as a grain fumigant; solvent for pesticides, adhesives (IARC, 1972-1985) fats, oils, rubbers, alkaloids, waxes (Merck, 1976); chemical intermediate for dyes and pesticides; and a component of cough syrups, toothpastes, and liniments (SRI, 1983). Not registered as a pesticide in the U.S. (USEPA/Pesticide Index, 1985).

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VI. BIBLIOGRAPHY

Substance Name -- Chloroform
Primary Synonym -- Trichloromethane
CASRN -- 67-66-3

Not available at this time

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SYNONYMS

67-66-3
Chloroform
Formyl Trichloride
Freon 20
Methane Trichloride
Methane, Trichloro-
Methenyl Chloride
Methenyl Trichloride
Methyl Trichloride
NCI-C02686
R-20
TCM
Trichloroform
Trichloromethane

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STATUS OF DATA FOR Copper

File On-Line 09/07/88

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	no data	
Inhalation RfD Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	on-line	09/07/88
Drinking Water Health Advisories (III.A.)	no data	
U.S. EPA Regulatory Actions (IV.)	no data	
Supplementary Data (V.)	no data	

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_I. CHRONIC HEALTH HAZARD ASSESSMENT FOR NONCARCINOGENIC EFFECTS

Substance Name -- Copper
CASRN -- 7440-50-8

Not available at this time

==========

_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Copper
CASRN -- 7440-50-8
Last Revised -- 09/07/88

Section II provides information on three aspects of the carcinogenic risk assessment for the agent in question; the U.S. EPA classification, and quantitative estimates of risk from oral exposure and from inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen. 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. Background Document 2 (Service Code 5) provides details on the rationale and methods used to derive

the carcinogenicity values found in IRIS. Users are referred to Section I for information on long-term toxic effects other than carcinogenicity.

<<< Copper >>>

Substance Name -- Copper
CASRN -- 7440-50-8
Preparation Date -- 09/01/87

II.A. EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

II.A.1. WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification -- D; not classified

Basis -- There are no human data, inadequate animal data from assays of copper compounds, and equivocal mutagenicity data.

II.A.2. HUMAN CARCINOGENICITY DATA

None.

<<< Copper >>>

II.A.3. ANIMAL CARCINOGENICITY DATA

Inadequate. Bionetics Research Labs (1968) studied the carcinogenicity of a copper-containing compound, copper hydroxyquinoline, in two strains of mice (B6C3F1 and B6AKF1). Groups of 18 male and 18 female 7-day-old mice were administered 1000 mg copper hydroxyquinoline/kg bw (180.6 mg Cu/kg) suspended in 0.5% gelatin daily until they were 28 days old, after which they were administered 2800 ppm (505.6 ppm Cu) in the feed for 50 additional weeks. No statistically significant increases in tumor incidence were observed in the treated 78-week-old animals.

In the same study, Bionetics Research Labs (1968) administered a single subcutaneous injection of gelatin (control) or 1000 mg of copper hydroxyquinoline/kg bw (180.6 mg Cu/kg) suspended in 0.5% gelatin to groups of 28-day-old mice of both strains. After 50 days of observation, the male B6C3F1 had an increased incidence of reticulum cell sarcomas compared with controls. No tumors were observed in the treated male B6AKF1 mice, and a low incidence of reticulum cell sarcomas was observed in the treated female mice of both strains.

Gilman (1962) administered intramuscular injections containing 20 mg of cupric oxide (16 mg Cu), cupric sulfide (13.3 mg Cu), and cuprous sulfide (16 mg Cu) into the left and right thighs of 2- to 3-month-old Wistar rats. After 20 months of observations, no injection-site tumors were observed in any animals, but other tumors were observed at very low incidence in the animals receiving cupric sulfide (2/30) and cuprous sulfide (1/30). As the

___II.D.1. EPA DOCUMENTATION

U.S. EPA. 1987. Drinking Water Criteria Document for Copper. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. ECAO-CIN 417.

Bionetics Research Labs. 1968. Evaluation of carcinogenic, teratogenic and mutagenic activities of selected pesticides and industrial chemicals. Vol. I. Carcinogenic study prepared for National Cancer Institute. NCI-DCCP-CG-1973-1-1.

Castro, B.C., J. Meyers and J.A. DiPaolo. 1979. Enhancement of viral transformation for evaluation of the carcinogenic or mutagenic potential of inorganic metal salts. Cancer Res. 30: 193.

Demerec, M., G. Bertani and J. Flint. 1951. A survey of chemicals for mutagenic action on E. coli. Am. Natur. 85: 119.

Gilman, J.P.W. 1962. Metal carcinogenesis. II. A study on the carcinogenic activity of cobalt, copper, iron and nickel compounds. Cancer Res. 22: 158-166.

Kanematsu, N., M. Hara and T. Kada. 1980. Rec assay and mutagenicity studies on metal compounds. Mutat. Res. 77: 109-116.

Matsui, S. 1980. Evaluation of a Bacillus subtilis rec-assay for the detection of mutagens which may occur in water environments. Water Res. 14(11): 1613-1619.

Moriya, M., T. Ohta, K. Watanabe, T. Miyazawa, K. Kato and Y. Shirasu. 1983. Further mutagenicity studies on pesticides in bacterial reversion assay systems. Mutat. Res. 116(3-4): 185-216.

Nishioka, H. 1975. Mutagenic activities of metal compounds in bacteria. Mutat. Res. 31: 185-189.

Sina, J.F., C.L. Bean, G.R. Dysart, V.I. Taylor and M.O. Bradley. 1983. Evaluation of the alkaline elution/rat hepatocyte assay as a predictor of carcinogenic/mutagenic potential. Mutat. Res. 113(5): 357-391.

Singh, I. 1983. Induction of reverse mutation and mitotic gene conversion by some metal compounds in Saccharomyces cerevisiae. Mutat. Res. 117(1-2): 149-152.

Sirover, M.A. and L.A. Loeb. 1976. Infidelity of DNA synthesis in vitro: Screening for potential metal mutagens or carcinogens. Science. 194: 1434-1436.

<<< Copper >>>

___II.D.2. REVIEW (CARCINOGENICITY ASSESSMENT)

The values in the 1987 Drinking Water Criteria Document for Copper have

received peer and administrative review.

Agency Work Group Review: 09/15/87

Verification Date: 09/15/87

___II.D.3. U.S. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

David J. Reisman / ORD -- (513)569-7588 / FTS 684-7588

W. Bruce Peirano / ORD -- (513)569-7540 / FTS 684-7540

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_III. HEALTH HAZARD ASSESSMENTS FOR VARIED EXPOSURE DURATIONS

Substance Name -- Copper
CASRN -- 7440-50-8

Not available at this time

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_IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- Copper
CASRN -- 7440-50-8

Not available at this time

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_V. SUPPLEMENTARY DATA

Substance Name -- Copper
CASRN -- 7440-50-8

Not available at this time

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relevance of the organic copper compound to the observation of sarcoma induction is uncertain and the incidence of tumors in rats treated i.m. with inorganic copper was very low, data are considered inadequate for classification.

<<< Copper >>>

__II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Moriya et al. (1983) reported no increase in mutations in E. coli and S. typhimurium strains TA98, TA1535, TA1537 and TA1538 incubated with up to 5 mg copper quinolinolate/plate and in S. typhimurium TA98 and TA100 incubated with up to 5 mg copper sulfate/plate. Demerec et al. (1951) reported dose-related mutagenic effects in E. coli with 2 to 10 ppm copper sulfate in a reverse mutation assay. Negative results were obtained with copper sulfate or copper chloride in assays using S. cerevisiae (Singh, 1983) and Bacillus subtilis (Nishioka, 1975, Matsui, 1980, Kanematsu et al., 1980). Errors in DNA synthesis from poly(c)templates have been induced in viruses incubated with copper chloride or copper acetate (Sirover and Loeb, 1976). Chromosomal aberrations were induced in isolated rat hepatocytes when incubated with copper sulfate (Sina et al., 1983). Casto et al. (1979) showed enhanced cell transformation in Syrian hamster embryo cells infected with simian adenovirus with the addition of cuprous sulfide and copper sulfate. High concentrations of copper compounds have been reported to induce mitosis in rat ascites cells and recessive lethals in Drosophila melanogaster. Law (1983) reported increases in the percent lethals observed in Drosophila larvae and eggs when exposed to copper by microinjection (0.1% copper sulfate) or immersion (concentrated aqueous copper sulfate), respectively.

__II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

Not available.

__II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

Not available.

__II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)
<<< Copper >>>

_VI. REFERENCES

Substance Name -- Copper
CASRN -- 7440-50-8

Not available at this time

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SYNONYMS

7440-50-8
Copper

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3.9.2 (am)

Dibenzofuran; CASRN 132-64-9 (10/01/90)

Health risk assessment information on a chemical is included in IRIS only after a comprehensive review of chronic toxicity data by work groups composed of U.S. EPA scientists from several Program Offices. The summaries presented in Sections I and II represent a consensus reached in the review process. The other sections contain U.S. EPA information which is specific to a particular EPA program and has been subject to review procedures prescribed by that Program Office. The regulatory actions in Section IV may not be based on the most current risk assessment, or may be based on a current, but unreviewed, risk assessment, and may take into account factors other than health effects (e.g., treatment technology). When considering the use of regulatory action data for a particular situation, note the date of the regulatory action, the date of the most recent risk assessment relating to that action, and whether technological factors were considered. Background information and explanations of the methods used to derive the values given in IRIS are provided in the five Background Documents in Service Code 5, which correspond to Sections I through V of the chemical files.

STATUS OF DATA FOR Dibenzofuran

File On-Line 10/01/90

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	no data	
Inhalation RfC Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	on-line	10/01/90
Drinking Water Health Advisories (III.A.)	no data	
U.S. EPA Regulatory Actions (IV.)	no data	
Supplementary Data (V.)	no data	

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_I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

__I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name -- Dibenzofuran
CASRN -- 132-64-9

Not available at this time.

__I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

Substance Name -- Dibenzofuran
CASRN -- 132-64-9

Not available at this time.

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_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Dibenzofuran
CASRN -- 132-64-9
Last Revised -- 10/01/90

Section II provides information on three aspects of the carcinogenic risk assessment for the agent in question; the U.S. EPA classification, and quantitative estimates of risk from oral exposure and from inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen. 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. Background Document 2 (Service Code 5) provides details on the rationale and methods used to derive the carcinogenicity values found in IRIS. Users are referred to Section I for information on long-term toxic effects other than carcinogenicity.

<<< Dibenzofuran >>>

__II.A. EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

___II.A.1. WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification -- D; not classifiable as to human carcinogenicity

Basis -- Based on no human data and no animal data for dibenzofuran alone.

<<< Dibenzofuran >>>

___II.A.2. HUMAN CARCINOGENICITY DATA

None. There are no data on the possible carcinogenicity of dibenzofuran alone in humans. Studies have evaluated exposure to a mixture of polychlorinated biphenyls (PCBs), polychlorinated dibenzofurans (PCDFs) and polychlorinated quinones (PCQs) by consumption of contaminated rice oil (Yusho incident) (reviewed in U.S. EPA, 1986, 1987). However, these studies have limited value because they do not assess dibenzofuran or correlate exposure with cancer risk. Additionally, because of the multiple exposures, the extent to which the various components contributed to the increase in cancer mortality cannot be determined.

<<< Dibenzofuran >>>

___II.A.3. ANIMAL CARCINOGENICITY DATA

None. No animal carcinogenicity data on dibenzofuran are currently available. U.S. EPA (1986) noted that the biological activity of PCDFs varies greatly, so that risk assessment of dibenzofuran by analogy to any of these more widely studied compounds would not be recommended.

<<< Dibenzofuran >>>

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Dibenzofuran is not mutagenic with or without metabolic activation in several strains of Salmonella typhimurium assay (Schoeny, 1982).

In a comparison of Toxic Equivalency Factor (TEF) values for chlorinated dibenzofurans, mono-, di- and tri-chlorinated dibenzofuran had TEF values of 0 (U.S. EPA, 1989). Based on these results and the fact that toxicity of polychlorinated dibenzofurans (PCDF) depends on the number of chlorine substituents and their position (U.S. EPA, 1986), the TEF for dibenzofuran, with no chlorine substituents, is set equal to 0.

---------<<< Dibenzofuran >>>---------

__II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

None.

---------<<< Dibenzofuran >>>---------

__II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

None.

---------<<< Dibenzofuran >>>---------

__II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

___II.D.1. EPA DOCUMENTATION

U.S. EPA. 1986. Health Assessment Document for Polychlorinated Dibenzofurans. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Air Quality Planning and Standards, Research Triangle Park, NC. EPA 600/8-86/018A. NTIS PB86-221256/AS.

U.S. EPA. 1987. Health Effects Assessment for Dibenzofuran. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC. ECAO-CIN-H088.

U.S. EPA. 1989. Interim Procedures for Estimating Risks Associated with Exposures to Mixtures of Chlorinated Dibenzo-p-Dioxins and -Dibenzofurans (CDDs and CDFs) and 1989 Update. Risk Assessment Forum, Washington, DC. EPA/625/3-89/016.

<<< Dibenzofuran >>>

___II.D.2. REVIEW (CARCINOGENICITY ASSESSMENT)

The 1986 Health Assessment for Polychlorinated Dibenzofurans is an external draft for review purposes only and does not constitute Agency policy.

The 1987 Health Effects Assessment Document for Dibenzofuran has been reviewed in accordance with the U.S. Environmental Protection Agency's peer and administrative review policies and has been approved for publication.

Agency Work Group Review: 10/05/89

Verification Date: 10/05/89

___II.D.3. U.S. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

Charles Ris / ORD -- (202)382-5898 / FTS 382-5898

Rita Schoeny / ORD -- (513)569-7544 / FTS 684-7544

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_III. HEALTH HAZARD ASSESSMENTS FOR VARIED EXPOSURE DURATIONS

__III.A. DRINKING WATER HEALTH ADVISORIES

Substance Name -- Dibenzofuran

CASRN -- 132-64-9

Not available at this time.

__III.B. OTHER ASSESSMENTS

Substance Name -- Dibenzofuran
CASRN -- 132-64-9

Content to be determined.

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_IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- Dibenzofuran
CASRN -- 132-64-9

Not available at this time.

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_V. SUPPLEMENTARY DATA

Substance Name -- Dibenzofuran
CASRN -- 132-64-9

Not available at this time.

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_VI. BIBLIOGRAPHY

Substance Name -- Dibenzofuran
CASRN -- 132-64-9
Last Revised -- 10/01/90

__VI.A. ORAL RfD REFERENCES

None

---------<<< Dibenzofuran >>>---------

__VI.B. INHALATION RfD REFERENCES

None

---------<<< Dibenzofuran >>>---------

__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

Schoeny, R. 1982. Mutagenicity testing of chlorinated biphenyls and chlorinated dibenzofurans. Mutat. Res. 101: 45-56.

U.S. EPA. 1986. Health Assessment Document for Polychlorinated Dibenzofurans. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Air Quality Planning and Standards, Research Triangle Park, NC. EPA 600/8-86/018A. NTIS PB86-221256/AS.

U.S. EPA. 1987. Health Effects Assessment for Dibenzofuran. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC. ECAO-CIN-H088.

U.S. EPA. 1989. Interim Procedures for Estimating Risks Associated with Exposures to Mixtures of Chlorinated Dibenzo-p-Dioxins and -Dibenzofurans (CDDs and CDFs) and 1989 Update. Risk Assessment Forum, Washington, DC. EPA/625/3-89/016.

---------<<< Dibenzofuran >>>---------

__VI.D. DRINKING WATER HA REFERENCES

None

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SYNONYMS

Substance Name -- Dibenzofuran
CASRN -- 132-64-9
Last Revised -- 10/01/90

132-64-9
(1,1'-BIPHENYL)-2,2'-DIYL OXIDE
2,2'-BIPHENYLENE OXIDE
2,2'-BIPHENYLYLENE OXIDE
DIBENZOFURAN
DIBENZO(B,D)FURAN
DIPHENYLENE OXIDE
HSDB 2163
NSC 1245

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Acenaphthene; CASRN 83-32-9 (11/01/90)

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Di-n-butyl phthalate

STATUS OF DATA FOR Dibutyl phthalate

File On-Line 01/31/87

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	08/01/90
Inhalation RfC Assessment (I.B.)	message	10/01/90
Carcinogenicity Assessment (II.)	on-line	05/01/90
Drinking Water Health Advisories (III.A.)	no data	
U.S. EPA Regulatory Actions (IV.)	on-line	09/01/90
Supplementary Data (V.)	on-line	01/31/87

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_I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

__I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name -- Dibutyl phthalate
CASRN -- 84-74-2
Last Revised -- 08/01/90

The Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. 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 Background Document 1 in Service Code 5 for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of compounds which 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 when a review of that evaluation is completed.

<<< Dibutyl phthalate >>>

NOTE: The Oral RfD for dibutyl phthalate may change in the near future pending the outcome of a further review now being conducted by the Oral RfD Work Group.

___I.A.1. ORAL RfD SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfD
Increased mortality	NOAEL: 0.25% of diet (125 mg/kg/day)	1000	1	1E-1 mg/kg/day
Rat Subchronic to Chronic, Oral Bioassay	LOAEL: 1.25% of diet (600 mg/kg bw/day)			
Smith, 1953				

*Conversion Factors: The values of 125 mg/kg/day for 0.25% dibutyl phthalate in the diet and 600 mg/kg/day for 1.25% were estimated from a figure depicting daily intake in mg/kg in Smith (1953).

<<< Dibutyl phthalate >>>

___I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

Smith, C.C. 1953. Toxicity of butyl sterate, dibutyl sebacate, dibutyl phthalate and methoxyethyl oleate. Arch. Hyg. Occup. Med. 7: 310-318.

Male Sprague-Dawley rats in groups of 10 were fed diets containing 0, 0.01, 0.05, 0.25, and 1.25% dibutyl phthalate for a period of 1 year. One-half of all rats receiving the highest dibutyl phthalate concentration died during the first week of exposure. The remaining animals survived the study with no apparent ill effects. There was no effect of treatment on gross pathology or hematology. While it was stated that several organs were sectioned and stained, no histopathologic evaluation was reported.

<<< Dibutyl phthalate >>>

___I.A.3. UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

UF = 1000. A factor of 10 was applied to account for interspecies variation, a factor of 10 for protection of sensitive human subpopulations, and an additional factor of 10 to account for both the less-than-chronic duration of the study and deficiencies in the study, such as the use of only male animals.

MF = 1.

<<< Dibutyl phthalate >>>

___I.A.4. ADDITIONAL COMMENTS (ORAL RfD)

Fetotoxicity was observed when mice were fed 2100 mg/kg/day dibutyl phthalate throughout gestation (Shiota and Nishimura, 1982). An increase in terata of borderline statistical significance was observed in progeny of this treatment group. Dibutyl phthalate produces degeneration of the seminiferous tubules, probably as a result of increased urinary excretion of zinc (Gangolli, 1982).

<<< Dibutyl phthalate >>>

___I.A.5. CONFIDENCE IN THE ORAL RfD

Study: Low
Data Base: Low
RfD: Low

The study by Smith (1953) used few animals of one sex only. It was not indicated in the paper whether the 50% mortality observed early in the study was considered treatment-related, nor was the cause of death indicated. This is the only subchronic bioassay of dibutyl phthalate reported in the literature. Confidence in the study, data base, and RfD are all rated low.

<<< Dibutyl phthalate >>>

___I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

U.S. EPA. 1980. Ambient Water Quality Criteria for Phthalate Esters. 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 440/5-80-067. NTIS PB 81-117780.

The RfD in the 1980 Ambient Water Quality Criteria document received extensive peer and public review.

Agency RfD Work Group Review: 01/22/86

Verification Date: 01/22/86

___I.A.7. EPA CONTACTS (ORAL RfD)

Michael L. Dourson / ORD -- (513)569-7544 / FTS 684-7544

Christopher T. DeRosa / ORD -- (513)569-7534 / FTS 684-7534

__I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

Substance Name -- Dibutyl phthalate
CASRN -- 84-74-2

The health effects data for dibutyl phthalate were reviewed by the U.S. EPA RfD/RfC Work Group and determined to be inadequate for derivation of an inhalation RfC. The verification status of this chemical is currently not verifiable. For additional information on health effects of this chemical interested parties are referred to the EPA documentation listed below.

U.S. EPA. 1987. Drinking Water Criteria Document for Phthalic Acid Esters Prepared by the Office of Health and Environmental Assessement, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. (External Review Draft)

Agency Work Group Review: 07/26/90

EPA Contacts:

Gary L. Foureman / OHEA -- (919)541-1183 / FTS 629-1183

Annie M. Jarabek / OHEA -- (919)541-4847 / FTS 629-4847

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_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Dibutyl phthalate
CASRN -- 84-74-2
Last Revised -- 05/01/90

Section II provides information on three aspects of the carcinogenic risk assessment for the agent in question; the U.S. EPA classification, and quantitative estimates of risk from oral exposure and from inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen. 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. Background Document 2 (Service Code 5) provides details on the rationale and methods used to derive the carcinogenicity values found in IRIS. Users are referred to Section I for information on long-term toxic effects other than carcinogenicity.

<<< Dibutyl phthalate >>>

__II.A. EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

___II.A.1. WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification -- D; not classifiable.

Basis -- Pertinent data regarding carcinogenicity was not located in the available literature.

<<< Dibutyl phthalate >>>

___II.A.2. HUMAN CARCINOGENICITY DATA

None.

<<< Dibutyl phthalate >>>

___II.A.3. ANIMAL CARCINOGENICITY DATA

None.

<<< Dibutyl phthalate >>>

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

DBP did not induce mutations in a modified reverse mutation plate incorporation assay in Salmonella strains TA100 and TA98 at concentrations up to 1000 ug/plate in the presence or the absence of S9 hepatic homogenate (Kozumbo et al., 1982). It was a weak direct-acting mutagen in a forward mutation assay in Salmonella typhimurium (Seed, 1982). DBP was mutagenic in the mouse lymphoma forward mutation assay only in the presence of metabolic activation (CMA, 1986). In addition, DBP showed some evidence of clastogenic activity in Chinese hamster fibroblasts (Ishidate and Odashima, 1977) but was negative in human leukocytes (Tsuchiya and Hattori, 1977). Research indicates that DBP is hydrolyzed to monoesters (Kluwe, 1982; Rowland et al., 1977; Albro and Moore, 1974). There is evidence that DBP induces peroxisome proliferation (U.S. EPA, 1987).

---------<<< Dibutyl phthalate >>>---------

__II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

Not available.

---------<<< Dibutyl phthalate >>>---------

__II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

Not available.

---------<<< Dibutyl phthalate >>>---------

__II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

___II.D.1. EPA DOCUMENTATION

U.S. EPA. 1987. Drinking Water Criteria Document for Phthalic Acid Esters. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. External Review Draft.

<<< Dibutyl phthalate >>>

___II.D.2. REVIEW (CARCINOGENICITY ASSESSMENT)

The Drinking Water Criteria Document for Phthalic Acid Esters has received OHEA review.

Agency Work Group Review: 08/26/87

Verification Date: 08/26/87

___II.D.3. U.S. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

Robert Vanderslice / ODW -- (202)382-5546 / FTS 382-5546

Annette Gatchett / ORD -- (513)569-7813 / FTS 684-7813

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_III. HEALTH HAZARD ASSESSMENTS FOR VARIED EXPOSURE DURATIONS

__III.A. DRINKING WATER HEALTH ADVISORIES

Substance Name -- Dibutyl phthalate
CASRN -- 84-74-2

Not available at this time.

__III.B. OTHER ASSESSMENTS

Substance Name -- Dibutyl phthalate
CASRN -- 84-74-2

Content to be determined.

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_IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- Dibutyl phthalate
CASRN -- 84-74-2

Last Revised -- 09/01/90

EPA risk assessments may be updated as new data are published and as assessment methodologies evolve. Regulatory actions are frequently not updated at the same time. Compare the dates for the regulatory actions in this section with the verification dates for the risk assessments in sections I and II, as this may explain inconsistencies. Also note that some regulatory actions consider factors not related to health risk, such as technical or economic feasibility. Such considerations are indicated for each action. In addition, not all of the regulatory actions listed in this section involve enforceable federal standards. Please direct any questions you may have concerning these regulatory actions to the U.S. EPA contact listed for that particular action. Users are strongly urged to read the background information on each regulatory action in Background Document 4 in Service Code 5.

<<< Dibutyl phthalate >>>

__IV.A. CLEAN AIR ACT (CAA)

No data available

---------<<< Dibutyl phthalate >>>---------

__IV.B. SAFE DRINKING WATER ACT (SDWA)

No data available

---------<<< Dibutyl phthalate >>>---------

__IV.C. CLEAN WATER ACT (CWA)

___IV.C.1. AMBIENT WATER QUALITY CRITERIA, Human Health

Water and Fish Consumption: 3.4E+4 ug/L

Fish Consumption Only: 1.54E+5 ug/L

Considers technological or economic feasibility? -- NO

Discussion -- The WQC of 3.4E+4 ug/L is based on consumption of contaminated aquatic organisms and water. A WQC of 1.54E+5 ug/L has also been established based on consumption of contaminated aquatic organisms alone.

Reference -- 45 FR 79318 (11/28/80)

EPA Contact -- Criteria and Standards Division, OWRS
(202)475-7315 / FTS 475-7315

<<< Dibutyl phthalate >>>

___IV.C.2. AMBIENT WATER QUALITY CRITERIA, Aquatic Organisms

Freshwater:

Acute LEC -- 9.4E+2 ug/L
Chronic LEC -- 3.0E+0 ug/L

Marine:

Acute LEC -- 2.9E+3 ug/L
Chronic LEC -- None

Considers technological or economic feasibility? -- NO

Discussion -- The values that are indicated as "LEC" are not criteria, but are the lowest effect levels found in the literature. LECs are given when the minimum data required to derive water quality criteria are not available. The values given are for the general class of phthalate esters and not specifically for dibutyl phthalate.

Reference -- 45 FR 79318 (11/28/80)

EPA Contact -- Criteria and Standards Division, OWRS
(202)475-7315 / FTS 475-7315

---------<<< Dibutyl phthalate >>>---------

__IV.D. FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT (FIFRA)

No data available

---------<<< Dibutyl phthalate >>>---------

__IV.E. TOXIC SUBSTANCES CONTROL ACT (TSCA)

No data available

---------<<< Dibutyl phthalate >>>---------

__IV.F. RESOURCE CONSERVATION AND RECOVERY ACT (RCRA)

___IV.F.1. RCRA APPENDIX IX, for Ground Water Monitoring

Status -- Listed

Reference -- 52 FR 25942 (07/09/87)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)382-3000 / FTS 382-3000

---------<<< Dibutyl phthalate >>>---------

__IV.G. SUPERFUND (CERCLA)

___IV.G.1. REPORTABLE QUANTITY (RQ) for Release into the Environment

Value (status) -- 10 pounds (Final, 1985)

Considers technological or economic feasibility? -- NO

Discussion -- The final RQ is based on aquatic toxicity. The available data indicate that the aquatic 96-Hour Median Threshold Limit for dibutyl phthalate is between 0.1 and 1 ppm.

Reference -- 50 FR 13456 (04/04/85)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)382-3000 / FTS 382-3000

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_V. SUPPLEMENTARY DATA

Substance Name -- Dibutyl phthalate
CASRN -- 84-74-2
Last Revised -- 01/31/87

The information contained in this section (subsections A and B) has been extracted from the EPA Chemical Profiles Database, which has been compiled from a number of secondary sources and has not undergone formal Agency review. The complete reference listings for the citations in this section are provided in Service Code 5. The user is urged to read Background Document 5 in Service Code 5 for further information on the sources and limitations of the data presented here.

<<< Dibutyl phthalate >>>

__V.A. ACUTE HEALTH HAZARD INFORMATION

Toxicity -- Dibutyl phthalate is generally non-irritating to humans (Martin and Worthing, 1974).

Medical Conditions Generally Aggravated by Exposure -- Not Found

Signs and Symptoms of Exposure -- Eye irritation with profuse tearing. Contact with surface of eye has caused severe stinging pain with profuse tearing (Grant, 1974). Mild throat irritation has been observed (Lefaux, 1968). Ingestion has caused nausea, dizziness, photophobia, lachrymation, and conjunctivitis (ACGIH, 1980a).

---------<<< Dibutyl phthalate >>>---------

__V.B. PHYSICAL-CHEMICAL PROPERTIES

Chemical Formula -- C16H22O4

Molecular Weight -- 278.34

Boiling Point -- 644F, 340C

Specific Gravity (H2O=1) -- 1.0484 at 20C/20C

Vapor Pressure (mmHg) -- 1.1 at 150C

Melting Point -- -31F, -35C

Vapor Density (AIR=1) -- 9.58

Evaporation Rate (Butyl acetate=1) -- Not Found

Solubility in Water -- 13 mg/L at 25C

Flash Point [Method Used] -- 315F, 157C (CC); 339.8F, 171.1C (OC)

Flammable Limits --
    LEL -- 0.5% at 456F (235C)
    UEL -- Not Found

Appearance and Odor -- Colorless, oily liquid with a weak aromatic odor (NIOSH/OSHA, 1978, p. 80)

Conditions or Materials to Avoid -- Liquid chlorine reacts explosively with dibutyl phthalate (NFPA, 1978). Avoid contact with nitrates, strong oxidizers, strong alkalies, strong acids (NIOSH/OSHA, 1978, p. 80) and chlorine (Sax, 1984, p. 926).

Hazardous Decomposition or Byproducts -- None (NFPA, 1978)

Use -- Plasticizer in nitrocellulose lacquers, elastomers, explosives, nail polish, and solid rocket propellants; solvent for perfume oils; perfume fixative; textile lubricating agent; safety glass; insecticides; printing inks; resin solvent; paper coatings; adhesives; insect repellants for textiles (Hawley, 1981, p. 330). Not registered as a pesticide in the U.S. (USEPA/Pesticide Index, 1985).

_VI. BIBLIOGRAPHY

Substance Name -- Dibutyl phthalate
CASRN -- 84-74-2
Last Revised -- 10/01/90

__VI.A. ORAL RfD REFERENCES

Gangolli, S.D. 1982. Testicular effects of phthalate esters. Environ. Health Perspect. 45: 77-84.

Shiota, K. and H. Nishimura. 1982. Teratogenicity of di-2-ethylhexyl phthalate and di-n-butyl phthalate in mice. Environ. Health Perspect. 45(0): 65-70.

Smith C.C. 1953. Toxicity of butyl sterate, dibutyl sebacate, dibutyl phthalate and methoxyethyl oleate. Arch. Hyg. Occup. Med. 7: 310-318.

U.S. EPA. 1980. Ambient Water Quality Criteria for Phthalate Esters. 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 440/5-80-067. NTIS PB 81-117780.

---------<<< Dibutyl phthalate >>>---------

__VI.B. INHALATION RfD REFERENCES

U.S. EPA. 1987. Drinking Water Criteria Document for Phthalic Acid Esters Prepared by the Office of Health and Environmental Assessement, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. (External Review Draft)

---------<<< Dibutyl phthalate >>>---------

__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

Albro, P.W. and B. Moore. 1974. Identification of the metabolites of simple phthalate diesters in rat urine. J. Chromatogr. 94: 209-218.

CMA (Chemical Manufacturers Association). 1986. Mutagenicity of 1C (di-n-butyl phthalate) in a mouse lymphoma mutation assay. Final report. Submitted to Hazleton Biotechnologies Company. HB Project No. 20989. September, 1986.

Ishidate, M., Jr. and S. Odashima. 1977. Chromosome tests with 134 compounds on Chinese hamster cells in vitro -- A screening test for chemical carcinogens. Mutat. Res. 48: 337-354.

Kluwe, W.M. 1982. Overview of phthalate ester pharmacokinetics in mammalian species. Environ. Health Perspect. 45: 3-10.

Kozumbo, W.J., R. Kroll and R.J. Rubin. 1982. Assessment of the mutagenicity of phthalate esters. Environ. Health Perspect. 45: 103-109.

Rowland, I.R., R.C. Cottrell and J.C. Phillips. 1977. Hydrolysis of phthalate esters by the gastro-intestinal contents of the rat. Food Cosmet. Toxicol. 15: 17-21.

Seed, J.L. 1982. Mutagenic activity of phthalate esters in bacterial liquid suspension assays. Environ. Health Perspect. 45: 111-114.

Tsuchiya, K. and K. Hattori. 1977. Chromosomal study on human leukocyte cultures treated with phthalic acid ester. Hokkaidoritus Eisei Kenkyusho Ho. 26: 114. (Abstract)

U.S. EPA. 1987. Drinking Water Criteria Document for Phthalic Acid Esters. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. External Review Draft.

---------<<< Dibutyl phthalate >>>---------

__VI.D. DRINKING WATER HA REFERENCES

None

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SYNONYMS

Substance Name -- Dibutyl phthalate
CASRN -- 84-74-2
Last Revised -- 01/31/87

84-74-2
1,2-Benzenedicarboxylic Acid Dibutyl Ester
o-Benzenedicarboxylic Acid, Dibutyl Ester
Benzene-o-Dicarboxylic Acid Di-n-Butyl Ester
Butylphthalate
Celluflex DPB
Dibutyl 1,2-Benzene dicarboxylate
Dibutyl phthalate

STATUS OF DATA FOR p,p'-Dichlorodiphenyl dichloroethane (DDD)

File On-Line 08/22/88

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	no data	
Inhalation RfD Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	on-line	08/22/88
Drinking Water Health Advisories (III.A.)	no data	
U.S. EPA Regulatory Actions (IV.)	no data	

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_I. CHRONIC HEALTH HAZARD ASSESSMENT FOR NONCARCINOGENIC EFFECTS

Substance Name -- p,p'-Dichlorodiphenyl dichloroethane (DDD)
CASRN -- 72-54-8

Not available at this time

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_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- p,p'-Dichlorodiphenyl dichloroethane (DDD)
CASRN -- 72-54-8
Last Revised -- 08/22/88

Section II provides information on three aspects of the carcinogenic risk assessment for the agent in question; the U.S. EPA classification, and quantitative estimates of risk from oral exposure and from inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen. 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. Background Document 2 (Service Code 5) provides details on the rationale and methods used to derive the carcinogenicity values found in IRIS. Users are referred to Section I for information on long-term toxic effects other than carcinogenicity.

<<< DDD >>>

II.A. EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

II.A.1. WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification -- B2; probable human carcinogen

Basis -- based on an increased incidence of lung tumors in male and female mice, liver tumors in male mice and thyroid tumors in male rats. DDD is structurally similar to, and is a known metabolite of DDT, a probable human carcinogen.

II.A.2. HUMAN CARCINOGENICITY DATA

None. Human epidemiological data are not available for DDD. Evidence for the carcinogenicity in humans of DDT, a structural analog, is based on autopsy studies relating tissue levels of DDT to cancer incidence. These studies have yielded conflicting results. Three studies reported that tissue levels of DDT and DDE were higher in cancer victims than in those dying of other diseases (Casarett et al., 1968; Dacre and Jennings, 1970; Wasserman et al., 1976). In other studies no such relationship was seen (Maier-Bode, 1960; Robinson et al., 1965; Hoffman et al., 1967). Studies of occupationally exposed workers and volunteers have been of insufficient duration to determine the carcinogenicity of DDT to humans.

<<< DDD >>>

II.A.3. ANIMAL CARCINOGENICITY DATA

Sufficient. Tomatis et al. (1974) fed DDD for 130 weeks at 250 ppm (TWA) to 60 CF-1 mice/sex. A statistically significant increase in incidence of lung tumors was seen in both sexes compared with controls. In males, a statistically significant increase in incidence of liver tumors was also seen.

NCI (1978) fed DDD at 411 and 822 ppm (TWA) to 50 B6C3F1 mice/sex/dose for 78 weeks. Actual doses were 350 or 630 ppm for 5 weeks, 375 or 750 ppm for 11 weeks, and 425 or 850 ppm for the next 62 weeks. After an additional 15 weeks, an increased incidence of hepatocellular carcinomas was seen in both sexes by comparison to controls, but the increase was not statistically significant.

NCI (1978) also fed DDD at 1647 and 3294 ppm TWA for males and 850 and 1700 ppm TWA for females for 78 weeks to 50 Osborne-Mendel rats/sex/dose. Males were fed 1400 or 2800 ppm for 23 weeks followed by 1750 or 3500 ppm for 55 weeks. Females were fed 850 or 1700 ppm for the entire 78 weeks. After an additional 35 weeks, an increased incidence of thyroid tumors (follicular cell adenomas and carcinomas) was observed in males. Due to a wide variation in incidence of these tumors in the control groups for DDD, DDE and DDT, the increased incidence was not statistically significant by

comparison to concurrent controls. Although tumor incidence did not appear to be dose-related, the increase was significant at the low dose by comparison to historical controls. Thus, the pathologists' judgment and statistical results suggest a possible carcinogenic effect of DDD in male rats. NCI concluded that a definitive interpretation of the data was not possible.

<<< DDD >>>

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

DDD is structurally similar to, and is a metabolite of, DDT, a probable human carcinogen, in rats (Peterson and Robinson, 1964), mice (Gingell and Wallcave, 1976), and humans (Morgan and Roan, 1977).

Positive effects were found with DDD in mammalian cytogenetic assays and a host-mediated assay (ICPEMC, 1984).

__II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE
<<< DDD >>>

___II.B.1. SUMMARY OF RISK ESTIMATES

Oral Slope Factor -- 2.4E-1/mg/kg/day

Drinking Water Unit Risk -- 6.9E-6/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)	1E+1 ug/L
E-5 (1 in 100,000)	1 ug/L
E-6 (1 in 1,000,000)	1E-1 ug/L

<<< DDD >>>

___II.B.2. DOSE-RESPONSE DATA (CARCINOGENICITY, ORAL EXPOSURE)

Tumor Type -- Liver
Test Animals -- Mouse/CF-1, males
Route -- oral (diet)
Reference -- Tomatis et al., 1974

---- Dose -----		Tumor
Admin-istered	Human Equivalent	Incidence

(ppm)	(mg/kg/day)	
0	0	33/98
250	245	31/59

___II.B.3. ADDITIONAL COMMENTS (CARCINOGENICITY, ORAL EXPOSURE)

DDD used in the Tomatis study was 99% pure p,p'-isomer. In the NCI bioassay, technical grade DDD was used, in which 60% of the material consisted of the p,p'-isomer. The composition of the remaining 40% was unspecified, but it was stated that analysis by gas chromatography revealed at least 19 impurities.

The unit risk should not be used if the water concentration exceeds 1E+3 ug/L, since above this concentration the slope factor may differ from that stated.

<<< DDD >>>

___II.B.4. DISCUSSION OF CONFIDENCE (CARCINOGENICITY, ORAL EXPOSURE)

An adequate number of animals was tested. The slope factor was calculated using tumor incidence data from only one dose. The slope factor was similar to, and within a factor of 2, of the slope factors for this same site of three other structurally similar compounds: DDT, 3.4E-1/mg/kg/day; DDE, 3.4E-1/mg/kg/day; and dicofol, 4.4E-1/mg/kg/day.

__II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

Not available

__II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)
<<< DDD >>>

___II.D.1. EPA DOCUMENTATION

U.S. EPA. 1980. Hazard Assessment Report on DDT, DDD, DDE. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

U.S. EPA. 1985. The Carcinogenic Assessment Group's Calculation of the Carcinogenicity of Dicofol (Kelthane), DDT, DDE and DDD (TDE). Prepared by the Office of Health and Environmental Assessment, carcinogen Assessment

Group, Washington, DC, for the Hazard Evaluation Division, Office of Toxic Substances, Washington, DC. (Internal Report) EPA-600/X-85-097.

___II.D.2. REVIEW (CARCINOGENICITY ASSESSMENT)

The 1985 Carcinogen Assessment Group's report has received Agency review.

The 1980 Hazard Assessment Report has received peer review.

Agency Work Group Review: 06/03/87, 06/24/87

Verification Date: 06/24/87

___II.D.3. U.S. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

James H. Holder / ORD -- (202)382-5721 / FTS 382-5721

Chao W. Chen / ORD -- (202)382-5898 / FTS 382-5898

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_III. HEALTH HAZARD ASSESSMENTS FOR VARIED EXPOSURE DURATIONS

Substance Name -- p,p'-Dichlorodiphenyl dichloroethane (DDD)
CASRN -- 72-54-8

Not available at this time

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_IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- p,p'-Dichlorodiphenyl dichloroethane (DDD)
CASRN -- 72-54-8

Not available at this time

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_V. SUPPLEMENTARY DATA

Substance Name -- p,p'-Dichlorodiphenyl dichloroethane (DDD)

CASRN -- 72-54-8

Not available at this time

_VI. BIBLIOGRAPHY

Substance Name -- p,p'-Dichlorodiphenyl dichloroethane (DDD)
CASRN -- 72-54-8
Last Revised -- 08/01/89

__VI.A. ORAL RfD REFERENCES

None

------<<< DDD >>>------

__VI.B. INHALATION RfD REFERENCES

None

------<<< DDD >>>------

__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

Casarett, L.J., G.C. Fryer, W.L. Yauger, Jr. and H. Klemmer. 1968. Organochlorine pesticide residues in human tissue. Hawaii. Arch. Environ. Health. 17: 306-311.

Dacre, J.C. and R.W. Jennings. 1970. Organochlorine insecticides in normal and carcinogenic human lung tissues. Toxicol. Appl. Pharmacol. 17: 277.

Gingell, R. and L. Wallcave. 1976. Metabolism of 14C-DDT in the mouse and hamster. Xenobiotica. 6: 15.

Hoffman, W.S., H. Adler, W.I. Fishbein and F.C. Bauer. 1967. Relation of pesticide concentrations in fat to pathological changes in tissues. Arch. Environ. Health. 15: 758-765.

ICPEMC (International Commission for Protection Against Environmental Mutagens and Carcinogens). 1984. Report of ICPEMC task group 5 on the differentiation between genotoxic and nongenotoxic carcinogens. ICPEMC Publication No. 9.

Mutat. Res. 133: 1-49.

Maier-Bode, H. 1960. DDT in Koperfett des Menschen. Med. Exp. 1: 132-137. (Russian)

Morgan, D.P. and C.C. Roan. 1977. The metabolism of DDT in man. Essays Toxicol. 5: 39.

NCI (National Cancer Institute). 1978. Bioassay of DDT, TDE and p,p'-DDE for possible carcinogenicity. NCI Report No. 131. DHEW Publ. No. (NIH) 78-1386.

Peterson, J.R. and W.H. Robinson. 1964. Metabolic products of p.p'-DDT in the rat. Toxicol. Appl. Pharmacol. 6: 321.

Robinson, J., A. Richardson, C.G. Hunter, A.N. Crabtree and H.J. Rees. 1965. Organochlorine insecticide content of human adipose tissue in south-eastern England. Br. J. Ind. Med. 22: 220-224.

Tomatis, L., V. Turusov, R.T. Charles and M. Boicchi. 1974. Effect of long-term exposure to 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene, to 1,1-dichloro-2,2-bis(p-chlorophenyl)-ethane, and to the two chemicals combined on CF-1 mice. J. Natl. Cancer Inst. 52(3): 883-891.

U.S. EPA. 1980. Hazard Assessment Report on DDT, DDD, DDE. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

U.S. EPA. 1985. The Carcinogenic Assessment Group's Calculation of the Carcinogenicity of Dicofol (Kelthane), DDT, DDE and DDD (TDE). Prepared by the Office of Health and Environmental Assessment, carcinogen Assessment Group, Washington, DC, for the Hazard Evaluation Division, Office of Toxic Substances, Washington, DC. (Internal Report) EPA-600/X-85-097.

Wasserman, M., D.P. Nogueira, L. Tomatis, et al. 1976. Organochlorine compounds in neoplastic and adjacent apparently normal breast tissue. Bull. Environ. Contam. Toxicol. 15: 478-484.

------<<< DDD >>>------

__VI.D. DRINKING WATER HA REFERENCES

None

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SYNONYMS

72-54-8
1,1-bis(4-chlorophenyl)-2,2-dichloroethane

Supersedes 3.7.2 (AH) 007

STATUS OF DATA FOR p,p'-Dichlorodiphenyldichloroethylene (DDE)

File On-Line 08/22/88

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	no data	
Inhalation RfD Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	on-line	08/22/88
Drinking Water Health Advisories (III.A.)	no data	
U.S. EPA Regulatory Actions (IV.)	no data	

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_I. CHRONIC HEALTH HAZARD ASSESSMENT FOR NONCARCINOGENIC EFFECTS

Substance Name -- p,p'-Dichlorodiphenyldichloroethylene (DDE)
CASRN -- 72-55-9

Not available at this time

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_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- p,p'-Dichlorodiphenyldichloroethylene (DDE)
CASRN -- 72-55-9
Last Revised -- 08/22/88

Section II provides information on three aspects of the carcinogenic risk assessment for the agent in question; the U.S. EPA classification, and quantitative estimates of risk from oral exposure and from inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen. 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. Background Document 2 (Service Code 5) provides details on the rationale and methods used to derive the carcinogenicity values found in IRIS. Users are referred to Section I for information on long-term toxic effects other than carcinogenicity.

<<< DDE >>>

II.A. EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

II.A.1. WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification -- B2; probable human carcinogen

Basis -- increased incidence of liver tumors including carcinomas in two strains of mice and in hamsters and of thyroid tumors in female rats by diet.

II.A.2. HUMAN CARCINOGENICITY DATA

Human epidemiological data are not available for DDE. Evidence for the carcinogenicity in humans of DDT, a structural analog, is based on autopsy studies relating tissue levels of DDT to cancer incidence. These studies have yielded conflicting results. Three studies reported that tissue levels of DDT and DDE were higher in cancer victims than in those dying of other diseases (Casarett et al., 1968; Dacre and Jennings, 1970; Wasserman et al., 1976). In other studies no such relationship was seen (Maier-Bode, 1960; Robinson et al., 1965; Hoffman et al., 1967). Studies of volunteers and workers occupationally exposed to DDT have been of insufficient duration to determine the carcinogenicity of DDT to humans.

<<< DDE >>>

II.A.3. ANIMAL CARCINOGENICITY DATA

Sufficient. NCI (1978) administered DDE in feed at TWA doses of 148 and 261 ppm to 50 B6C3F1 mice/sex/dose for 78 weeks. After an additional 15 weeks, a dose-dependent and statistically significant increase in incidence of hepatocellular carcinomas was observed in males and females in comparison with controls. Increased weight loss and mortality was observed in females.

Tomatis et al. (1974) administered 250 ppm DDE in feed for lifetime (130 weeks) to 60 CF-1 mice/sex. A statistically significant increase in incidence of hepatomas was observed in both males and females in comparison with controls. In females, 98% of the 55 surviving exposed animals developed hepatomas, compared to 1% of the surviving controls.

Rossi et al. (1983) administered DDE in feed for 128 weeks to 40-46 Syrian Golden hamsters/sex/dose at doses of 500 and 1000 ppm. After 76 weeks, a statistically significant increase in incidence of neoplastic nodules of the liver were observed in both sexes in comparison with vehicle-treated controls.

NCI (1978) also fed DDE at TWA doses of 437 and 839 ppm for males and 242 and 462 ppm for females for 78 weeks to 50 Osborne-Mendel rats/sex/ dose, with an additional 35 week observation period. A dose-dependent trend in incidence of thyroid tumors was observed in females which was statistically significant by the Cochran Armitage trend test after adjustment for

survival. The Fischer Exact test, however, was not statistically significant. Overall, the results of the bioassay were not considered by NCI to provide convincing evidence for carcinogenicity.

<<< DDE >>>

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

DDE was mutagenic in mouse lymphoma (L5178Y) cells and chinese hamster (V79) cells, but not in Salmonella (ICPEMC, 1984). DDE is structurally similar to and a metabolite of DDT (Peterson and Robinson, 1964; Gingell and Wallcave, 1976; Morgan and Roan, 1977) which is a probable human carcinogen.

__II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

___II.B.1. SUMMARY OF RISK ESTIMATES

Oral Slope Factor -- 3.4E-1/mg/kg/day

Drinking Water Unit Risk -- 9.7E-6/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)	1E+1 ug/L
E-5 (1 in 100,000)	1 ug/L
E-6 (1 in 1,000,000)	1E-1 ug/L

<<< DDE >>>

___II.B.2. DOSE-RESPONSE DATA (CARCINOGENICITY, ORAL EXPOSURE)

Species/Strain Tumor Type	Dose: Administered (ppm)	Dose: Human Equivalent (mg/kg/day)	Tumor Incidence (female)	Tumor Incidence (male)	Reference
Mouse/B6C3F1; hepatocellular carcinomas	0	0.0	0/19	0/19	NCI, 1978
	148	0.90	19/47	7/41	
	261	1.584	34/48	17/47	
Mouse/CF-1; hepatomas	0	0	1/90	33/98	Tomatis et al., 1974
	250	2.45	54/55	39/53	

Hamsters/Syrian Golden; neoplastic nodules (hepatomas)	0	0	0/31	0/42	Rossi et al., 1983
	500	4.79	7/30	4/39	
	1000	9.57	8/39	6/39	

Route: oral (diet)

<<< DDE >>>

___II.B.3. ADDITIONAL COMMENTS (CARCINOGENICITY, ORAL EXPOSURE)

NCI (1978) used DDE of about 95% purity, while that used by Tomatis et al. (1974) and Rossi et al. (1983) was 99% pure. In the hamster study, Rossi et al. described the observed lesions as neoplastic liver nodules or hepatocellular tumors, using these terms interchangeably. The oral quantitative estimate is a geometric mean of six slope factors computed from incidence data by sex from the studies cited in Section II.A.3.

The unit risk should not be used if the water concentration exceeds 1E+3 ug/L, since above this concentration the slope factor may differ from that stated.

<<< DDE >>>

___II.B.4. DISCUSSION OF CONFIDENCE (CARCINOGENICITY, ORAL EXPOSURE)

An adequate number of animals was observed. The geometric mean obtained using the slope factors from the mouse studies alone is 7.8E-1/mg/kg/day. This is within a factor of 2 of that derived from the mouse and hamster studies combined. In addition, the slope factor for DDE was within a factor of 2 of the slope factors for liver tumors for three structurally similar compounds: DDT, 3.4E-1/mg/kg/day; DDD, 2.4E-1/mg/kg/day; and Dicofol, 4.4E-1/mg/kg/day.

__II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

Not available.

__II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

<<< DDE >>>

___II.D.1. EPA DOCUMENTATION

U.S. EPA. 1980. Hazard Assessment Report on DDT, DDD, DDE. Prepared by the

Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

U.S. EPA. 1985. The Carcinogen Assessment Group's Calculation of the Carcinogenicity of Dicofol (Kelthane), DDT, DDE and DDD (TDE). Prepared by the Office of Health and Environmental Assessment, Carcinogen Assessment Group, Washington, DC for the Hazard Evaluation Division, Office of Toxic Substances, Washington, DC.

___II.D.2. REVIEW (CARCINOGENICITY ASSESSMENT)

The 1985 Carcinogen Assessment Group's report has received Agency review. The 1980 Hazard Assessment Report has received peer review.

Agency Work Group Review: 06/24/87

Verification Date: 06/24/87

___II.D.3. U.S. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

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Chao Chen / ORD -- (202)382-5719 / FTS 382-5719

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_III. HEALTH HAZARD ASSESSMENTS FOR VARIED EXPOSURE DURATIONS

Substance Name -- p,p'-Dichlorodiphenyldichloroethylene (DDE)
CASRN -- 72-55-9

Not available at this time

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_IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- p,p'-Dichlorodiphenyldichloroethylene (DDE)
CASRN -- 72-55-9

Not available at this time

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_V. SUPPLEMENTARY DATA

Substance Name -- p,p'-Dichlorodiphenyldichloroethylene (DDE)
CASRN -- 72-55-9

Not available at this time

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_VI. BIBLIOGRAPHY

Substance Name -- p,p'-Dichlorodiphenyldichloroethylene (DDE)
CASRN -- 72-55-9
Last Revised -- 08/01/89

__VI.A. ORAL RfD REFERENCES

None

------<<< DDE >>>------

__VI.B. INHALATION RfD REFERENCES

None

------<<< DDE >>>------

__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

Casarett, L.J., G.C. Fryer, W.L. Yauger, Jr. and H. Klemmer. 1968. Organochlorine pesticide residues in human tissue. Hawaii. Arch. Environ. Health. 17: 306-311.

Dacre, J.C. and R.W. Jennings. 1970. Organochlorine insecticides in normal and carcinogenic human lung tissues. Toxicol. Appl. Pharmacol. 17: 277.

Gingell, R. and L. Wallcave. 1976. Species differences in the acute toxicity and tissue distribution of DDT in mice and hamsters. Toxicol. Appl. Pharmacol. 28: 385.

Hoffman, W.S., H. Adler, W.I. Fishbein and F.C. Bauer. 1967. Relation of pesticide concentrations in fat to pathological changes in tissues. Arch.

Environ. Health. 15: 758-765.

ICPEMC (International Commision for Protection Against Environmental Mutagens and Carcinogens). 1984. Report of ICPEMC Task Group 5 on the differentiation between genotoxic and nongenotoxic carcinogens. ICPEMC Publication No. 9. Mutat. Res. 133: 1-49.

Maier-Bode, H. 1960. DDT im Korperfett des Menschen. Med. Exp. 1: 146-152.

Morgan, D.P. and C.C. Roan. 1977. The metabolism of DDT in man. Essays Toxicol. 5: 39.

NCI (National Cancer Institute). 1978. Bioassay of DDT, TDE and p,p'-DDE for possible carcinogenicity. NCI Report No. 131. DHEW Publ. No. (NIH) 78-1386.

Peterson, J.E. and W.H. Robinson. 1964. Metabolic products of p,p'-DDT in the rat. Toxicol. Appl. Pharmacol. 6: 321-327.

Robinson, J., A. Richardson, C.G. Hunter, A.N. Crabtree and H.J. Rees. 1965. Organochlorine insecticide content of human adipose tissue in south-eastern England. Br. J. Ind. Med. 22: 220-224.

Rossi, L., O. Barbieri, M. Sanguineti, J.R.P. Cabral, P. Bruzzi and L. Santi. 1983. Carcinogenicity study with technical-grade DDT and DDE in hamsters. Cancer Res. 43: 776-781.

Tomatis, L., V. Turusov, R.t. Charles and M. Boicchi. 1974. Effect of long-term exposure to 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene, to 1,1-dichloro-2,2-bis(p-chlorophenyl)ethane, and the two chemicals combined on CF-1 mice. J. Natl. Cancer Inst. 52: 883-891.

U.S. EPA. 1980. Hazard Assessment Report on DDT, DDD, DDE. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

U.S. EPA. 1985. The Carcinogen Assessment Group's Calculation of the Carcinogenicity of Dicofol (Kelthane), DDT, DDE and DDD (TDE). Prepared by the Office of Health and Environmental Assessment, Carcinogen Assessment Group, Washington, DC for the Hazard Evaluation Division, Office of Toxic Substances, Washington, DC.

Wasserman, M., D.P. Nogueira, L. Tomatis, et al. 1976. Organochlorine compounds in neoplastic and adjacent apparently normal breast tissue. Bull. Environ. Contam. Toxicol. 15: 478-484.

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VI.D. DRINKING WATER HA REFERENCES

None

Sullivan's Leg. 3.9.2 (AHC) OOII

STATUS OF DATA FOR p,p'-Dichlorodiphenyltrichloroethane (DDT)

File On-Line 03/31/87

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	09/30/87
Inhalation RfD Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	on-line	08/22/88
Drinking Water Health Advisories (III.A.)	no data	
U.S. EPA Regulatory Actions (IV.)	on-line	03/01/88
Supplementary Data (V.)	no data	

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_I. CHRONIC HEALTH HAZARD ASSESSMENT FOR NONCARCINOGENIC EFFECTS

Substance Name -- p,p'-Dichlorodiphenyltrichloroethane (DDT)
CASRN -- 50-29-3
Last Revised -- 09/30/87

The Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. 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 Background Document 1 in Service Code 5 for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of compounds which 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 when a review of that evaluation is completed.

<<< DDT >>>

__I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfDo)

___I.A.1. ORAL RfD SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfD

Liver lesions	NOEL: 1 ppm diet (0.05 mg/kg bw/day)	100	1	5E-4 mg/kg/day
27-Week Rat Feeding Study	LOAEL: 5 ppm			
Laug et al., 1950				

*Dose Conversion Factors & Assumptions: Food consumption = 5% bw/day

<<< DDT >>>

___I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

Laug, E.P., A.A. Nelson, O.G. Fitzhugh and F.M. Kunze. 1950. Liver cell alteration and DDT storage in the fat of the rat induced by dietary levels of 1-50 ppm DDT. J. Pharmacol. Exp. Therap. 98: 268-273.

Weanling rats (25/sex/group) were fed commercial DDT (81% P,P isomer and 19% O,P isomer) at levels of 0, 1, 5, 10 or 50 ppm for 15-27 weeks. The diet was prepared by mixing appropriate amounts of DDT in corn oil solution with powdered chow. No interference with growth was noted at any level. Females stored more DDT in peripheral fat than did males, but pathologic changes were seen to a greater degree in males. Increasing hepatocellular hypertrophy, especially centrilobularly, increased cytoplasmic oxyphilia, and peripheral basophilic cytoplasmic granules (based on H and E paraffin sections) were observed at dose levels of 5 ppm and above. The effect was minimal at 5 ppm (LOAEL) and more pronounced at higher doses. No effects were reported at 1 ppm, the NOEL level used as the basis for the RfD calculation. The authors believe the effect seen at 5 ppm "represents the smallest detectable morphologic effect, based on extensive observations of the rat liver as affected by a variety of chemicals."

DDT fed to rats for 2 years (Fitzhugh, 1948) caused liver lesions at all dose levels (10-800 ppm of diet). A LOAEL of 0.5 mg/kg bw/day was established. Application of a factor of 10 each for uncertainty of estimating a NOEL from a LOAEL, as well as for interspecies conversion and protection of sensitive human subpopulations (1000 total) results in the same RfD level as that calculated from the critical study. DDT-induced liver effects were observed in mice, hamsters and dogs as well.
C

The Laug et al. (1950) study was chosen for the RfD calculation because: 1) male rats appear to be the most sensitive animals to DDT exposure; 2) the study was of sufficient length to observe toxic effects; and 3) several doses were administered in the diet over the range of the dose-response curve. This study also established a LOAEL and a NOEL, with the LOAEL (0.25 mg/kg/day) being the lowest of any observed for this compound.

<<< DDT >>>

___I.A.3. UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

UF = 100. A factor of 10 each was applied for the uncertainty of interspecies conversion and to protect sensitive human subpopulations. An uncertainty

factor for subchronic to chronic conversion was not included because of the corroborating chronic study in the data base.

MF = 1

___I.A.4. ADDITIONAL COMMENTS (ORAL RfD)

In one 3-generation rat reproduction study (Treon and Cleveland, 1955), offspring mortality increased at all dose levels, the lowest of which corresponds to about 0.2 mg/kg bw/day. Three other reproduction studies (rat and mouse) show no reproductive effects at much higher dose levels.

<<< DDT >>>

___I.A.5. CONFIDENCE IN THE ORAL RfD

Study: Medium
Data Base: Medium
RfD: Medium

The principal study appears to be adequate, but of shorter duration than that desired; therefore, confidence in the study can be considered medium to low. The data base is only moderately supportive of both the critical effect and the magnitude, and lacks a clear NOEL for reproductive effects; therefore, confidence in the data base can also be considered medium to low. Medium to low confidence in the RfD follows.

___I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

The only U.S. EPA documentation at present is on IRIS.

Agency RfD Work Group Review: 12/18/85

Verification Date: 12/18/85

___I.A.7. EPA CONTACTS (ORAL RfD)

Michael L. Dourson / ORD -- (513)569-7544 / FTS 684-7544

Christopher T. DeRosa / ORD -- (513)569-7534 / FTS 684-7534

------<<< DDT >>>------

__I.B. REFERENCE DOSE FOR CHRONIC INHALATION EXPOSURE (RfDi)

Not available at this time

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_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- p,p'-Dichlorodiphenyltrichloroethane (DDT)
CASRN -- 50-29-3
Last Revised -- 08/22/88

Section II provides information on three aspects of the carcinogenic risk assessment for the agent in question; the U.S. EPA classification, and quantitative estimates of risk from oral exposure and from inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen. 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. Background Document 2 (Service Code 5) provides details on the rationale and methods used to derive the carcinogenicity values found in IRIS. Users are referred to Section I for information on long-term toxic effects other than carcinogenicity.

<<< DDT >>>

__II.A. EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

___II.A.1. WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification -- B2; probable human carcinogen.

Basis -- Observation of tumors (generally of the liver) in seven studies in various mouse strains and three studies in rats. DDT is structurally similar to other probable carcinogens, such as DDD and DDE.

___II.A.2. HUMAN CARCINOGENICITY DATA

Inadequate. The existing epidemiological data are inadequate. Autopsy studies relating tissue levels of DDT to cancer incidence have yielded conflicting results. Three studies reported that tissue levels of DDT and DDE were higher in cancer victims than in those dying of other diseases (Casarett et al., 1968; Dacre and Jennings, 1970; Wasserman et al., 1976). In other studies no such relationship was seen (Maier-Bode, 1960; Robinson et al., 1965; Hoffman et al., 1967). Studies of occupationally exposed workers and volunteers have been of insufficient duration to be useful in assessment of the carcinogenicity of DDT to humans.

<<< DDT >>>

II.A.3. ANIMAL CARCINOGENICITY DATA

Sufficient. Twenty-five animal carcinogenicity assays have been reviewed for DDT. Nine feeding studies, including two multigenerational studies, have been conducted in the following mouse strains: BALB/C, CF-1, A strain, Swiss/Bombay and (C57B1)x(C3HxAkR). Only one of these studies, conducted for 78 weeks, showed no indication of DDT tumorigenicity (NCI, 1978). Both hepatocellular adenomas and carcinomas were observed in six mouse liver tumor studies (Walker et al., 1973; Thorpe and Walker, 1973; Kashyap et al., 1977; Innes et al., 1969; Terracini et al., 1973; Turusov et al., 1973). Both benign and malignant lung tumors were observed in two studies wherein mice were exposed both in utero and throughout their lifetime (Shabad et al., 1973; Tarjan and Kemeny, 1969). Doses producing increased tumor incidence ranged from 0.15-37.5 mg/kg/day.

Three studies using Wistar, MRC Porton and Osborne-Mendel rats and doses from 25-40 mg/kg/day produced increased incidence of benign liver tumors (Rossi et al., 1977; Cabral et al., 1982; Fitzhugh and Nelson, 1946). Another study wherein Osborne-Mendel rats were exposed in this dietary dose range for 78 weeks was negative (NCI, 1978) as were three additional assays in which lower doses were given.

Tests of DDT in hamsters have not resulted in increased tumor incidence. Unlike mice and humans, hamsters accumulate DDT in tissue but do not metabolize it to DDD or DDE. Studies of DDT in dogs (Lehman, 1952, 1965) and monkeys (Adamson and Sieber, 1979, 1983) have not shown a carcinogenic effect. However, the length of these studies (approximately 30% of the animals' lifetimes) was insufficient to assess the carcinogenicity of DDT. DDT has been shown to produce hepatomas in trout (Halver, 1967).

<<< DDT >>>

II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

DDT has been shown to act as a liver tumor promoter in rats initiated with 2-acetylaminofluorene, 2-acetamidophenanthrene or trans-4-acetylaminostilbene (Peraino et al., 1975; Scribner and Mottet, 1981; Hilpert et al., 1983).

DDT has produced both negative and positive responses in tests for genotoxicity. Positive responses have been noted in V79 mutation assays, for chromosome aberrations in cultured human lymphocytes, and for sister chromatid exchanges in V79 and CHO cells (Bradley et al., 1981; Rabello et al., 1975; Preston et al., 1981; Ray-Chaudhuri et al., 1982). In one study, DDT was reported to interact directly with DNA; this result was not confirmed in the absence of a metabolizing system (Kubinski et al., 1981; Griffin and Hill, 1978).

DDT is structurally related to the following chemicals which produce liver tumors in mice: DDE, DDD, dicofol and chlorobenzilate.

II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

<<< DDT >>>

II.B.1. SUMMARY OF RISK ESTIMATES

Oral Slope Factor -- 3.4E-1/mg/kg/day

Drinking Water Unit Risk -- 9.7E-6/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)	1 E+1 ug/L
E-5 (1 in 100,000)	1 ug/L
E-6 (1 in 1,000,000)	1 E-1 ug/L

<<< DDT >>>

II.B.2. DOSE-RESPONSE DATA (CARCINOGENICITY, ORAL EXPOSURE)

Tumor Type -- Liver
Test Animals -- mouse/CF-1, mouse/BALB/C, rat/MRC Porton, rat/Wistar
Route -- oral (diet)
Reference -- Turusov et al., 1973; Terracini et al., 1973; Thorpe and Walker, 1973; Tomatis and Turusov, 1975; Cabral et al., 1982; Rossi et al., 1977

Species/Strain Tumor Type	Slope Factor Male	Slope Factor Female	Reference
Mouse/CF-1, Benign	0.80	0.42	Turusov et al., 1973
Mouse/BALB/C, Benign	0.082		Terracini et al., 1973
Mouse/CF-1, Benign, Malignant	0.52	0.81	Thorpe and Walker, 1973
Mouse/CF-1, Benign	1.04	0.49	Tomatis and Turusov, 1975
Rat/MRC Porton		0.084	Cabral et al., 1982
Rat/Wistar, Benign	0.16	0.27	Rossi et al., 1977

<<< DDT >>>

II.B.3. ADDITIONAL COMMENTS (CARCINOGENICITY, ORAL EXPOSURE)

The estimate of the slope factor did not increase in the multigeneration feeding studies (Terracini et al., 1973; Turusov et al., 1973) but remained the same from generation to generation. A geometric mean of the above slope factors was used for the overall slope factor of 3.4E-1. This was done in

order to avoid excluding relevant data (note that the appropriateness of this procedure is currently under study by U.S. EPA). All tumors were of the liver; there were no metastases. A few malignancies were observed in the Turusov study; possible neoplasms were indicated in the Terracini and Tomatis studies. The Turusov study was carried out over six generations, the Terracini assay for two. The slope factor derived from data of Tarjan and Kemeny (1969) was not included in the calculation of the geometric mean because the tumors developed at different sites than in any other studies. In addition, there was a problem in this study with possible DDT contamination of the feed.

DDT is known to be absorbed by humans in direct proportion to dietary exposure; t(1/2) for clearance is 10-20 years.

The unit risk should not be used if the water concentraion exceeds 1E+3 ug/L, since above this concentration the slope factor may differ from that stated.

<<< DDT >>>

___II.B.4. DISCUSSION OF CONFIDENCE (CARCINOGENICITY, ORAL EXPOSURE)

Ten slope factors derived from six studies were within a 13-fold range. The slope factor derived from the mouse data alone was 4.8E-1 while that derived from the rat data alone was 1.5E-1. There was no apparent difference in slope factor as a function of sex of the animals. The geometric mean of the slope factors from the mouse and rat data combined was identical for the same tumor site as that for DDE (3.4E-1/mg/kg/day), a structural analog.

__II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE
<<< DDT >>>

___II.C.1. SUMMARY OF RISK ESTIMATES

Inhalation Slope Factor -- 3.4E-1/mg/kg/day

Inhalation Unit Risk -- 9.7E-5/ug/cu.m

Extrapolation Method -- Linear multistage procedure, extra risk

Air Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	1 ug/cu.m
E-5 (1 in 100,000)	1 E-1 ug/cu.m
E-6 (1 in 1,000,000)	1 E-2 ug/cu.m

___II.C.2. DOSE-RESPONSE DATA FOR CARCINOGENICITY, INHALATION EXPOSURE

The slope factor was calculated from the oral data presented in Section II.B.2.

<<< DDT >>>

___II.C.3. ADDITIONAL COMMENTS (CARCINOGENICITY, INHALATION EXPOSURE)

The unit risk should not be used if the air concentration exceeds 1E+2 ug/cu.m, since above this concentration the slope factor may differ from that stated.

___II.C.4. DISCUSSION OF CONFIDENCE (CARCINOGENICITY, INHALATION EXPOSURE)

This inhalation risk estimate was calculated from the oral data presented in Section II.B.2.

__II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)
<<< DDT >>>

___II.D.1. EPA DOCUMENTATION

U.S. EPA. 1985. The Carcinogenic Assessment Groups Calculation of the Carcinogenicity of Dicofol (Kelthane), DDT, DDE and DDD (TDE). Prepared by the Office of Health and Environmental Assessment, Carcinogen Assessment Group, Washington, DC for the Hazard Evaluation Division, Office of Toxic Substances, Washington, DC.

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___II.D.2. REVIEW (CARCINOGENICITY ASSESSMENT)

The U.S. EPA risk assessment document on DDT is an internal report and has not received external review.

Agency Work Group Review: 10/29/86, 11/12/86, 06/24/87

Verification Date: 06/24/87

___II.D.3. U.S. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

James W. Holder / ORD -- (202)382-5721 / FTS 382-5721

Chao W. Chen / ORD -- (202)382-5898 / FTS 382-5898

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_III. HEALTH HAZARD ASSESSMENTS FOR VARIED EXPOSURE DURATIONS

Substance Name -- p,p'-Dichlorodiphenyltrichloroethane (DDT)
CASRN -- 50-29-3

Not available at this time

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_IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- p,p'-Dichlorodiphenyltrichloroethane (DDT)
CASRN -- 50-29-3
Last Revised -- 03/01/88

EPA risk assessments may be updated as new data are published and as assessment methodologies evolve. Regulatory actions are frequently not updated at the same time. Compare the dates for the regulatory actions in this section with the verification dates for the risk assessments in sections I and II, as this may explain inconsistencies. Also note that some regulatory actions consider factors not related to health risk, such as technical or economic feasibility. Such considerations are indicated for each action. In addition, not all of the regulatory actions listed in this section involve enforceable federal standards. Please direct any questions you may have concerning these regulatory actions to the U.S. EPA contact listed for that particular action. Users are strongly urged to read the background information on each regulatory action in Background Document 4 in Service Code 5.

__IV.A. CLEAN AIR ACT (CAA)

No data available

------<<< DDT >>>------

__IV.B. SAFE DRINKING WATER ACT (SDWA)

No data available

------<<< DDT >>>------

__IV.C. CLEAN WATER ACT (CWA)

___IV.C.1. AMBIENT WATER QUALITY CRITERIA, Human Health

Water and Fish Consumption -- 2.4E-5 ug/L

Fish Consumption Only -- 2.4E-5 ug/L

Considers technological or economic feasibility? -- NO

Discussion -- For the maximum protection from the potential carcinogenic properties of this chemical, the ambient water concentration should be zero. However, zero may not be attainable at this time, so the recommended criteria represents a E-6 estimated incremental increase of cancer risk over a lifetime.

Reference -- 45 FR 79318 (11/28/80)

EPA Contact -- Criteria and Standards Division, OWRS
(202)475-7315 / FTS 475-7315

<<< DDT >>>

___IV.C.2. AMBIENT WATER QUALITY CRITERIA, Aquatic Organisms

Freshwater:

Acute -- 1.1E+0 ug/L (at any time)
Chronic -- 1.0E-3 ug/L (24-hour average)

Marine:

Acute -- 1.3E-1 ug/L (at any time)
Chronic -- 1.0E-3 ug/L (24-hour average)

Considers technological or economic feasibility? -- NO

Discussion --

Reference -- 45 FR 79318 (11/28/80)

EPA Contact -- Criteria and Standards Division, OWRS
(202)475-7315 / FTS 475-7315

------<<< DDT >>>------

__IV.D. FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT (FIFRA)

___IV.D.1. PESTICIDE ACTIVE INGREDIENT, Registration Standard

None

___IV.D.2. PESTICIDE ACTIVE INGREDIENT, Special Review

Action -- Most uses cancelled (1972)

Considers technological or economic feasibility? -- YES

Summary of regulatory action -- Cancelled, all products, except the following list of uses: 1) the U.S. Public Health Service and other Health Service Officials for control of vector diseases, 2) the USDA or military for health quarantine, 3) in drugs, for controlling body lice (to be dispensed only by a physician), 4) in the formulation of prescription drugs for controlling body lice. PR Notice 71-1 (January 15, 1971) and 37 FR 13369 (July 7, 1972).

Reference -- 37 FR 13369 (07/07/72)

EPA Contact -- Special Review Branch, OPP / (703)557-7400 / FTS 557-7400

------<<< DDT >>>------

__IV.E. TOXIC SUBSTANCES CONTROL ACT (TSCA)

No data available

------<<< DDT >>>------

__IV.F. RESOURCE CONSERVATION AND RECOVERY ACT (RCRA)

___IV.F.1. RCRA APPENDIX IX, for Ground Water Monitoring

Status -- Listed

Reference -- 52 FR 25942 (07/09/87)

EPA Contact -- Jerry Garman / OSW / (202)382-4658 / FTS 382-4658

------<<< DDT >>>------

__IV.G. SUPERFUND (CERCLA)

___IV.G.1. REPORTABLE QUANTITY (RQ) for Release into the Environment

Value (status) -- 1 pound (Proposed, 1987)

Considers technological or economic feasibility? -- NO

Discussion -- The proposed RQ for DDT is 1 pound, based on the aquatic toxicity, as established under CWA Section 311 (40 CFR 117.3). The available data indicate the aquatic 96-hour Median Threshold Limit for DDT is less than 0.1 ppm. This corresponds to an RQ of 1 pound. DDT has also been found to bioaccumulate in the tissues of aquatic and marine organisms, and has the potential to concentrate in the food chain.

Reference -- 52 FR 8140 (03/16/87)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)382-3000 / FTS 382-3000

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_V. SUPPLEMENTARY DATA

Substance Name -- p,p'-Dichlorodiphenyltrichloroethane (DDT)
CASRN -- 50-29-3

Not available at this time

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_VI. REFERENCES

Substance Name -- p,p'-Dichlorodiphenyltrichloroethane (DDT)
CASRN -- 50-29-3

Not available at this time

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SYNONYMS: ETHANE, 1,1,1-TRICHLORO-2,2-BIS(p-CHLOROPHENYL)-; AGRITAN; ANOFEX; ARKOTINE; AZOTOX; BENZENE, 1,1'-(2,2,2-TRICHLOROETHYLIDENE)BIS(4-CHLORO-); alpha,alpha-BIS(p-CHLOROPHENYL)-beta,beta,beta-TRICHLORETHANE; 1,1-BIS-(p-CHLOROPHENYL)-2,2,2-TRICHLOROETHANE; 2,2-BIS(p-CHLOROPHENYL)-1,1,1-

Sullivan's Ledge
3972 (2nd)
0051

Methylene chloride

STATUS OF DATA FOR Dichloromethane

File On-Line 01/31/87

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	03/01/88
Inhalation RfC Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	on-line	09/01/90
Drinking Water Health Advisories (III.A.)	on-line	03/01/88
U.S. EPA Regulatory Actions (IV.)	on-line	08/01/90
Supplementary Data (V.)	no data	

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_I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

__I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name -- Dichloromethane
CASRN -- 75-09-2
Primary Synonym -- Methylene Chloride
Last Revised -- 03/01/88

The Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. 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 Background Document 1 in Service Code 5 for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of compounds which 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 when a review of that evaluation is completed.

<<< Dichloromethane >>>

___I.A.1. ORAL RfD SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfD

Liver toxicity 2-Year Rat Drinking Water Bioassay National Coffee Association, 1982	NOAEL: 5.85 and 6.47 mg/kg/day for males and females, respectively LOAEL: 52.58 and 58.32 mg/kg/day for males and females, respectively	100	1	6E-2 mg/kg/day

*Conversion Factors: Doses reflect actual values and not nominal ones.

<<< Dichloromethane >>>

___I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

National Coffee Association. 1982. 24-Month chronic toxicity and oncogenicity
study of methylene chloride in rats. Final Report. Prepared by Hazleton Laboratories America, Inc., Vienna, VA. (Unpublished)

The chosen study appears to have been very well conducted, with 85 rats/sex at each of four nominal dose groups (i.e., 5, 50, 125 and 250 mg/kg/day) for 2 years. A high-dose recovery group of 25 rats/sex, as well as two control groups of 85 and 50 rats/sex, was also tested. Many effects were monitored. Treatment related histological alterations of the liver were evident at nominal doses of 50 mg/kg/day or higher. The low nominal dose of 5 mg/kg/day was a NOAEL.

The supporting data base is limited. A NOAEL of 87 mg/cu.m was reported in one inhalation study (Haun et al., 1972). [The equivalent oral dose is about 28 mg/kg bw/day (i.e., 87 mg/cu.m x 0.5 x 0.223 cu.m/day/0.35 kg; these exposure values are for rats).]

<<< Dichloromethane >>>

___I.A.3. UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

UF = 100. (10a x 10h) The 100-fold factor accounts for both the expected intra- and interspecies variability to the toxicity of this chemical in lieu of specific data.

MF = 1.

<<< Dichloromethane >>>

___I.A.4. ADDITIONAL COMMENTS (ORAL RfD)

None.

<<< Dichloromethane >>>

___I.A.5. CONFIDENCE IN THE ORAL RfD

Study: High
Data Base: Medium
RfD: Medium

The study is given a high confidence rating because a large number of animals of both sexes were tested in four dose groups, with a large number of controls. Many effects were monitored and a dose-related increase in severity was observed. The data base is rated medium to low because only a few studies support the NOAEL. Medium confidence in the RfD follows.

<<< Dichloromethane >>>

___I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

U.S. EPA. 1985. Drinking Water Criteria Document for Methylene Chloride. Office of Drinking Water, Washington, DC.

Agency RfD Work Group Review: 06/24/85, 07/08/85, 11/06/85

Verification Date: 11/06/85

___I.A.7. EPA CONTACTS (ORAL RfD)

Krishan Khanna / ODW -- (202)382-7588 / FTS 382-7588

Michael L. Dourson / ORD -- (513)569-7544 / FTS 684-7544

__I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

Substance Name -- Dichloromethane
CASRN -- 75-09-2
Primary Synonym -- Methylene Chloride

Not available at this time.

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_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Dichloromethane
CASRN -- 75-09-2
Primary Synonym -- Methylene Chloride
Last Revised -- 09/01/90

Section II provides information on three aspects of the carcinogenic risk assessment for the agent in question; the U.S. EPA classification, and quantitative estimates of risk from oral exposure and from inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen. 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. Background Document 2 (Service Code 5) provides details on the rationale and methods used to derive the carcinogenicity values found in IRIS. Users are referred to Section I for information on long-term toxic effects other than carcinogenicity.

<<< Dichloromethane >>>

II.A. EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

II.A.1. WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification --B2; probable human carcinogen

Basis -- Based on inadequate human data and sufficient evidence of carcinogenicity in animals; increased incidence of hepatocellular neoplasms and alveolar/bronchiolar neoplasms in male and female mice, and increased incidence of benign mammary tumors in both sexes of rats, salivary gland sarcomas in male rats and leukemia in female rats. This classification is supported by some positive genotoxicity data, although results in mammalian systems are generally negative.

<<< Dichloromethane >>>

II.A.2. HUMAN CARCINOGENICITY DATA

Inadequate. Neither of two studies of chemical factory workers exposed to dichloromethane showed an excess of cancers (Ott et al., 1983; Friedlander et al., 1978; Hearne and Friedlander, 1981). The Ott et al. (1983) study was designed to examine cardiovascular effects, and consequently the study period was too short to allow for latency of site-specific cancers. In the Friedlander et al. (1978) study, exposures were low, but the data provided some suggestion of an increased incidence of pancreatic tumors. This study was recently updated to include a larger cohort, followed through 1984, and an investigation of possible confounding factors (Hearne et al., 1986, 1987). A nonsignificant excess in pancreatic cancer deaths was observed, which was interpreted by EPA (1987a) as neither clear evidence of carcinogenicity in humans, nor evidence of noncarcinogenicity. An update of the Ott et al. (1983) study, based on longer follow-up, indicated possible elevation of liver and biliary tract cancers (TSCA section 8(e) submission no. 8eHQ-0198-0772 FLWP et seq., 1989).

<<< Dichloromethane >>>

II.A.3. ANIMAL CARCINOGENICITY DATA

Sufficient. Dichloromethane administered in the drinking water induced a significant increase in combined hepatocellular carcinoma and neoplastic nodules in female F344 rats and a nonsignificant increase in combined hepatocellular carcinoma and neoplastic nodules in male B6C3F1 mice (NCA, 1982, 1983). Two inhalation studies with dichloromethane have shown an increased incidence of benign mammary tumors in both sexes of Sprague-Dawley (Burek et al., 1984) and F344 (NTP, 1986) rats. Male Sprague-Dawley rats had increased salivary gland sarcoma (Burek et al., 1984) and female F344 rats had increased leukemia incidence (NTP, 1986). Both sexes of B6C3F1 mice developed liver and lung tumors after dichloromethane treatment (NTP, 1986).

In a 2-year study by the National Coffee Association (1982, 1983), groups of 85 F344 rats/sex/dose received 5, 50, 125, or 250 (mg/kg)/day of dichloromethane in the drinking water. Control groups consisted of 135 rats/sex. In female rats the incidence of combined hepatocellular carcinoma and neoplastic nodules was statistically significantly increased in the 50 and 250 mg/kg dose groups when compared with matched controls (0/134, 1/85, 4/83, 1/85, and 6/85 in the five dose groups 0, 5, 50, 125, and 250 (mg/kg)/day, respectively). The incidence of hepatocellular carcinoma alone was not significantly increased (0/134, 0/85, 2/83, 0/85, 2/85). The combined incidence of hepatocellular carinoma and neoplastic nodules in controls and the 4 dose groups (472 rats: 4 with carcinoma and 8 with neoplastic nodules) was similar to that for historical controls (419 rats; 5 with carcinoma, 19 with neoplastic nodules). Male rats showed no increase in liver tumors.

In the same National Coffee Association study (1982, 1983), B6C3F1 mice received 0, 60, 125, 185, or 250 (mg/kg)/day of dichloromethane in drinking water. Treatment groups consisted of 50 female mice and 200, 100, 100, and 125 male mice (low to high dose). One hundred females and 125 males served as controls. Male mice had an increased incidence of combined neoplastic nodules and hepatocellular carcinoma (24/125, 51/200, 30/100, 31/99, 35/125). The increase was not dose-related, but the pairwise comparisons for the two mid-dose groups were reported to be statistically significant (U.S. EPA, 1985a). The hepatocellular carcinoma incidence alone for male mice (which was about 55 to 65% of the total) was not significantly elevated. Female mice did not have increased liver tumor incidence. The EPA (1985b) regarded this study as suggestive but not conclusive evidence for carcinogenicity of dichloromethane.

A gavage bioassay of dichloromethane conducted by NTP (1982) has not been published because of high mortality, much of which was attributed to gavage accidents.

Inhalation exposure of 107 to 109 Syrian hamsters/sex/dose to 0, 500, 1500, or 3500 ppm of dichloromethane for 6 hours/day, 5 days/week for 2 years did not induce neoplasia (Burek et al., 1984). Sprague-Dawley rats (129/sex/dose) were exposed under the same conditions. Female rats administered the highest dose experienced significantly reduced survival from 18-24 months. Female rats showed a dose-related increase in the average number of benign mammary tumors per rat (1.7, 2.3, 2.6, 3.0), although the numbers of rats with tumors were not significantly increased. A similar response was observed in male rats, but to a lesser degree. In the male rats there was a statistically significant positive trend in the incidence of sarcomas of the salivary gland

(1/93, 0/94, 5/91, 11/88); the incidence was significantly elevated at the high dose. There is a question as to whether these doses reached the MTD, particularly in the hamsters and the male rats. In another study (Dow Chemical Co., 1982), 90 Sprague-Dawley rats/sex were exposed by inhalation to 0, 50, 200, or 500 ppm dichloromethane for 20 months (male) or 24 months (female). No salivary tumors were observed, but there was an exposure-related increase in the total number of benign mammary tumors in female rats, although the increase was not statistically significant in any individual exposure group.

Groups of 50 each male and female F344/N rats and B6C3F1 mice were exposed to dichloromethane by inhalation, 6 hours/day, 5 days/week for 2 years (NTP, 1986). Exposure concentrations were 0, 1000, 2000, or 4000 ppm for rats and 0, 2000, or 4000 ppm for mice. Survival of male rats was low; however, this apparently was not treatment-related. Survival was decreased in a treatment-related fashion for male and female mice and female rats. Mammary adenomas and fibroadenomas were significantly increased in male and female rats after survival adjustment, as were mononuclear cell leukemias in female rats. Among treated mice of both sexes there were significantly increased incidences of hepatocellular adenomas and carcinomas, and of alveolarbronchiolar adenomas and carcinomas, by life table tests. Adenomas and carcinomas were significantly increased alone as well as in combination. In addition, there were significant dose-related increases in the number of lung tumors per animal multiplicity in both sexes of mice.

Two inhalation assays using dogs, rabbits, guinea pigs, and rats showed no tumors, but were not conducted for the lifetime of the animals (Heppel et al., 1944; MacEwen et al., 1972). Theiss et al., (1977) injected Strain A male mice intraperitoneally with 0, 160, 400, or 800 mg/kg of dichloromethane 16 to 17 times, over 5 to 6 weeks. Survival of the animals was poor. The animals remaining 24 weeks after the first treatment were killed and examined for lung tumors; pulmonary adenomas were found.

<<< Dichloromethane >>>

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Dichloromethane was mutagenic for Salmonella typhimurium with or without the addition of hepatic enzymes (Green, 1983) and produced mitotic recombination in yeast (Callen et al., 1980). Results in cultured mammalian cells have generally been negative, but dichloromethane has been shown to transform rat embryo cells and to enhance viral transformation of Syrian hamster embryo cells (Price et al., 1978; Hatch et al., 1983). Although chlorinated solvents have often been suspected of acting through a nongenotoxic mechanism of cell proliferation, Lefevre and Ashby (1989) found methylene chloride to be unable to induce hepatocellular division in mice.

---------<<< Dichloromethane >>>---------

__II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

___II.B.1. SUMMARY OF RISK ESTIMATES

Oral Slope Factor -- 7.5E-3 per (mg/kg)/day

Drinking Water Unit Risk -- 2.1E-7 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)	5E+2 ug/L
E-5 (1 in 100,000)	5E+1 ug/L
E-6 (1 in 1,000,000)	5 ug/L

<<< Dichloromethane >>>

___II.B.2. DOSE-RESPONSE DATA (CARCINOGENICITY, ORAL EXPOSURE)

Tumor Type -- hepatocellular adenomas or carcinomas (NTP) and hepatocellular cancer and neoplastic nodules (NCA)
Test Animals -- mouse/B6C3F1 (female, NTP; male, NCA)
Route -- inhalation (NTP); oral/drinking water (NCA)
Reference -- NTP, 1986; National Coffee Association (NCA), 1983

Dose				
Administered (ppm)	mg/kg/day	Human Equivalent (mg/kg)/day	Tumor Incidence	Reference
0	0	0	3/50	NTP, 1986
2000	1582	122	16/48	
4000	3162	244	40/48	
	0	0	24/125	NCA, 1983
	60	4.5	51/200	
	125	9.4	30/100	
	185	14.0	31/99	
	250	18.9	35/125	

<<< Dichloromethane >>>

___II.B.3. ADDITIONAL COMMENTS (CARCINOGENICITY, ORAL EXPOSURE)

The slope factor is an arithmetic mean of slope factors derived from NTP(1986) and the National Coffee Association (1983) data, 2.6E-3 per (mg/kg)/day and 1.2E-2 per (mg/kg)/day, respectively. The use of liver tumor data from the NTP inhalation bioassay was considered valid since dichloromethane is rapidly absorbed following either inhalation or ingestion.

Dose conversions used the mean body weight for female mice at the midpoint of the bioassay, and an estimated inhalation rate of 0.0407 cu.m/day. To obtain estimates of unit risk for humans, an inhalation rate of 20 cu.m/day was assumed. Dichloromethane was considered to be well-absorbed as a vapor at low doses. No pharmacokinetic or metabolism data have been used to modify the oral unit risk estimate, because such analyses have not yet been carried out.

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

<<< Dichloromethane >>>

___II.B.4. DISCUSSION OF CONFIDENCE (CARCINOGENICITY, ORAL EXPOSURE)

Adequate numbers of animals were used in both assays. Risk estimates were based on the more sensitive sex in each study. The two risk estimates were within a factor of 5.

---------<<< Dichloromethane >>>---------

__II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

___II.C.1. SUMMARY OF RISK ESTIMATES

Inhalation Slope Factor -- Not available; Calculation of a slope factor from the unit risk is inappropriate when pharmacokinetic models are used. (When dose-response relationships are figured on the basis of internal or metabolized dose, a slope factor in terms of (mg/kg/day)-1 represents a back calculation using different absorption assumptions than the pharmacokinetic models. This introduces possible contradictions.)

Inhalation Unit Risk -- 4.7E-7 per (ug/cu.m)

Extrapolation Method -- Linearized multistage procedure, extra risk

Air Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	2E+2 ug/cu.m
E-5 (1 in 100,000)	2E+1 ug/cu.m
E-6 (1 in 1,000,000)	2 ug/cu.m

<<< Dichloromethane >>>

___II.C.2. DOSE-RESPONSE DATA FOR CARCINOGENICITY, INHALATION EXPOSURE

Tumor Type -- combined adenomas and carcinomas
Test Animals -- mouse/B6C3F1, female

Route -- inhalation
Reference -- NTP, 1986

	Dose			
Tumor Type	Administered (ppm)	Transformed Animal (mg/kg)/day	Human Equivalent (mg/kg)/day	Tumor Incidence
Liver	0	0	0	3/45
	2000	1582	356	16/46
	4000	3162	712	40/46
Lung	0	0	0	3/45
	2000	1582	356	30/46
	4000	3162	712	41/46

<<< Dichloromethane >>>

___II.C.3. ADDITIONAL COMMENTS (CARCINOGENICITY, INHALATION EXPOSURE)

The unit risk of 4.7E-7 per (ug/cu.m), which incorporates information on pharmacokinetics and metabolism of dichloromethane, is approximately nine-fold lower than the previous applied dose estimate (U.S. EPA, 1987a,b). Internal dose estimates were based on the metabolism of dichloromethane by the glutathione-s-transferase pathway, as estimated by the model developed by Andersen et al. (1987). The internal dose was corrected for interspecies differences in sensitivity by using the surface area correction factor.

The unit risk should not be used if the air concentration exceeds 2E+4 ug/cu.m, since above this concentration the unit risk may differ from that stated. Since the unit risk is based on a pharmacokinetic model, the risk may change with alterations in exposure patterns. Thus, the unit risk presented here may not be applicable to acute, high exposures.

<<< Dichloromethane >>>

___II.C.4. DISCUSSION OF CONFIDENCE (CARCINOGENICITY, INHALATION EXPOSURE)

Adequate numbers of animals were observed and tumor incidences were significantly increased in a dose-dependent fashion. Analysis excluding animals that died before observation of the first tumors produced similar risk estimates, as did time-to-tumor analysis. The use of animal and human metabolism and pharmacokinetic data reduces some of the uncertainty typically associated with dose-risk extrapolation. A great deal of uncertainty still exists, however, in the estimates of internal dose generated by the model of Andersen et al. (1987). Important uncertainties remain regarding the pharmacokinetics, pharmacodynamics, and mechanisms of carcinogenicity for dichloromethane.

---------<<< Dichloromethane >>>---------

__II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

___II.D.1. EPA DOCUMENTATION

U.S. EPA. 1985a. Health Assessment Document for Dichloromethane (Methylene Chloride). Final Report. Office of Health and Environmental Assessment, Washington, D.C. EPA/600/8-82/004F.

U.S. EPA. 1985b. Addendum to the Health Assessment Document for Dichloromethane (methylene chloride). Updated carcinogenicity assessment. Prepared by the Carcinogen Assessment Group, OHEA, Washington, DC. EPA/600/8-82/004FF.

U.S. EPA. 1987a. Update to the Health Assessment Document and Addendum for Dichloromethane (Methylene Chloride): Pharmacokinetics, Mechanism of Action and Epidemiology. Review Draft. Office of Health and Environmental Assessment, Washington, DC. EPA/600/8-87/030A.

U.S. EPA. 1987b. Technical Analysis of New Methods and Data Regarding Dichloromethane Hazard Assessments. Review Draft. Office of Health and Environmental Assessment, Washington, DC. EPA/600/8- 87/029A.

<<< Dichloromethane >>>

___II.D.2. REVIEW (CARCINOGENICITY ASSESSMENT)

The Addendum to the Health Assessment Document, the Update to the Health Assessment Document and Addendum, and the Technical Analysis of New Methods and Data for dichloromethane have received Agency and external review, including a review by the Science Advisory Board (SAB). Although the last two documents are not yet finalized and the SAB comments are not yet incorporated, these do not alter this document's analyses or conclusions.

Agency Work Group Review: 11/12/86, 12/04/86, 04/06/89

Verification Date: 04/06/89

___II.D.3. U.S. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

Lorenz Rhomberg / ORD -- (202)382-5723 / FTS 382-5723

Dharm V. Singh / ORD -- (202)382-5898 / FTS 382-5898

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_III. HEALTH HAZARD ASSESSMENTS FOR VARIED EXPOSURE DURATIONS

__III.A. DRINKING WATER HEALTH ADVISORIES

Substance Name -- Dichloromethane
CASRN -- 75-09-2
Primary Synonym -- Methylene Chloride
Last Revised -- 03/01/88

The Office of Drinking Water provides Drinking Water Health Advisories (HAs) as technical guidance for the protection of public health. HAs are not enforceable Federal standards. HAs are concentrations of a substance in drinking water estimated to have negligible deleterious effects in humans, when ingested, for a specified period of time. Exposure to the substance from other media is considered only in the derivation of the lifetime HA. Given the absence of chemical-specific data, the assumed fraction of total intake from drinking water is 20%. The lifetime HA is calculated from the Drinking Water Equivalent Level (DWEL) which, in turn, is based on the Oral Chronic Reference Dose. Lifetime HAs are not derived for compounds which are potentially carcinogenic for humans because of the difference in assumptions concerning toxic threshold for carcinogenic and noncarcinogenic effects. A more detailed description of the assumptions and methods used in the derivation of HAs is provided in Background Document 3 in Service Code 5.

<<< Dichloromethane >>>

___III.A.1. ONE-DAY HEALTH ADVISORY FOR A CHILD

One-day HA -- 1.33E+1 mg/L

LOAEL -- 1326 mg/kg/day
UF -- 1000 (allows for interspecies and intrahuman variability with the use of
a LOAEL from an animal study)
Assumptions -- 1 L/day water consumption for a 10-kg child

Principal Study -- Kimura et al., 1971

Single oral doses of dichloromethane were administered to young adult Sprague-Dawley rats. An approximate dose of 1.3 g/kg was the lowest dose to induce the first observable gross signs of toxicity.

<<< Dichloromethane >>>

___III.A.2. TEN-DAY HEALTH ADVISORY FOR A CHILD

Ten-day HA -- 1.5E+0 mg/L

NOAEL -- 15 mg/kg/day
UF -- 100 (allows for interspecies and intrahuman variability with the use of
a NOAEL from an animal study)
Assumptions -- 1 L/day water consumption for a 10-kg child

Principal Study -- Bornmann and Loeser, 1967

Male and female Wistar rats were administered dichloromethane in drinking

water for 13 weeks at a dose of 15 mg/kg/day. No treatment-related effects were observed.

<<< Dichloromethane >>>

___III.A.3. LONGER-TERM HEALTH ADVISORY FOR A CHILD

Appropriate data for calculating a Longer-term HA is not available. It is recommended that a modified DWEL (adjusted for a 10-kg child) of 0.5 mg/L be used as the Longer-term HA.

<<< Dichloromethane >>>

___III.A.4. LONGER-TERM HEALTH ADVISORY FOR AN ADULT

Appropriate data for calculating a Longer-term HA is not available. It is recommended that the DWEL of 1.75 mg/L be used as the Longer-term HA for the 70-kg adult.

<<< Dichloromethane >>>

___III.A.5. DRINKING WATER EQUIVALENT LEVEL / LIFETIME HEALTH ADVISORY

DWEL -- 1.75E+0 mg/L

Assumptions -- 2 L/day water consumption for a 70-kg adult

RfD Verification Date = 11/06/85

Lifetime HA -- None

Dichloromethane is considered to be a probable human carcinogen. Refer to Section II of this file for information on the carcinogenicity of this substance.

Principal Study (DWEL) -- National Coffee Association, 1982 (This study was used in the derivation of the chronic oral RfD; see Section I.A.2.)

<<< Dichloromethane >>>

___III.A.6. ORGANOLEPTIC PROPERTIES

No data available

<<< Dichloromethane >>>

___III.A.7. ANALYTICAL METHODS FOR DETECTION IN DRINKING WATER

Analysis of dichloromethane is by a purge-and-trap gas chromatographic procedure used for the detection of volatile organohalides in drinking water. Confirmatory analysis is by mass spectrometry.

<<< Dichloromethane >>>

___III.A.8. WATER TREATMENT

The available information suggests that adsorption by granular activated carbon and air stripping are feasible technologies to remove dichloromethane from drinking water.

<<< Dichloromethane >>>

___III.A.9. DOCUMENTATION AND REVIEW OF HAs

U.S. EPA. 1985. Final Draft of the Drinking Water Criteria Document on Dichloromethane. Office of Drinking Water, Washington, DC.

EPA review of HAs in 1985.

Public review of HAs following notification of availability in October, 1985.

Scientific Advisory Panel review of HAs in January, 1986.

Preparation date of this IRIS summary -- 06/24/87

___III.A.10. EPA CONTACTS

Krishan Khanna / ODW -- (202)382-7588 / FTS 382-7588

Edward V. Ohanian / ODW -- (202)382-7571 / FTS 382-7571

__III.B. OTHER ASSESSMENTS

Substance Name -- Dichloromethane
CASRN -- 75-09-2
Primary Synonym -- Methylene Chloride

Content to be determined.

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_IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- Dichloromethane
CASRN -- 75-09-2
Primary Synonym -- Methylene Chloride
Last Revised -- 08/01/90

EPA risk assessments may be updated as new data are published and as assessment methodologies evolve. Regulatory actions are frequently not

updated at the same time. Compare the dates for the regulatory actions in this section with the verification dates for the risk assessments in sections I and II, as this may explain inconsistencies. Also note that some regulatory actions consider factors not related to health risk, such as technical or economic feasibility. Such considerations are indicated for each action. In addition, not all of the regulatory actions listed in this section involve enforceable federal standards. Please direct any questions you may have concerning these regulatory actions to the U.S. EPA contact listed for that particular action. Users are strongly urged to read the background information on each regulatory action in Background Document 4 in Service Code 5.

<<< Dichloromethane >>>

__IV.A. CLEAN AIR ACT (CAA)

No data available

---------<<< Dichloromethane >>>---------

__IV.B. SAFE DRINKING WATER ACT (SDWA)

No data available

---------<<< Dichloromethane >>>---------

__IV.C. CLEAN WATER ACT (CWA)

___IV.C.1. AMBIENT WATER QUALITY CRITERIA, Human Health

Water and Fish Consumption: 1.9E-1 ug/L

Fish Consumption Only: 1.57E+1 ug/L

Considers technological or economic feasibility? -- NO

Discussion -- Methylene chloride is classified as a carcinogen, and under the assumption of no threshold for a carcinogen, the recommended WQC is zero. However, if zero cannot be obtained and exposure is via ingestion of water and aquatic organisms, 0.19 ug/L is associated with an upper-bound excess lifetime risk of 1.0E-6 [other risk levels to consider: 1.0E-5 (1.9 ug/L) and 1.0E-7 (0.019 ug/L)]. If exposure is only via ingestion of aquatic organisms, the WQC associated with an upper-bound excess lifetime risk of 1.0E-6 is 15.7 ug/L.
The criteria are based on halomethanes as a class.

Reference -- 45 FR 79318 (11/13/80)

EPA Contact -- Criteria and Standards Division, OWRS
(202)475-7315 / FTS 475-7315

<<< Dichloromethane >>>

___IV.C.2. AMBIENT WATER QUALITY CRITERIA, Aquatic Organisms

Freshwater:

Acute LEC -- 1.1E+4 ug/L
Chronic -- None

Marine:

Acute LEC -- 1.2E+4 ug/L
Chronic LEC -- 6.4E+3 ug/L

Considers technological or economic feasibility? -- NO

Discussion -- The values that are indicated as "LEC" are not criteria, but are the lowest effect levels found in the literature. LECs are given when the minimum data required to derive water quality criteria are not available.

Reference -- 45 FR 79318 (11/13/80)

EPA Contact -- Criteria and Standards Division, OWRS
(202)475-7315 / FTS 475-7315

---------<<< Dichloromethane >>>---------

__IV.D. FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT (FIFRA)

No data available

---------<<< Dichloromethane >>>---------

__IV.E. TOXIC SUBSTANCES CONTROL ACT (TSCA)

___IV.E.1. TSCA, SECTION 6

Status -- Advance Notice of Proposed Rulemaking (ANPR) (1985)

Discussion -- Initiated priority review under TSCA, sect. 6, of risks from cancer which may be associated with certain exposures to methylene chloride. Receipt of a positive NTP bioassay triggered an accelerated analysis under TSCA, sect. 4(f). Based on its preliminary analysis, zhe Agency decided that methylene chloride should be classified as a B2 probable human carcinogen under its Interim Cancer Guidelines. TSCA, sect. 4(f), requires that the Agency initiate appropriate action under sect. 5, 6, or 7 within a 180-day period of receipt of health effect information which triggers a sect. 4(f) decision. The sect. 6 ANPR initiated appropriate action.

Reference: 50 FR 42005 (10/17/85)

EPA Contact -- Chemical Control Division, OTS / (202)382-3749 / FTS 382-3749

---------<<< Dichloromethane >>>---------

__IV.F. RESOURCE CONSERVATION AND RECOVERY ACT (RCRA)

___IV.F.1. RCRA APPENDIX IX, for Ground Water Monitoring

Status -- Listed

Reference -- 52 FR 25942 (07/09/87)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)382-3000 / FTS 382-3000

---------<<< Dichloromethane >>>---------

__IV.G. SUPERFUND (CERCLA)

___IV.G.1. REPORTABLE QUANTITY (RQ) for Release into the Environment

Value (status) -- 1000 pounds (Final, 1985)

Considers technological or economic feasibility? -- NO

Discussion -- The final adjusted RQ of 1000 pounds is based upon a chronic toxicity score of 10. This substance has recently been identified for assessment of carcinogenicity, and the RQ will be reevaluated when that assessment is completed.

Reference -- 50 FR 13456 (04/04/85)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)382-3000 / FTS 382-3000

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_V. SUPPLEMENTARY DATA

Substance Name -- Dichloromethane
CASRN -- 75-09-2
Primary Synonym -- Methylene Chloride

Not available at this time.

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_VI. BIBLIOGRAPHY

Substance Name -- Dichloromethane
CASRN -- 75-09-2
Primary Synonym -- Methylene Chloride
Last Revised -- 09/01/90

__VI.A. ORAL RfD REFERENCES

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National Coffee Association. 1982. 24-Month chronic toxicity and oncogenicity
study of methylene chloride in rats. Final Report. Prepared by Hazleton Laboratories America, Inc., Vienna, VA. (Unpublished)

U.S. EPA. 1985. Drinking Water Criteria Document for Methylene Chloride. Office of Drinking Water, Washington, DC.

---------<<< Dichloromethane >>>---------

__VI.B. INHALATION RfD REFERENCES

None

---------<<< Dichloromethane >>>---------

__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

Andersen, M.E., H.J. Clewell, III, M.L. Gargas, F.A. Smith and R.H. Reitz. 1987. Physiologically based pharmacokinetics and the risk assessment process for methylene chloride. Toxicol. Appl. Pharmacol. 87: 185-205.

Burek, J.D., K.D. Nitschke, T.J. Bell, et al. 1984. Methylene chloride: A two year inhalation toxicity and oncogenicity study in rats and hamsters. Fund. Appl. Toxicol. 4: 30-47.

Callen, D.F., C.R. Wolf and R.M. Philpot. 1980. Cytochrome P450- mediated genetic activity and cytotoxicity of seven halogenated aliphatic hydrocarbons in Saccharomyces cerevisiae. Mutat. Res. 77: 55-63.

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Unpublished. NTP-82-061.

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U.S. EPA. 1985a. Health Assessment Document for Dichloromethane (Methylene Chloride). Final Report. Office of Health and Environmental Assessment, Washington, D.C. EPA/600/8-82/004F.

U.S. EPA. 1985b. Addendum to the Health Assessment Document for Dichloromethane (methylene chloride). Updated carcinogenicity assessment. Prepared by the Carcinogen Assessment Group, OHEA, Washington, DC. EPA/600/8-82/004FF.

U.S. EPA. 1987a. Update to the Health Assessment Document and Addendum for Dichloromethane (Methylene Chloride): Pharmacokinetics, Mechanism of Action and Epidemiology. Review Draft. Office of Health and Environmental Assessment, Washington, DC. EPA/600/8-87/030A.

U.S. EPA. 1987b. Technical Analysis of New Methods and Data Regarding Dichloromethane Hazard Assessments. Review Draft. Office of Health and Environmental Assessment, Washington, DC. EPA/600/8- 87/029A.

__VI.D. DRINKING WATER HA REFERENCES

Bornmann, G., and A. Loeser. 1967. Zur Frage einer chronisch-toxischen Wirkung von Dichloromethan. Z. Lebensm.-Unters. Forsch. 136: 14-18.

Kimura, E.T., D.M. Ebert and P.W. Dodge. 1971. Acute toxicity and limits of solvent residue for sixteen organic solvents. Toxicol. Appl. Pharmacol. 19: 699-704.

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study of methylene chloride in rats. Final Report. Prepared by Hazleton Laboratories America, Inc., Vienna, VA. (Unpublished)

U.S. EPA. 1985. Final Draft of the Drinking Water Criteria Document on Dichloromethane. Office of Drinking Water, Washington, DC.

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SYNONYMS

Substance Name -- Dichloromethane
CASRN -- 75-09-2
Primary Synonym -- Methylene Chloride
Last Revised -- 01/31/87

75-09-2
Aerothene MM
Chlorure de methylene
DCM
Dichlormethan, uvasol
Dichloromethane
1,1-Dichloromethane.
Freon 30
Methane dichloride
Methane, dichloro-
Methylene bichloride
Methylene Chloride
Methylene dichloride
Metylenu chlorek
Narkotil
NCI-C50102
R 30
Solaesthin
Solmethine
WLN: G1G

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Solubility
3.9.2 (m)
00 II

STATUS OF DATA FOR Fluoranthene

File On-Line 09/01/90

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	09/01/90
Inhalation RfC Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	pending	
Drinking Water Health Advisories (III.A.)	no data	
U.S. EPA Regulatory Actions (IV.)	no data	
Supplementary Data (V.)	no data	

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_I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

__I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name -- Fluoranthene
CASRN -- 206-44-0
Last Revised -- 09/01/90

The Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. 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 Background Document 1 in Service Code 5 for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of compounds which 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 when a review of that evaluation is completed.

<<< Fluoranthene >>>

___I.A.1. ORAL RfD SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfD
Nephropathy, increased	NOAEL: 125 mg/kg/day	3000	1	4E-2

liver weights, hematological alterations, and clinical effects | LOAEL: 250 mg/kg/day | mg/kg/day

Mouse Subchronic Study

U.S. EPA, 1988

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*Conversion Factors: None

<<< Fluoranthene >>>

___I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

U.S. EPA. 1988. 13-Week mouse oral subchronic toxicity study. Prepared by Toxicity Research Laboratories, Ltd., Muskegon, MI for the Office of Solid Waste, Washington, DC.

Male and female CD-1 mice (20/sex/group) were gavaged for 13 weeks with 0, 125, 250, or 500 mg/kg/day fluoranthene. A fifth group of mice (30/sex) was established in the study for baseline blood evaluations. Body weight, food consumption, and hematological and serum parameter values were recorded at regular intervals during the experiment. At the end of 13 weeks, the animals were sacrificed and autopsied, which included organ weight measurement and histological evaluation. All treated mice exhibited nephropathy, increased salivation, and increased liver enzyme levels in a dose-dependent manner. However, these effects were either not significant, not dose-related, or not considered adverse at 125 mg/kg/day. Mice exposed to 500 mg/kg/day had increased food consumption and increased body weight. Mice exposed to 250 and 500 mg/kg/day had statistically increased SGPT values and increased absolute and relative liver weights. Compound-related microscopic liver lesions (indicated by pigmentation) were observed in 65 and 87.5% of the mid- and high-dose mice, respectively. Based on increased SGPT levels, kidney and liver pathology, and clinical and hematological changes, the LOAEL is considered to be 250 mg/kg/day, and the NOAEL is 125 mg/kg/day.

<<< Fluoranthene >>>

___I.A.3. UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

UF = 3000. An uncertainty factor of 3000 reflects 10 for interspecies conversion, 10 for intraspecies variability, and 30 for use of a subchronic study for chronic RfD derivation, and for lack of supporting reproductive/developmental toxicity data and toxicity data in a second species.

MF = 1.

<<< Fluoranthene >>>

___I.A.4. ADDITIONAL COMMENTS (ORAL RfD)

A developmental study was performed in which fluoranthene was administered once via intraperitoneal injection to pregnant C57/B6 mice on gestational day

6, 7, 8 or 9 (Irvin and Martin, 1987). An increased rate of embryo resorption was observed. The data were reported in an abstract, but a complete report was not located. No inhalation studies were located.

IARC (1983) cites several acute studies in which fluoranthene was administered to mice or rats intraperitoneally. No adverse effects were observed; however, only survival or body weight was monitored. Gerarde (1960, cited by IARC, 1983) administered 500 mg/kg/day for 7 days to mice, and Haddow et al. (1937) administered a single 30 mg dose of fluoranthene to rats.

<<< Fluoranthene >>>

___I.A.5. CONFIDENCE IN THE ORAL RfD

Study: Medium
Data Base: Low
RfD: Low

Confidence in the principal study is medium, as it is a well-designed study that identified both a LOAEL and a NOAEL for several sensitive endpoints using an adequate number of animals. Confidence in the data base is low; developmental, reproductive, or toxicity data in a second species following oral exposure to fluoranthene has not been adequately tested. Reflecting medium confidence in the principal study and low confidence in the database, confidence in the RfD is low.
<<< Fluoranthene >>>

___I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

Source Document -- This assessment is not presented in any existing U.S. EPA document.

Agency RfD Work Group Review: 01/22/86, 10/19/89, 11/15/89

Verification Date: 11/15/89

___I.A.7. EPA CONTACTS (ORAL RfD)

John Risher / ORD -- (513)569-7633 / FTS 684-7633

Harlal Choudhury / ORD -- (513)569-7536 / FTS 684-7536

__I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

Substance Name -- Fluoranthene
CASRN -- 206-44-0

Not available at this time.

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_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Fluoranthene
CASRN -- 206-44-0

This substance/agent has been evaluated by the U.S. EPA for evidence of human carcinogenic potential. This does not imply that this chemical is necessarily a carcinogen. The evaluation for this chemical is under review by an inter-office Agency work group. A risk assessment summary will be included on IRIS when the review has been completed.

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_III. HEALTH HAZARD ASSESSMENTS FOR VARIED EXPOSURE DURATIONS

__III.A. DRINKING WATER HEALTH ADVISORIES

Substance Name -- Fluoranthene
CASRN -- 206-44-0

Not available at this time.

__III.B. OTHER ASSESSMENTS

Substance Name -- Fluoranthene
CASRN -- 206-44-0

Content to be determined.

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_IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- Fluoranthene
CASRN -- 206-44-0

Not available at this time.

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_V. SUPPLEMENTARY DATA

Substance Name -- Fluoranthene
CASRN -- 206-44-0

Not available at this time.

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_VI. BIBLIOGRAPHY

Substance Name -- Fluoranthene
CASRN -- 206-44-0
Last Revised -- 09/01/90

__VI.A. ORAL RfD REFERENCES

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Irvin, T.R. and J.E. Martin. 1987. In vitro and in vivo embryotoxicity of fluoranthene, a major prenatal toxic component of diesel soot. Teratology. 35: 65A. (Abstract)

U.S. EPA. 1988. 13-Week mouse oral subchronic toxicity study. Prepared by Toxicity Research Laboratories, Ltd., Muskegon, MI for the Office of Solid Waste, Washington, DC.

---------<<< Fluoranthene >>>---------

__VI.B. INHALATION RfD REFERENCES

None

---------<<< Fluoranthene >>>---------

__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

None

---------<<< Fluoranthene >>>---------

__VI.D. DRINKING WATER HA REFERENCES

None

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SYNONYMS

Substance Name -- Fluoranthene
CASRN -- 206-44-0
Last Revised -- 09/01/90

206-44-0
1,2-BENZACENAPHTHENE
BENZENE, 1,2-(1,8-NAPHTHALENEDIYL)-
BENZENE, 1,2-(1,8-NAPHTHYLENE)-
BENZO(JK)FLUORENE
FLUORANTHENE
HSDB 5486
IDRYL
1,2-(1,8-NAPHTHYLENE)BENZENE
NSC 6803
RCRA WASTE NUMBER U120

Enter keywords or Read or Scan or Mail
--129-00-0
Searching - Please wait...
1 Occurrences...

Enter keywords or Read or Scan or Mail
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Summary Page
3-9-2 (IRIS)
OSF

STATUS OF DATA FOR Fluorene

File On-Line 11/01/90

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	11/01/90
Inhalation RfC Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	on-line	12/01/90
Drinking Water Health Advisories (III.A.)	no data	
U.S. EPA Regulatory Actions (IV.)	no data	
Supplementary Data (V.)	no data	

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_I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

__I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name -- Fluorene
CASRN -- 86-73-7
Last Revised -- 11/01/90

The Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. 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 Background Document 1 in Service Code 5 for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of compounds which 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 when a review of that evaluation is completed.

<<< Fluorene >>>

___I.A.1. ORAL RfD SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfD
Decreased RBC,	NOAEL: 125 mg/kg/day	3000	1	4E-2

packed cell volume and hemoglobin | LOAEL: 250 mg/kg/day | mg/kg/day

Mouse Subchronic Study

U.S. EPA, 1989

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*Conversion Factors: None

<<< Fluorene >>>

___I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

U.S. EPA. 1989. Mouse oral subchronic toxicity study. Prepared by Toxicity Research Laboratories, LTD., Muskegon, MI for the Office of Solid Waste, Washington, DC.

CD-1 mice (25/sex/group) were exposed to 0, 125, 250, or 500 mg/kg/day fluorene suspended in corn oil by gavage for 13 weeks. Parameters used to assess toxicity included food intake, body weight, clinical observations, hematology and serum chemistry and gross and histopathological examinations. Increased salivation, hypoactivity, and urine-wet abdomens in males were observed in all treated animals. The percentage of mice exhibiting hypoactivity was dose-related. In mice exposed at 500 mg/kg/day, labored respiration, ptosis (drooping eyelids), and unkempt appearance were also observed. A significant decrease in red blood cell count and packed cell volume were observed in females treated with 250 mg/kg/day fluorene and in males and females treated with 500 mg/kg/day. Decreased hemoglobin concentration and increased total serum bilirubin levels were also observed in the 500 mg/kg/day group. Decreases in erythrocyte count, packed cell volume, and hemoglobin concentration were all observed at 125 mg/kg; however, these effects, although apparently dose-dependent, were not statistically significant. A significant decreasing trend in BUN and a significant increasing trend in total serum bilirubin were observed in both high-dose males and females. A dose-related increase in relative liver weight was observed in treated mice; a significant increase in absolute liver weight was also observed in the mice treated with 250 and 500 mg/kg/day fluorene. A significant increase in absolute and relative spleen and kidney weight was observed in males and females exposed to 500 mg/kg/day and males at 250 mg/kg/day. Increases in the absolute and relative liver and spleen weights in the high-dose males and females were accompanied by histopathological increases in the amounts of hemosiderin in the spleen and in the Kupffer cells of the liver. No other histopathological lesions were observed. The LOAEL is 250 mg/kg/day based on hematological effects; the NOAEL is 125 mg/kg/day.

<<< Fluorene >>>

___I.A.3. UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

UF = 3000. An uncertainty factor of 3000 was used: 10 for use of a subchronic study for chronic RfD derivation, 10 each for inter- and intraspecies variability, and 3 for lack of adequate toxicity data in a second species and reproductive/developmental data.

MF = 1.

<<< Fluorene >>>

___I.A.4. ADDITIONAL COMMENTS (ORAL RfD)

Morris et al. (1960) fed 18 female Buffalo strain rats 12.3 mg fluorene/kg/day for 6 months or 13.1 mg fluorene/kg/day for 18 months. The diet in the 6-month study was composed of purified materials, low in protein and fat, and prepared in 3% propylene glycol. The diet in the longer study was composed of a mixture of natural foodstuffs in 3% corn oil. In the 6-month study, of 11 animals examined, the incidences of non-neoplastic reactions were reported by organ as follows: forestomach (acanthosis, hyperkeratosis), 5 animals; kidney (squamous metaplasia of pelvis), 7 animals; uterus (squamous metaplasia), 1 animal; small intestine (epithelial ulcer, acute), 1 animal; and liver (cirrhosis), 3 animals.

In the longer study using 18 rats, none of the effects seen in the 6-month study were observed. The only effect reported in this experiment was hyperplasia of the pituitary (predominantly chromophobe cells) in two animals.

It appears that the effects observed in the 6-month study were related to either dietary composition or propylene glycol, since none of these effects were observed after 18 months at a similar dosage using a different diet and vehicle. Consequently, this study is not considered acceptable as a basis for chronic RfD derivation.

No other studies on the toxicity of orally administered fluorene were located.

<<< Fluorene >>>

___I.A.5. CONFIDENCE IN THE ORAL RfD

Study: Medium
Data Base: Low
RfD: Low

Confidence in the principal study is medium: it is a well-designed study that examined and identified both a LOAEL and NOAEL for several sensitive endpoints using an adequate number of animals. Confidence in the data base is low; developmental, reproductive, and chronic toxicity following oral exposure to fluorene have not been tested, and a NOAEL was not identified. Confidence in the RfD is accordingly low.

<<< Fluorene >>>

___I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

Source Document -- This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation - U.S. EPA, 1987

Agency Work Group Review: 10/19/89, 11/15/89

Verification Date: 11/15/89

___I.A.7. EPA CONTACTS (ORAL RfD)

Harlal Choudhury / ORD -- (513)569-7536 / FTS 684-7536

Kenneth A. Poirier / ORD -- (513)569-7462 / FTS 684-7462

__I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

Substance Name -- Fluorene
CASRN -- 86-73-7

Not available at this time.

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_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Fluorene
CASRN -- 86-73-7
Last Revised -- 12/01/90

Section II provides information on three aspects of the carcinogenic risk assessment for the agent in question; the U.S. EPA classification, and quantitative estimates of risk from oral exposure and from inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen. 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. Background Document 2 (Service Code 5) provides details on the rationale and methods used to derive the carcinogenicity values found in IRIS. Users are referred to Section I for information on long-term toxic effects other than carcinogenicity.

<<< Fluorene >>>

__II.A. EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

___II.A.1. WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification -- D; not classifiable as to human carcinogenicity

Basis -- Based on no human data and inadequate data from animal bioassays.

<<< Fluorene >>>

___II.A.2. HUMAN CARCINOGENICITY DATA

None.

<<< Fluorene >>>

___II.A.3. ANIMAL CARCINOGENICITY DATA

Inadequate. Morris et al. (1960) fed female buffalo rats a diet containing 0.05% fluorene in 3% corn oil for approximately 18 months or in propylene glycol for about 6 months (approximately 11 mg/kg/day). Various types of tumors occurred in controls and exposed animals at approximately the same incidences, ranging from 6 to 34%. No statistical analysis was reported.

Studies of fluorene for complete carcinogenic activity, inititating activity or co-carcinogenicity with 3-methylcholanthrene in mouse skin painting assays were not positive or were inconclusive (Kennaway, 1924; Riegel et al., 1951; LaVoie et al., 1979, 1981).

No injection site tumors occurred within 18 months in 10 strain A mice after seven subcutaneous injections of 10 mg fluorene in glycol (Shear, 1938). No control groups appear to have been utilized in this study.

Wilson et al. (1947) fed two groups of albino rats various concentrations of fluorene in the diet. One set of rats was exposed to several concentrations (number not specified) ranging from 0.062-1.0% fluorene in the diet for 104 days. These rats were maintained on diets with fluorene concentrations of 0.5 and 1.0%; they experienced significant decreases in their rate of growth, but in other aspects they appeared normal. The second set received either 0.125, 0.25 or 0.5% fluorene in the diet for 453 days. One rat exposed to 0.125% fluorene in the diet developed a small benign kidney tubular adenoma. The total number of animals treated was not indicated, nor was a control group described.

<<< Fluorene >>>

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Fluorene produced no positive results in reverse mutation assays in five strains of Salmonella typhimurium (1000 ug/plate) or in forward mutation assays in Salmonella strain TM677 (50 ug/mL) (McCann et al., 1975; LaVoie et al., 1979, 1981; Sakai et al., 1985; Bos et al., 1988; Kaden et al., 1979; Mamber et al., 1983). In a DNA damage assay using S. typhimurium TA1535, Nakamura et al. (1987) reported that fluorene at concentrations of up to 16.7 ug/mL was not positive. DNA damage assays with fluorene were not positive in Escherichia coli at concentrations of up to 2 mg/mL (Mamber et al., 1983, 1984) or in primary rat hepatocyte cultures at a maximum concentration of 3 mM (Sina et al., 1983). In a phage induction assay using Escherichia coli as a

host, fluorene was not positive at concentrations of up to 1 mg/mL (Mamber et al., 1984).

In an unscheduled DNA synthesis assay the exposure of primary rat hepatocytes to 10 nmol and 100 nmol/mL fluorene did not yield positive results (Probst et al., 1981; Williams et al., 1989). Fluorene produced positive results in a DNA dammage assay (strand-break assay) in L5178Y/mouse lymphoma cells at 0.15 uM in the presence of hepatic homogenates and at 0.5 uM in the absence of hepatic homogenates (Garberg et al., 1988). In forward mutation assays in L5178Y/mouse lymphoma cells, fluorene was not positive at concentrations of up to 30 and 60 ug/mL in the presence and absence of hepatic homogenates, respectively (Amacher et al., 1981; Oberly et al., 1984).

---------<<< Fluorene >>>---------

__II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

None.

---------<<< Fluorene >>>---------

__II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

None.

---------<<< Fluorene >>>---------

__II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

___II.D.1. EPA DOCUMENTATION

U.S. EPA. 1990. Drinking Water Criteria Document for Polycyclic Aromatic Hydrocarbons (PAHs). Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. Final Draft. ECAO-CIN-D010.

<<< Fluorene >>>

___II.D.2. REVIEW (CARCINOGENICITY ASSESSMENT)

The 1990 Drinking Water Criteria Document for Polycyclic Aromatic Hydrocarbons has received Agency and external review.

Agency Work Group Review: 02/07/90

Verification Date: 02/07/90

___II.D.3. U.S. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

Rita S. Schoeny / ORD -- (513)569-7544 / FTS 684-7544

Robert E. McGaughy / ORD -- (202)382-5889 / FTS 382-5889

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_III. HEALTH HAZARD ASSESSMENTS FOR VARIED EXPOSURE DURATIONS

__III.A. DRINKING WATER HEALTH ADVISORIES

Substance Name -- Fluorene
CASRN -- 86-73-7

Not available at this time.

__III.B. OTHER ASSESSMENTS

Substance Name -- Fluorene
CASRN -- 86-73-7

Content to be determined.

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_IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- Fluorene
CASRN -- 86-73-7

Not available at this time.

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_V. SUPPLEMENTARY DATA

Substance Name -- Fluorene
CASRN -- 86-73-7

Not available at this time.

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_VI. BIBLIOGRAPHY

Substance Name -- Fluorene
CASRN -- 86-73-7
Last Revised -- 12/01/90

__VI.A. ORAL RfD REFERENCES

Morris, H.P., C.A. Velat, B.P. Wagner, M. Dahlgard and F.E. Ray. 1960. Studies of carcinogenicity in the rate of derivatives of aromatic amines related to N-2-fluorenylacetamide. J. Natl. Cancer Inst. 24: 149-180.

U.S. EPA. 1987. Health Effects Assessment for Fluorenes. 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. 1989. 13-Week Mouse Oral Subchronic Toxicity Study. Prepared by Toxicity Research Laboratories, Ltd., Muskegon, MI for the Office of Solid Waste, Washington, DC.

---------<<< Fluorene >>>---------

__VI.B. INHALATION RfC REFERENCES

None

---------<<< Fluorene >>>---------

__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

Amacher, D., S. Paillet and J. Elliott. 1981. The metabalism of N-acetyl-2-aminofluorene to a mutagen in L5178Y/TK+/- mouse lymphoma cells. Mutat. Res. 89: 311-320.

Bos, R.P., J.L.G. Theuws, F.J. Jongeneelen and P.Th. Henderson. 1988. Mutagenicity of bi-, tri and tetra-cyclic aromatic hydrocarbons in the "taped-plate assay" and in the conventional Salmonella mutagenicity assay. Mutat. Res. 204: 203-206.

Garberg, P., E. Akerblom and G. Bolcsfoldi. 1988. Evaluation of a genotoxicity test measuring DNA-strand breaks in mouse lymphoma cells by alkaline unwinding and hydroxyapatite elution. Mutat. Res. 203: 155-176.

Kaden, D.A., R.A. Hites and W.G. Thilly. 1979. Mutagenicity of soot and associated polycyclic aromatic hydrocarbons to Salmonella typhimurium. Cancer Res. 39: 4152-4159.

Kennaway, E.L. 1924. On cancer-producing tars and tar-fractions. J. Ind. Hyg. 5(12): 462-488.

LaVoie, E.J., E.V. Bedenko, N. Hirota, S.S. Hecht and D. Hoffmann. 1979. A comparison of the mutagenicity, tumor-initiating activity and complete carcinogenicity of polynuclear aromatic hydrocarbons. In: Polynuclear Aromatic Hydrocarbons, P.W. Jones and P. Leber, Ed. Ann Arbor Science Publishers, Ann Arbor, MI. p. 705-721.

LaVoie, E.J., J.L. Tulley-Freiler, V. Bedenko, Z. Girach and D. Hoffmann. 1981. Comparative studies on the tumor inititating activity and metabolism of methylfluorenes and methylbenzofluorenes. In: Polynuclear Aromatic Hydrocarbons: Chemical Analysis and Biological Fate, M. Cooke and A.J. Dennis, Ed. Batelle Press, Columbus, OH. p. 417-427.

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Mamber, S., V. Bryson and S. Katz. 1984. Evaluation of the Escherichia coli K12 inductest for detection of potential chemical carcinogens. Mutat. Res. 130: 141-151.

McCann, J.E., E. Choi, E. Yamasaki and B.N. Ames. 1975. Detection of carcinogens as mutagens in the Salmonella/microsome test: Assay of 300 chemicals. Proc. Natl. Acad. Sci. USA. 72(12): 5135-5139.

Morris, H.P., C.A. Velat, B.P. Wagner, M. Dahlgard and F.E. Ray. 1960. Studies of carcinogenicity in the rate of derivatives of aromatic amines related to N-2-fluorenylacetamide. J. Natl. Cancer Inst. 24(1): 149-180.

Nakamura, S., Y. Oda, T. Shimada, I. Oki and K. Sugimoto. 1987. SOS-inducing activity of chemical carcinogens and mutagens in Salmonella typhimurium TA1535/pSK 1002: Examination with 151 chemicals. Mutat. Res. 192: 239-246.

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Probst, G.S., R.E. McMahon, L.E. Hill, C.Z. Thompson, J.K. Epp and S.B. Neal. 1981. Chemically-induced unscheduled DNA synthesis in primary rat hepatocyte cultures: A comparison with bacterial mutagenicity using 218 compounds. Environ. Mutagen. 3: 11-32.

Riegel, B., W.B. Watman, W.T. Hill, et al. 1951. Delay of methylcholanthrene skin carcinogensis in mice by 1,2,5,6-dibenzofluorene. Cancer Res. 11:

301-303.

Sakai, M., D. Yoshida and S. Mizusdki. 1985. Mutagenicity of polycyclic aromatic hydrocarbons and quinones on Salmonella typhimurium TA97. Mutat. Res. 156: 61-67.

Shear, M.J. 1938. Studies in carcinogenesis. V. Methyl derivatives of 1,2-benzanthracene. Am. J. Cancer. 33(4): 499-537.

Sina, J., C. Bean, G. Dysart, V. Taylor and M. Bradley. 1983. Evaluation of the alkaline elution/rat hepatocyte assay as a predictor of carcinogenic/ mutagenic potential. Mutat. Res. 113: 357-391.

U.S. EPA. 1990. Drinking Water Criteria Document for Polycyclic Aromatic Hydrocarbons (PAHs). Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. Final Draft. ECAO-CIN-D010.

Williams, G., H. Mori and C. McQueen. 1989. Structure-activity relationships in the rat hepatocyte DNA-repair test for 300 chemicals. Mutat. Res. 221: 263-286.

Wilson, R.H., F. DeEds and A.J. Cox. 1947. The carcinogenic activity of 2-acetominofluorene. IV. Action of related compounds. Cancer Res. 7: 453-458.

---------<<< Fluorene >>>---------

__VI.D. DRINKING WATER HA REFERENCES

None

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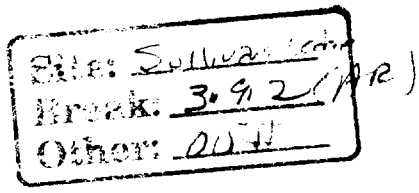
SYNONYMS

Substance Name -- Fluorene
CASRN -- 86-73-7
Last Revised -- 11/01/90

86-73-7
9H-Fluorene
Diphenylenemethane
Fluorene
HSDB 2165
Methane, diphenylene-
NSC 6787
o-BIPHENYLENEMETHANE
2,2'-METHYLENEBIPHENYL
9H-fluorene



STATUS OF DATA FOR Lead and compounds (inorganic)

File On-Line 03/01/88

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	message	07/01/90
Inhalation RfC Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	on-line	12/01/89
Drinking Water Health Advisories (III.A.)	no data	
U.S. EPA Regulatory Actions (IV.)	on-line	07/01/90
Supplementary Data (V.)	no data	

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_I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

__I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name -- Lead and compounds (inorganic)
CASRN -- 7439-92-1

A great deal of information on the health effects of lead has been obtained through decades of medical observation and scientific research. This information has been assessed in the development of air and water quality criteria by the Agency's Office of Health and Environmental Assessment (OHEA) in support of regulatory decision-making by the Office of Air Quality Planning and Standards (OAQPS) and by the Office of Drinking Water (ODW). By comparison to most other environmental toxicants, the degree of uncertainty about the health effects of lead is quite low. It appears that some of these effects, particularly changes in the levels of certain blood enzymes and in aspects of children's neurobehavioral development, may occur at blood lead levels so low as to be essentially without a threshold. The Agency's RfD Work Group discussed inorganic lead (and lead compounds) at two meetings (07/08/85 and 07/22/85) and considered it inappropriate to develop an RfD for inorganic lead. For additional information, interested parties are referred to the 1986 Air Quality Criteria for Lead (EPA-600/8-83/028a-dF) or the following Agency scientists:

J. Michael Davis / OHEA -- (919)541-4162 / FTS 629-4162

Jeff Cohen / ODW -- (202)382-5456 / FTS 382-5456

Gregory Helms / ODW -- (202)475-8049 / FTS 475-8049

William Marcus / ODW -- (202)475-7580/ FTS 475-7580

__I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

Substance Name -- Lead and compounds (inorganic)
CASRN -- 7439-92-1

Not available at this time.

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_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Lead and compounds (inorganic)
CASRN -- 7439-92-1
Last Revised -- 12/01/89

Section II provides information on three aspects of the carcinogenic risk assessment for the agent in question; the U.S. EPA classification, and quantitative estimates of risk from oral exposure and from inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen. 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. Background Document 2 (Service Code 5) provides details on the rationale and methods used to derive the carcinogenicity values found in IRIS. Users are referred to Section I for information on long-term toxic effects other than carcinogenicity.

<<< Lead and compounds (inorganic) >>>

__II.A. EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

___II.A.1. WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification -- B2; probable human carcinogen

Basis -- Sufficient animal evidence. Ten rat bioassays and one mouse assay have shown statistically significant increases in renal tumors with dietary and subcutaneous exposure to several soluble lead salts. Animal assays provide reproducible results in several laboratories, in multiple rat strains with some evidence of multiple tumor sites. Short term studies show

that lead affects gene expression. Human evidence is inadequate.

<<< Lead and compounds (inorganic) >>>

___II.A.2. HUMAN CARCINOGENICITY DATA

Inadequate. There are four epidemiologic studies in occupational cohorts exposed to lead and lead compounds. Two studies (Dingwall-Fordyce and Lane 1963, Nelson et al., 1982) did not find any association between exposure to lead and cancer mortality. Selevan et al. (1985) in their retrospective cohort mortality study of primary lead smelter workers found a slight decrease in the total cancer mortality (SMR=95). Apparent excesses were observed for respiratory cancer (SMR=111, obs=41, $p>0.05$) and kidney cancer (SMR=204, obs=6, $p>0.05$). Cooper and Gaffey (1975) and Cooper (1985 update) in their cohort mortality study of battery plant workers and lead smelter workers found statistically significant excesses for total cancer mortality (SMR=113, obs=344), stomach cancer (SMR=168, obs=34) and lung cancer (SMR=124, obs=109) in battery plant workers. Although similar excesses were observed in smelter workers, they were not statistically significant. Cooper and Gaffey (1975) felt it was possible that individual subjects were monitored primarily on the basis of obvious signs of lead exposure, while others who show no symptoms of lead poisoning would not be monitored.

All of the available studies lacked quantitative exposure information, as well as information on the possible contribution of smoking. All studies also had exposures to other metals such as arsenic, cadmium and zinc for which no adjustment was done. The cancer excesses observed in the lung and stomach were relatively small (<200). There was no consistency of site among the various studies, and no study showed any dose-response relationship. Thus, the available human evidence is considered to be inadequate to refute or demonstrate potential carcinogenicity for humans from lead exposure.

<<< Lead and compounds (inorganic) >>>

___II.A.3. ANIMAL CARCINOGENICITY DATA

Sufficient. The carcinogenic potential of lead salts, primarily phosphates and acetates, administered by the oral route, diet or by injection has been demonstrated in rats and mice by more than 10 investigators. The most characteristic cancer response is bilateral renal carcinoma. Rats given lead acetate or subacetate orally have developed gliomas, and lead subacetate also produced lung adenomas in mice after i.p. adminstration. Most of these investigations found a carcinogenic response only at the highest dose. The lead compounds tested in animals are almost all soluble salts. Metallic lead, lead oxide and lead tetralkyls have not been tested adequately. Studies with inhalation exposure have not been located in the literature.

Azar et al. (1973) administerd 10, 50, 100, and 500 ppm lead as lead acetate in dietary concentrations to fifty rats/sex/treatment group for 2 years. One hundred control rats of each sex received the basal laboratory diet. In a second 2-year feeding study, 20 rats/group were given diets containing 0, 1000, and 2000 ppm lead as lead acetate. No renal tumors were reported in the control groups or in treated animals of either sex receiving 10 to 100 ppm. Male rats fed 500, 1000, and 2000 ppm lead acetate had an

increased renal tumor incidence of 5/50, 10/20, and 16/20, while 7/20 females in the 2000 ppm developed renal tumors.

The Azar et al. (1973) study is limited by the lack of experimental detail. The possibility of environmental contamination from lead in the air or drinking water was not mentioned. The strains of rats used were not specified in the study, but the Health Effects Assessment for Lead (U.S. EPA, 1984) indicated the rats were Wistar strain. The weight gain at 1000 and 2000 ppm was reported to be depressed, but details were not given.

Kasprzak et al. (1985), in investigating the interaction of dietary calcium on lead carcinogenicity, fed a diet with 1% lead subacetate (8500 ppm Pb) to male Sprague-Dawley rats for 79 weeks. Of the rats surviving (29/30) in this treatment group beyond 58 weeks, 44.8% had renal tumors. Four rats had adenocarcinomas; the remainaing nine had adenomas. Bilateral tumors were noted. No renal tumors were noted among the controls.

As part of a study to determine interactions between sodium nitrite, ethyl urea and lead, male Sprague-Dawley rats were given lead acetate in their drinking water for 76 weeks (Koller et al., 1986). The concentration of lead was 2600 ppm. No kidney tumors were detected among the 10 control rats. Thirteen of 16 (81%) lead-treated rats had renal tubular carcinoma, with three tumors detected at 72 weeks and the remainder detected at the termination of the study.

Van Esch and Kroes (1969) fed basic lead acetate at 0, 0.1%, and 1.0% in the diet to 25 Swiss mice/sex/treatment group for 2 years. No renal tumors developed in the control group, but 6/25 male mice of 0.1% basic lead acetate group had renal tumors (adenomas and carcinomas combined). In the 1.0% group, one female had a renal tumor. The authors felt that the low incidence in the 1.0% group was due to early mortality.

Hamsters given lead subacetate at 0.5% and 1% in the diet had no significant renal tumor response (Van Esch and Kroes, 1969).

<<< Lead and compounds (inorganic) >>>

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Lead acetate induces cell transformation in Syrian hamster embryo cells (DiPaolo et al., 1978) as well as enhances the incidence of simian adenovirus induction. Lead oxide showed similar enhanced adenovirus induction (Casto et al., 1979).

Under certain conditions lead compounds are capable of inducing chromosomal aberrations in vivo and in tissue cultures. Grandjean et al. (1983) showed a relationship between SCE and lead exposure in exposed workers. Lead has been shown, in a number of DNA structure and function assays, to affect the molecular processes associated with the regulation of gene expression (U.S. EPA, 1986).

---------<<< Lead and compounds (inorganic) >>>---------

__II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

Not available.

Quantifying lead's cancer risk involves many uncertainties, some of which may be unique to lead. Age, health, nutritional state, body burden, and exposure duration influence the absorption, release, and excretion of lead. It is also felt that current knowledge of lead pharmacokinetics indicates that an estimate derived by standard procedures would not truly describe the potential risk. Thus, the Carcinogen Assessment Group recommends that a numerical estimate not be used.

---------<<< Lead and compounds (inorganic) >>>---------

__II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

Not available.

---------<<< Lead and compounds (inorganic) >>>---------

__II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

___II.D.1. EPA DOCUMENTATION

U.S. EPA. 1984. Health Effects Assessment for Lead. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH, for the Office of Emergency and Remedial Response, Washington, DC. EPA/540/1-86/055. NTIS PB85-163996/AS.

U.S. EPA. 1986. Air Quality Criteria Document for Lead. Volumes III, IV. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Research Triangle Park, NC, for the Office of Air Quality Planning and Standards. EPA-600/8-83/028dF.

U.S. EPA. 1987. Preliminary review of the carcinogenic potential of lead associated with oral exposure. Prepared by the Office of Health and Environmental Assessment, Carcinogenic Assessment Group, Washington DC, for the Office of Drinking Water, Office of Solid Waste and the Office of Emergency and Remedial Response (Superfund). OHEA-C-267. Internal Review Draft.

<<< Lead and compounds (inorganic) >>>

___II.D.2. REVIEW (CARCINOGENICITY ASSESSMENT)

The review of the carcinogenic potential of lead associated with oral exposure has received Agency review.

The 1986 Air Quality Criteria Document for Lead has received Agency and

External Review.

Agency Work Group Review: 05/04/88

Verification Date: 05/04/88

___II.D.3. U.S. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

William Pepelko / ORD -- (202)382-5898 / FTS 382-5898

James Cogliano / ORD -- (202)382-5898 / FTS 382-5898

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_III. HEALTH HAZARD ASSESSMENTS FOR VARIED EXPOSURE DURATIONS

__III.A. DRINKING WATER HEALTH ADVISORIES

Substance Name -- Lead and compounds (inorganic)
CASRN -- 7439-92-1

Not available at this time.

__III.B. OTHER^PASSESSMENTS

Substance Name -- Lead and compounds (inorganic)
CASRN -- 7439-92-1

Content to be determined.

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_IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- Lead and compounds (inorganic)
CASRN -- 7439-92-1
Last Revised -- 07/01/90

EPA risk assessments may be updated as new data are published and as assessment methodologies evolve. Regulatory actions are frequently not

updated at the same time. Compare the dates for the regulatory actions in this section with the verification dates for the risk assessments in sections I and II, as this may explain inconsistencies. Also note that some regulatory actions consider factors not related to health risk, such as technical or economic feasibility. Such considerations are indicated for each action. In addition, not all of the regulatory actions listed in this section involve enforceable federal standards. Please direct any questions you may have concerning these regulatory actions to the U.S. EPA contact listed for that particular action. Users are strongly urged to read the background information on each regulatory action in Background Document 4 in Service Code 5.

<<< Lead and compounds (inorganic) >>>

__IV.A. CLEAN AIR ACT (CAA)

___IV.A.1. NATIONAL AMBIENT AIR QUALITY STANDARD (NAAQS)

Considers technological or economic feasibility? -- No

Discussion -- Under Section 109 of the CAA, EPA has set a primary (health-based) NAAQS for lead of 1.5 ug/cu.m, calendar quarter average not to be exceeded (43 FR 41258, 10/05/78). The secondary (welfare-based) NAAQS is identical to the primary standard. EPA is currently reviewing these standards to determine if changes are warranted.

Reference -- 40 CFR 50.12

U.S. EPA Contact -- Air Quality Management Division / OAQPS / (919)541-5656 / FTS 629-5656

---------<<< Lead and compounds (inorganic) >>>---------

__IV.B. SAFE DRINKING WATER ACT (SDWA)

___IV.B.1. MAXIMUM CONTAMINANT LEVEL GOAL (MCLG) for Drinking Water

Value (status) -- 0.02 mg/L (Proposed, 1985)

Considers technological or economic feasibility? -- NO

Discussion -- Neurological effects of lead in infants and adverse effects associated with blood lead levels of 15 ug/dL are the basis for this MCLG. Using a conversion factor of 6.25 to convert from blood lead concentrations to drinking water lead concentrations and an uncertainty factor of 5, an MCLG of 0.02 mg/L for lead was derived.

Reference -- 50 FR 46936 Part IV (11/13/85)

EPA Contact -- Criteria and Standards Division, ODW / (202)382-7571 / FTS 382-7571; or Drinking Water Hotline / (800)426-4791

<<< Lead and compounds (inorganic) >>>

___IV.B.2. MAXIMUM CONTAMINANT LEVEL (MCL) for Drinking Water

Value (status) -- 0.05 mg/L (Interim, 1980)

Considers technological or economic feasibility? -- YES

Discussion -- As an interim measure the U.S. EPA is using the value previously derived by the Public Health Service.

Reference -- 45 FR 57332 (08/27/80)

EPA Contact -- Criteria and Standards Division, ODW / (202)382-7571 / FTS 382-7571; or Drinking Water Hotline / (800)426-4791

---------<<< Lead and compounds (inorganic) >>>---------

__IV.C. CLEAN WATER ACT (CWA)

___IV.C.1. AMBIENT WATER QUALITY CRITERIA, Human Health

Water and Fish Consumption -- 5.0E+1 ug/L

Fish Consumption Only -- None

Considers technological or economic feasibility? -- NO

Discussion -- The criterion was set at the existing drinking water standard in 1980.

Reference -- 45 FR 79318 (11/28/80)

EPA Contact -- Criteria and Standards Division, OWRS (202)475-7315 / FTS 475-7315

<<< Lead and compounds (inorganic) >>>

___IV.C.2. AMBIENT WATER QUALITY CRITERIA, Aquatic Organisms

Freshwater:

Acute -- 8.2E+1 ug/L (1-hour average)
Chronic -- 3.2E+0 ug/L (4-day average)

Marine:

Acute -- 1.40E+2 ug/L (1-hour average)
Chronic -- 5.6E+0 ug/L (4-day average)

Considers technological or economic feasibility? -- NO

Discussion -- The toxicity of this compound in freshwater is hardness dependent. The values given are for a hardness of 100 mg/L CaCO3. For a more complete discussion, see the referenced notice.

Reference -- 50 FR 30784 (07/29/85)

EPA Contact -- Criteria and Standards Division, OWRS
(202)475-7315 / FTS 475-7315

---------<<< Lead and compounds (inorganic) >>>---------

__IV.D. FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT (FIFRA)

No data available

---------<<< Lead and compounds (inorganic) >>>---------

__IV.E. TOXIC SUBSTANCES CONTROL ACT (TSCA)

No data available

---------<<< Lead and compounds (inorganic) >>>---------

__IV.F. RESOURCE CONSERVATION AND RECOVERY ACT (RCRA)

___IV.F.1. RCRA APPENDIX IX, for Ground Water Monitoring

Status -- Listed

Reference -- 52 FR 25942 (07/09/87)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)382-3000 / FTS 382-3000

---------<<< Lead and compounds (inorganic) >>>---------

__IV.G. SUPERFUND (CERCLA)

___IV.G.1. REPORTABLE QUANTITY (RQ) for Release into the Environment

Value (status) -- 1 pound (Statutory, 1987)

Considers technological or economic feasibility? -- NO

Discussion -- The statutory 1-pound RQ for lead is retained pending assessment of its potential carcinogenicity and may be adjusted in a future notice of proposed rulemaking when the evaluation of available data is completed. Lead was evaluated for chronic toxicity, but was not ranked for toxicity because of insufficient data.

Reference -- 52 FR 8140 (03/16/87)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)382-3000 / FTS 382-3000

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_V. SUPPLEMENTARY DATA

Substance Name -- Lead and compounds (inorganic)
CASRN -- 7439-92-1

Not available at this time.

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_VI. BIBLIOGRAPHY

Substance Name -- Lead and compounds (inorganic)
CASRN -- 7439-92-1
Last Revised -- 12/01/89

__VI.A. ORAL RfD REFERENCES

None

---------<<< Lead and compounds (inorganic) >>>---------

__VI.B. INHALATION RfD REFERENCES

None

---------<<< Lead and compounds (inorganic) >>>---------

__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

Anderson, E.L., and CAG (Carcinogenic Assessment Group). 1983. Quantitative approaches in use to assess cancer risk. Risk Analysis. 3: 277-295.

Azar, A., H.J. Trochimowicz and M.E. Maxfield. 1973. Review of lead studies in animals carried out at Haskell Laboratory - Two year feeding study and response to hemorrhage study. In: Barth D., A. Berlin, R. Engel, P. Recht and J. Smeets, eds. Environmental health aspects of lead: proceedings international symposium; October 1972; Amsterdam, The Netherlands. Luxemberg: Commission of the European Communities, pp. 199-208.

Casto, B.C., J. Meyers and J.A. DiPaolo. 1979. Enhancement of viral transformation for evaluation of the carcinogenic or mutagenic potential of inorganic metal salts. Cancer Res. 39: 193-198.

Cooper, W.C. 1985. Mortality among employees of lead battery plants and lead producing plants, 1947-1980. Scand. J. Work Environ. Health. 11: 331-345.

Cooper, W.C. and W.R. Gaffey. 1975. Mortality of lead workers. In: Proceedings of the 1974 Conference on Standards of Occupational Lead Exposure, J.F. Cole, Ed., February, 1974. Washington, DC. J. Occup. Med. 17: 100-107.

Dingwall-Fordyce, I. and R.E. Lane. 1963. A follow-up study of lead workers. Br. J. Ind. Med. 20: 313-315.

DiPaolo, J.A., R.L. Nelson and B.C. Casto. 1978. In vitro neoplastic transformation of Syrian hamster cells by lead acetate and its relevance to environmental carcinogenesis. Br. J. Cancer. 38: 452-455.

Grandjean, P., H.C. Wulf and E. Niebuhr. 1983. Sister chromatid exchange in response to variations in occupational lead exposure. Environ. Res. 32: 199-204.

Kasprzak, K.S., K.L. Hoover and L.A. Poirier. 1985. Effects of dietary calcium acetate on lead subacetate carcinogenicity in kidneys of male Sprague-Dawley rats. Carcinogenesis. 6(2): 279-282.

Koller, L.D., N.I. Kerkvliet and J.H. Exon. 1986. Neoplasia induced in male rats fed lead acetate, ethyl urea and sodium nitrate. Toxicol. Pathol. 13: 50-57.

Nelson, D.J., L. Kiremidjian-Schumacher and G. Stotzky. 1982. Effects of cadmium, lead, and zinc on macrophage-mediated cytotoxicity toward tumor cells. Environ. Res. 28: 154-163.

Selevan, S.G., P.J. Landrigan, F.B. Stern and J.H. Jones. 1985. Mortality of lead smelter workers. Am. J. Epidemiol. 122: 673-683.

Van Esch, G.J. and R. Kroes. 1969. The induction of renal tumors by feeding of basic lead acetate to mice and hamsters. Br. J. Cancer. 23: 265-271.

U.S. EPA. 1984. Health Effects Assessment for Lead. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH, for the Office of Emergency and Remedial Response, Washington, DC. EPA/540/1-86/055. NTIS PB85-163996/AS.

U.S. EPA. 1986. Air Quality Criteria Document for Lead. Volumes III, IV. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Research Triangle Park, NC, for the Office of Air Quality Planning and Standards. EPA-600/8-83/028dF.

U.S. EPA. 1987. Preliminary review of the carcinogenic potential of lead associated with oral exposure. Prepared by the Office of Health and Environmental Assessment, Carcinogenic Assessment Group, Washington DC, for the Office of Drinking Water, Office of Solid Waste and the Office of Emergency and Remedial Response (Superfund). OHEA-C-267. Internal Review Draft.

---------<<< Lead and compounds (inorganic) >>>---------

__VI.D. DRINKING WATER HA REFERENCES

None

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SYNONYMS

Substance Name -- Lead and compounds (inorganic)
CASRN -- 7439-92-1
Last Revised -- / /

7439-92-1
Lead
Lead and compounds
plumbum

Enter keywords or Read or Scan or Mail
--7439-96-5
Searching - Please wait...
1 Occurrences...

Enter keywords or Read or Scan or Mail

STATUS OF DATA FOR Manganese

File On-Line 09/26/88

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	08/01/90
Inhalation RfC Assessment (I.B.)	pending	
Carcinogenicity Assessment (II.)	on-line	08/01/90
Drinking Water Health Advisories (III.A.)	no data	
U.S. EPA Regulatory Actions (IV.)	no data	
Supplementary Data (V.)	no data	

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_I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

__I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name -- Manganese
CASRN -- 7439-96-5
Last Revised -- 08/01/90

The Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. 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 Background Document 1 in Service Code 5 for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of compounds which 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 when a review of that evaluation is completed.

<<< Manganese >>>

___I.A.1. ORAL RfD SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfD
CNS effects	NOAEL = 0.14 mg/kg/day	1	1	1E-1

mg/kg/day

Human Chronic Ingestion Data

LOAEL = None

WHO, 1973;
Schroeder et al., 1966;
NRC, 1989

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*Conversion Factors: The NOAEL of 10 mg/day (0.14 mg/kg/day for 70 kg adult) for chronic human consumption of manganese is based on a composite of data from the above three references. WHO (1973) reported no adverse effects in humans consuming supplements of 8-9 mg Mn/day (0.11-0.13 mg/kg/day). Schroeder et al. (1966) reported a chronic human NOAEL OF 11.5 mg Mn/day (0.16 mg/kg/day). The NRC (1989) determined "safe and adequate" levels to be 2-5 mg Mn/day for adults (0.03-0.07 mg/kg/day). It is important to recognize that manganese is an essential element in human nutrition. It is also important to recognize that this oral RfD is based on a total dietary intake, and this amount of manganese is not necessarily acceptable if the intake were from drinking water alone. This difference is due to the fact that manganese in drinking water is more bioavailable than manganese in food.

<<< Manganese >>>

___I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

WHO (World Health Organization). 1973. Trace elements in human nutrition: Manganese. Report of a WHO Expert Committee. Technical Report Service, 532, WHO, Geneva, Switzerland. p. 34-36.

Schroeder, H.A., D.D. Balassa and I.H. Tipton. 1966. Essential trace metals in man: Manganese, a study in homeostasis. J. Chron. Dis. 19: 545-571.

NRC (National Research Council). 1989. Recommended Dietary Allowances, 10th ed. Food and Nutrition Board, National Research Council, National Academy Press, Washington, DC. p. 230-235.

The World Health Organization (WHO, 1973) reviewed several investigations of adult diets and reported the average daily consumption of manganese to range from 2.0 to 8.8 mg Mn/day. Higher manganese intakes are associated with diets high in whole cereals, nuts, green leafy vegetables, and tea. From manganese balance studies, the WHO concluded that 2 to 3 mg/day is adequate for adults and 8 to 9 mg/day is "perfectly safe."

Evaluations of standard diets from the United States, England, and Holland reveal average daily intakes of 2.3 to 8.8 mg Mn/day (Schroeder et al., 1966). However, depending on individual diets, a normal intake may be even higher, especially from a vegetarian diet. These levels are considered to be safe for chronic human ingestion.

No signs of toxicity were reported in patients (number not specified) given 30 mg manganese citrate (9 mg Mn/day) for many months. Assuming the patients also consumed 2.5 mg Mn/day in food, the total manganese intake would be approximately 11.5 mg Mn/day.

The Food and Nutrition Board of the National Research Council (NRC, 1989) determined an "adequate and safe" intake of manganese to be 2 to 5 mg/day for adults. This level was chosen because it includes an "extra margin of safety" from the level of 10 mg/day, which can be considered to be safe.

<<< Manganese >>>

___I.A.3. UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

UF = 1. The information used to determine the oral RfD for manganese was taken from many large populations. Humans exert an efficient homeostatic control over manganese such that body burdens are kept constant with variations in diet. There are no subpopulations which are believed to be more sensitive to manganese at this level. The use of an uncertainty factor of 1 is supported by the fact that manganese is an essential element, being required for normal human growth and maintenance of health. It has also been suggested that children are less susceptible to manganese intoxication and may require slightly higher levels of manganese than do adults.

MF = 1.

<<< Manganese >>>

___I.A.4. ADDITIONAL COMMENTS (ORAL RfD)

A small-scale epidemiologic study of manganese in drinking water was performed by Kondakis et al. (1989). Three areas in northwest Greece were chosen for this study, with manganese concentrations of 3.6 to 14.6 ug/L in area A, 81.6 to 252.6 ug/L in area B, and 1600 to 2300 ug/L in area C. The study included only individuals over the age of 50 drawn from a random sample of 10% of all households (n=62, 49 and 77 for areas A, B, and C, respectively). The authors reported that "all areas were similar with respect to social and dietary characteristics," but few details were reported. The amount of manganese in the diet was not reported. The individuals chosen were submitted to a neurological examination, the score of which represents a composite of the presence and severity of 33 symptoms (e.g., weakness/fatigue, gait disturbances, tremors, dystonia). Whole blood and hair manganese concentrations were also determined. The mean concentration of manganese in hair was 3.51, 4.49, and 10.99 ug/g dry weight for areas A, B, and C, respectively ($p<0.0001$ for area C vs. A). However, the concentration of manganese in whole blood did not differ between the three areas. The mean (x) and range (r) of neurologic scores were as follows: Area A (males: x=2.4, r=0-21; females: x=3.0, r=0-18; both: x=2.7, r=0-21); Area B (males: x=1.6, r=0-6; females: x=5.7, r=0-43; both: x=3.9, r=0-43); Area C (males: x=4.9, r=0-29; females: x=5.5, r=0-21; both: x=5.2, r=0-29). While there appears to be an increasing trend in the neurological scores, this data should be interpreted with caution. The authors did not provide any individual data, and the large range for females in area B indicates that a single outlier may have been responsible for the increased mean. The mean score for men in area B was actually lower than that in area A. The authors indicate that the difference in mean scores for area C vs. A was significantly increased (Mann-Whitnes z=3.16, p=0.002 for both sexes combined). While this finding should be acknowledged, its significance, particularly with regard to the concentration of manganese in drinking water, is questionable. This study has

several flaws, most notably: 1) the small number of individuals tested; 2) the lack of scatter data; 3) the lack of information provided on social and other dietary and drinking water factors; 4) this study may not have been truly unbiased because the examining neurologists were listed as authors of the paper. In summary, this study raises some questions about acceptable levels of manganese in drinking water, but is inadequate to serve as the basis for a separate water RfD. It may, however, serve to caution risk assessors against using a total oral RfD (based principally on dietary intake) to establish an acceptable drinking water concentration, without taking into consideration issues such as differential absorption.

A report by Kawamura et al. (1941) described toxicologic responses in humans consuming large amounts of manganese dissolved in drinking water. The source of the manganese came from about 400 dry-cell batteries which were buried near a drinking water well. Sixteen cases of manganese poisoning were reported, with symptoms including lethargy, increased muscle tonus, tremor, and mental disturbances. The most severe symptoms were seen in elderly people, with children being affected to a lesser degree. Three individuals died, one from suicide. The cause of death for the other two was not reported, but the autopsy of one individual revealed manganese concentration in the liver to be 2 to 3 times higher than controls. Zinc levels were also increased in the liver. The well water was not analyzed until 1 month after the outbreak, at which time it contained approximately 14 mg Mn/L. However, when re-analyzed 1 month later, the levels were decreased by about half. Therefore, by retrospective extrapolation, the concentration of manganese at the time of exposure was probably at least 28 mg Mn/L. Assuming an adult body weight of 70 kg and a water consumption of 2 L/day, this would be equivalent to an intake of 0.8 mg Mn/kg bw/day from drinking water alone.

While there is little information concerning manganese poisoning in humans by the oral route, there is a well-documented association of prolonged inhalation of manganese dusts with psychological and neurological disorders.

Several toxicity studies on manganese have been performed in laboratory animals. Most of these have been inhalation studies, demonstrating an effect on both the brain and lungs. Several oral studies have been performed in rodents that demonstrated biochemical changes in the brain following administration of 1 mg $MnCl_2 \cdot 4H_2O$/mL in drinking water (approximately 38.9 mg Mn/kg bw/day) (Lai et al., 1981, 1982; Leung et al., 1981). However, rodents do not exhibit the same neurological deficits that humans do following exposure to manganese, so the relevance of these biochemical changes has been challenged. While primates are considered to be the species of choice for modeling the human response to manganese poisoning, only one limited oral study
has been performed in a group of four rhesus monkeys (Gupta et al., 1980). Muscular weakness and rigidity of the lower limbs developed after 18 months of exposure to 6.9 mg Mn/kg bw/day (as $MnCl_2 \cdot 4H_2O$). Histological analysis showed degenerated neurons in the substantia nigra and scanty neuromelanin granules in some of the pigmented cells.

<<< Manganese >>>

___I.A.5. CONFIDENCE IN THE ORAL RfD

Study: High
Data Base: Medium
RfD: Medium

Many studies have reported similar findings with regard to the normal intake of manganese by humans. These data are considered to be superior to any data obtained from animal toxicity studies, especially as the physiologic requirements for manganese vary quite a bit among different species, with man requiring less than rodents (Schroeder et al., 1966).

It is again emphasized that this oral RfD is based on a total dietary intake of manganese and is not intended to be applied directly to drinking water.

<<< Manganese >>>

___I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

Source Document -- This assessment is not presented in any existing U.S. EPA document.

Agency RfD Work Group Review: 05/17/90; 06/21/90

Verification Date: 06/21/90

___I.A.7. EPA CONTACTS (ORAL RfD)

Sue Velazquez / ORD -- (513)569-7571 / FTS 684-7571

Julie Du / ODW -- (202)382-7583 / FTS 382-7588

__I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

Substance Name -- Manganese
CASRN -- 7439-96-5

A risk assessment for this substance/agent is under review by an EPA work group.

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_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Manganese
CASRN -- 7439-96-5
Last Revised -- 08/01/90

Section II provides information on three aspects of the carcinogenic risk assessment for the agent in question; the U.S. EPA classification, and quantitative estimates of risk from oral exposure and from inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen. 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. Background Document 2 (Service Code 5) provides details on the rationale and methods used to derive the carcinogenicity values found in IRIS. Users are referred to Section I for information on long-term toxic effects other than carcinogenicity.

<<< Manganese >>>

II.A. EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

II.A.1. WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification -- D; not classifiable as to human carcinogenicity

Basis -- Existing studies are inadequate to assess the carcinogenicity of manganese.

<<< Manganese >>>

II.A.2. HUMAN CARCINOGENICITY DATA

None.

<<< Manganese >>>

II.A.3. ANIMAL CARCINOGENICITY DATA - Inadequate

DiPaolo (1964) subcutaneously or intraperitoneally injected DBA/1 mice with 0.1 mL of an aqueous of solution 1% manganese chloride twice weekly for 6 months. A larger percentage of the mice exposed subcutaneously (24/36; 67%) and intraperitoneally (16/39; 41%) to manganese developed lymphosarcomas compared with controls injected with water (16/66; 24%). In addition, tumors appeared earlier in the exposed groups than in the control groups. The incidence of tumors other than lymphosarcomas (i.e., mammary adenocarcinomas, leukemias, injection site tumors) did not differ significantly between the exposed groups and controls. A thorough evaluation of the results of this study was not possible because the results were published in abstract form.

Stoner et al. (1976) tested manganous sulfate in a mouse lung adenoma screening bioassay. Groups of strain A/Strong mice (10/sex), 6-8 weeks old, were exposed by intraperitoneal injection to 0, 6, 15 or 30 mg/kg manganous sulfate 3 times/week for 7 weeks (a total of 21 injections). The animals were observed for an additional 22 weeks after the dosing period, before sacrifice

at 30 weeks. Lung tumors were observed in 12/20, 7/20, and 7/20 animals in the high, medium, and low dosage groups, respectively. The percentage of mice with tumors was elevated, but not significantly, at the highest dose level (Fisher Exact test) compared with that observed in the vehicle controls. In addition, there was an apparent increase in the average number of pulmonary adenomas per mouse both at the mid and high doses, as compared with the vehicle controls (10 mice/sex), but the increase was significant only at the high dose (Student's t-test, $p<0.05$).

In the mouse lung adenoma bioassay, certain specific criteria should be met in order for a response to be considered positive (Shimkin and Stoner, 1975). Among these criteria are an increase in the mean number of tumors per mouse and an evident dose-response relationship. While the results of this study are suggestive of carcinogenicity, the data cannot be considered conclusive since the mean number of tumors per mouse was significantly increased at only one dose, and the evidence for a dose-response relationship was marginal.

Furst (1978) exposed groups of F344 rats (25/sex) intramuscularly or by gavage to manganese powder, manganese dioxide, and manganese (II) acetylacetonate (MAA). Treatment consisted of either 9 i.m. doses of 10 mg each of manganese powder or manganese dioxide, 24 doses of 10 mg manganese powder by gavage, or 6 i.m. doses of 50 mg of MAA. In addition, female swiss mice (25/group) were exposed intramuscularly to manganese powder (single 10 mg dose) and manganese dioxide (6 doses of 3 or 5 mg each). There was an increased incidence of fibrosarcomas at the injection site in male (40%) and female (24%) rats exposed intramuscularly to MAA compared with vehicle controls (4% male, 4% female). EPA (1984) determined that these increases were statistically significant and noted that the study results regarding MAA, an organic manganese compound, cannot necessarily be extrapolated to pure manganese or other inorganic manganese compounds. No difference in tumor incidence was found between rats and mice exposed to manganese powder and manganese dioxide and controls.

Sunderman et al. (1974, 1976) exposed male 344 rats to 0.5 to 4.4 mg manganese dust intramuscularly and found that no tumors were induced at the injection site. It was further observed that co-administration of manganese with nickel subsulfide resulted in decreased sarcoma production by comparison to nickel subsulfide alone. Subsequent studies by Sunderman et al. (1980) suggest that manganese dust may inhibit local sarcoma induction by benzo(a)pyrene.

Witschi et al. (1981) exposed female A/J mice intraperitoneally to 80 mg/kg methylcyclopentadienyl manganese tricarbonyl (MMT) and found that although cell proliferation was produced in the lungs, lung tumor incidence did not increase.

<<< Manganese >>>

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

None.

Note: Manganese is an element considered essential to human health.

<<< Manganese >>>

___II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

Not available.

<<< Manganese >>>

___II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

Not available.

---------<<< Manganese >>>---------

__II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

___II.D.1. EPA DOCUMENTATION

U.S. EPA. 1984. Health Assessment Document for Manganese. Office of Research and Development, Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 600/8-83-013F.

U.S. EPA. 1988. Drinking Water Criteria Document for Manganese. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. ECAO-CIN-D008. (External Review Draft).

<<< Manganese >>>

___II.D.2. REVIEW (CARCINOGENICITY ASSESSMENT)

The Drinking Water Criteria Document for Manganese has received OHEA review.

Agency Work Group Review: 05/25/88

Verification Date: 05/25/88

___II.D.3. U.S. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

Cynthia Sonich-Mullin / ORD -- (513)569-7523 / FTS 684-7523

Julie Du / ODW -- (202)382-7583 / FTS 382-7583

_III. HEALTH HAZARD ASSESSMENTS FOR VARIED EXPOSURE DURATIONS

__III.A. DRINKING WATER HEALTH ADVISORIES

Substance Name -- Manganese
CASRN -- 7439-96-5

Not available at this time.

__III.B. OTHER ASSESSMENTS

Substance Name -- Manganese
CASRN -- 7439-96-5

Content to be determined.

_IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- Manganese
CASRN -- 7439-96-5

Not available at this time.

_V. SUPPLEMENTARY DATA

Substance Name -- Manganese
CASRN -- 7439-96-5

Not available at this time.

_VI. BIBLIOGRAPHY

Substance Name -- Manganese
CASRN -- 7439-96-5
Last Revised -- 08/01/90

__VI.A. ORAL RfD REFERENCES

Gupta, S.K., R.C. Murthy and S.V. Chandra. 1980. Neuromelanin in manganese-exposed primates. Toxicol. Lett. 6(1): 17-20.

Kawamura, R., H. Ikuta, S. Fukuzumi, et al. 1941. Intoxication by manganese in well water. Kitasato Arch. Exp. Med. 18: 145-169.

Kondakis, X.G., N. Makris, M. Leotsinidis, M. Prinou and T. Papapetropoulos. 1989. Possible health effects of high manganese concentration in drinking water. Arch. Environ. Health. 44(3): 175-178.

Lai, J.C.K., T.K.C. Leung and L. Lim. 1981. Brain regional distribution of glutamic acid decarboxylase, choline acetyltransferase, and acetylcholinesterase in the rat: Effects of chronic manganese chloride administration after two years. J. Neurochem. 36(4): 1443-1448.

Lai, J.C.K., T.K.C. Leung, J.F. Guest, A.N. Davison and L. Lim. 1982. The effects of chronic manganese chloride treatment expressed as age-dependent, transient changes in rat brain synaptosomal uptake of amines. J. Neurochem. 38(3): 844-847.

Leung, T.K.C., J.C.K. Lai and L. Lim. 1981. The regional distribution of monoamine oxidase activities towards different substrates: Effects in rat brain of chronic administration of manganese chloride and of aging. J. Neurochem. 36(6): 2037-2043.

NRC (National Research Council). 1989. Recommended Dietary Allowances, 9th rev. ed. Food and Nutrition Board, National Research Council, National Academy Press, Washington, DC. p. 230-235.

Schroeder, H.A., J.J. Balassa and I.H. Tipton. 1966. Essential trace metals in man: Manganese, a study in homeostasis. J. Chron. Dis. 19: 545-571.

WHO (World Health Organization). 1973. Trace elements in human nutrition: Manganese. Report of a WHO Expert Committee. Technical Report Service, 532, WHO, Geneva, Switzerland. p. 34-36.

---------<<< Manganese >>>---------

__VI.B. INHALATION RfD REFERENCES

None

---------<<< Manganese >>>---------

__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

DiPaolo, J.A. 1964. The potentiation of lymphosarcomas in mice by manganous chloride. Fed. Proc. 23: 393. (Abstract).

Furst, A. 1978. Tumorigenic effect of an organomanganese compound on F344 rats and Swiss albino mice: brief communication. J. Natl. Cancer Inst. 60(5): 1171-1173.

Shimkin, M.B. and G.D. Stoner. 1975. Lung tumors in mice: Application to carcinogenesis bioassay. Adv. Cancer Res. 21: 1-58.

Stoner, G.D., M.B. Shimkin, M.C. Troxell, T.L. Thompson and L.S. Terry. 1976. Test for carcinogenicity of metallic compounds by the pulmonary tumor response in strain A mice. Cancer Res. 36: 1744-1747.

Sunderman, F.W., Jr., T.J. Lau and L.J. Cralley. 1974. Inhibitory effect of manganese upon muscle tumorigenesis by nickel subsulfide. Cancer Res. 34: 92-95.

Sunderman, F.W., Jr., K.S. Kasprzak, P.P. Minghetti, R.M. Maenza, N. Becker, C. Onkelinx and P.J. Goldblatt. 1976. Effects of manganese on carcinogenicity and metabolism of nickel subsulfide. Cancer Res. 36: 1790-1800.

Sunderman, F.W., Jr., M.C. Reid, P.R. Allpass and S.B. Taubman. 1980. Manganese inhibition of sarcoma induction by benzo(a)pyrene in Fischer rats. Proc. Am. Assoc. Cancer Res. 21: 72. (Abstract)

U.S. EPA. 1984. Health Assessment Document for Manganese. Office of Research and Development, Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 600/8-83-013F.

U.S. EPA. 1988. Drinking Water Criteria Document for Manganese. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. ECAO-CIN-D008. (External Review Draft).

Witschi, H.P., P.J. Hakkinen and J.P. Kehrer. 1981. Modification of lung tumor development in A/J mice. Toxicology. 21: 37-45.

---------<<< Manganese >>>---------

__VI.D. DRINKING WATER HA REFERENCES

None

2-Butanone

STATUS OF DATA FOR Methyl ethyl ketone (MEK)

File On-Line 01/31/87

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	06/01/90
Inhalation RfD Assessment (I.B.)	pending	
Carcinogenicity Assessment (II.)	on-line	12/01/89
Drinking Water Health Advisories (III.A.)	no data	
U.S. EPA Regulatory Actions (IV.)	on-line	06/01/90

_I. CHRONIC HEALTH HAZARD ASSESSMENT FOR NONCARCINOGENIC EFFECTS

Substance Name -- Methyl ethyl ketone (MEK)
CASRN -- 78-93-3
Last Revised -- 06/01/90

The Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. 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 Background Document 1 in Service Code 5 for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of compounds which 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 when a review of that evaluation is completed.

<<< MEK >>>

__I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfDo)

NOTE: The Oral RfD for methyl ethyl ketone may change in the near future pending the outcome of a further review now being conducted by the Oral RfD Work Group.

___I.A.1. ORAL RfD SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfD
No adverse effects observed Rat Inhalation Subchronic Study LaBelle and Brieger, 1955	NOAEL: 235 ppm (693 mg/cu.m) converted to 46 mg/kg/day	1000	1	5E-2 mg/kg/day
Fetotoxicity in rats Rat Developmental Toxicity Study Schwetz et al., 1974	LOAEL: 130.5 mg/kg/day (estimated)			

*Conversion Factors: 7 hour/24 hour, 5 days/7 days, 0.223 cu.m/day/0.35 kg (rat breathing rate/rat body weight) 0.5 absorption rate; thus, 693 mg/cu.m x 7 hour/24 hour x 5 days/7 days x 0.223 cu.m/day / 0.35 kg x 0.5 = 46 mg/kg/day

<<< MEK >>>

___I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

LaBelle, W. and H. Brieger. 1955. The vapor toxicity of a composite solvent and its principal components. Am. Med. Assoc. Arch. Ind. Health. 12: 623-627.

Schwetz, B.A., B.K.J. Leong and P.J. Gehring. 1974. Embryo- and fetotoxicity of inhaled carbon tetrachloride, 1,1-dichloroethane and methyl ethyl ketone in rats. Toxicol. Appl. Pharmacol. 28(3): 452-464.

Adequate chronic toxicity testing has not been performed with methyl ethyl ketone. Although several more recent subchronic studies have been conducted (Freddi et al., 1982; Cavender et al., 1983; Takeuchi et al., 1983), only the NOAEL of the LaBelle and Brieger (1955) study provides the lowest and most protective dose for deriving an RfD. In this study, 25 rats were exposed to 235 ppm of methyl ethyl ketone for 7 hours/day, 5 days/week for 12 weeks. No effects were observed, but only a few parameters were measured. Methyl ethyl ketone has also been tested for teratogenicity (Schwetz et al., 1974; Deacon et al., 1981), and the observed LOAELs for fetotoxicity were higher than the NOAELs of LaBelle and Brieger (1955).

The route extrapolation introduced uncertainty because of differences in pharmacokinetic parameters, notably absorption and elimination.

<<< MEK >>>

___I.A.3. UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

UF = 1000. The uncertainty factor of 1000 reflects 10 for both intraspecies

and interspecies variability to the toxicity of this chemical in lieu of specific data, and 10 for extrapolation of a subchronic effect level to its chronic equivalent.

MF = 1.

___I.A.4. ADDITIONAL COMMENTS (ORAL RfD)

No oral chronic studies are available at this time.

___I.A.5. CONFIDENCE IN THE ORAL RfD

Study: Medium
Data Base: Medium
RfD: Medium

The study is given medium to low confidence because only 25 rats were exposed to only one dose, and the sex, strain, and amount of control animals were unspecified. Confidence in the data base can be considered medium to low because four different studies lend some support to the chosen NOAEL. Confidence in the RfD can also be considered medium to low.

<<< MEK >>>

___I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

The only U.S. EPA documentation at present is on IRIS.

Agency RfD Work Group Review: 06/24/85, 07/08/85

Verification Date: 07/08/85

___I.A.7. EPA CONTACTS (ORAL RfD)

Christopher T. DeRosa / ORD -- (513)569-7534 / FTS 684-7534

Michael L. Dourson / ORD -- (513)569-7544 / FTS 684-7544

------<<< MEK >>>------

__I.B. REFERENCE DOSE FOR CHRONIC INHALATION EXPOSURE (RfDi)

A risk assessment for this chemical is under review by an EPA work group.

_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Methyl ethyl ketone (MEK)
CASRN -- 78-93-3
Last Revised -- 12/01/89

Section II provides information on three aspects of the carcinogenic risk assessment for the agent in question; the U.S. EPA classification, and quantitative estimates of risk from oral exposure and from inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen. 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. Background Document 2 (Service Code 5) provides details on the rationale and methods used to derive the carcinogenicity values found in IRIS. Users are referred to Section I for information on long-term toxic effects other than carcinogenicity.

<<< MEK >>>

__II.A. EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

___II.A.1. WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification -- D; not classifiable as to human carcinogenicity

Basis -- Based on no human carcinogenicity data and inadequate animal data.

___II.A.2. HUMAN CARCINOGENICITY DATA

None.

___II.A.3. ANIMAL CARCINOGENICITY DATA

Inadequate. No data were available to assess the carcinogenic potential of methyl ethyl ketone by the oral or inhalation routes. In a skin carcinogenesis study, two groups of 10 male C3H/He mice received dermal applications of 50 mg of a solution containing 25 or 29% methyl ethyl ketone in 70% dodecylbenzene twice a week for 1 year. No skin tumors developed in the group of mice treated with 25% methyl ethyl ketone. After 27 weeks, a single skin tumor developed in 1 of 10 mice receiving 29% methyl ethyl ketone (Horton et al., 1965).

<<< MEK >>>

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Methyl ethyl ketone was not mutagenic for Salmonella typhimurium strains TA98, TA100, TA1535, or TA1537 with or without rat hepatic homogenates (Florin et al., 1980; Douglas et al., 1980). Methyl ethyl ketone induced aneuploidy in the diploid D61, M strain of Saccharomyces cerevisiae (Zimmermann et al., 1985). Low levels of methyl ethyl ketone combined with low levels of nocodazole (another inducer of aneuploidy), also produced significantly elevated levels of aneuploidy in the system (Mayer and Goin, 1987).

------<<< MEK >>>------

__II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

None.

__II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

None.

__II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

___II.D.1. EPA DOCUMENTATION

U.S. EPA. 1985. Health and Environmental Effects Profile for Methyl Ethyl Ketone. Prepared by the Office of Health and Environmental Assessme7t, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1988. Updated Health Effects Assessment for Methyl Ethyl Ketone. 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.

<<< MEK >>>

___II.D.2. REVIEW (CARCINOGENICITY ASSESSMENT)

The 1988 Updated Health Effects Assessment for Methyl Ethyl Ketone has received Agency review.

Agency Work Group Review: 05/30/89

Verification Date: 05/30/89

___II.D.3. U.S. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

Dharm V. Singh / ORD -- (202)382-5958 / FTS 382-5958

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_III. HEALTH HAZARD ASSESSMENTS FOR VARIED EXPOSURE DURATIONS

Substance Name -- Methyl ethyl ketone (MEK)
CASRN -- 78-93-3

Not available at this time

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_IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- Methyl ethyl ketone (MEK)
CASRN -- 78-93-3
Last Revised -- 06/01/90

EPA risk assessments may be updated as new data are published and as assessment methodologies evolve. Regulatory actions are frequently not updated at the same time. Compare the dates for the regulatory actions in this section with the verification dates for the risk assessments in sections I and II, as this may explain inconsistencies. Also note that some regulatory actions consider factors not related to health risk, such as technical or economic feasibility. Such considerations are indicated for each action. In addition, not all of the regulatory actions listed in this section involve enforceable federal standards. Please direct any questions you may have concerning these regulatory actions to the U.S. EPA contact listed for that particular action. Users are strongly urged to read the background information on each regulatory action in Background Document 4 in Service Code 5.

__IV.A. CLEAN AIR ACT (CAA)

No data available

------<<< MEK >>>------

__IV.B. SAFE DRINKING WATER ACT (SDWA)

No data available

------<<< MEK >>>------

__IV.C. CLEAN WATER ACT (CWA)

No data available

------<<< MEK >>>------

__IV.D. FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT (FIFRA)

No data available

------<<< MEK >>>------

__IV.E. TOXIC SUBSTANCES CONTROL ACT (TSCA)

No data available

------<<< MEK >>>------

__IV.F. RESOURCE CONSERVATION AND RECOVERY ACT (RCRA)

___IV.F.1. RCRA APPENDIX IX, for Ground Water Monitoring

Status -- Listed

Reference -- 52 FR 25942 (07/09/87)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)382-3000 / FTS 382-3000

------<<< MEK >>>------

__IV.G. SUPERFUND (CERCLA)

___IV.G.1. REPORTABLE QUANTITY (RQ) for Release into the Environment

Value (status) -- 5000 pounds (Final, 1985)

Considers technological or economic feasibility? -- NO

Discussion -- The final 5000-pound RQ takes into consideration the natural biodegradation of this hazardous substance. The lowest primary criteria RQ for methyl ethyl ketone (1000, pounds based on chronic toxicity and ignitability/reactivity) has been adjusted upward one RQ level.

Reference -- 50 FR 13456 (04/04/85)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)382-3000 / FTS 382-3000

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_V. SUPPLEMENTARY DATA

Substance Name -- Methyl ethyl ketone (MEK)
CASRN -- 78-93-3

Not available at this time

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_VI. BIBLIOGRAPHY

Substance Name -- Methyl ethyl ketone (MEK)
CASRN -- 78-93-3
Last Revised -- 12/01/89

__VI.A. ORAL RfD REFERENCES

Cavender, F.L., H.W. Casey, H. Salem, J.A. Swenberg and E.J. Gralla. A 90-day vapor inhalation toxicity study of methyl ethyl ketone. Fund. Appl. Toxicol. 3: 264-270.

Deacon, M., M. Pilny, D. John, et al. 1981. Embryo- and fetotoxicity of inhaled methyl ethyl ketone in rats. Toxicol. Appl. Pharmacol. 59: 620-622.

Freddi, A., A. Paci, O. Vittori, R. De Ciantis and P.F. Ottaviano. 1982. Clinical and electromyographic study of workers exposed to methyl ethyl ketone vapor. Ann. Fac. Med. Chir. Univ. Studi Perugio Atti Accad. Anat.-Chir. 73(1): 111-136. CA 100: 108491b. (Abstract)

LaBelle, C.W. and H. Brieger. 1955. The vapor toxicity of a composite solvent

and its principal components. Am. Med. Assoc. Arch. Ind. Health. 12: 623-627.

Schwetz, B.A., B.K.J. Leong and P.J. Gehring. 1974. Embryo- and fetotoxicity of inhaled carbon tetrachloride, 1,1-dichloroethane and methyl ethyl ketone in rats. Toxicol. Appl. Pharmacol. 28(3): 452-464.

Takeuchi, Y., Y. Ono, N. Hisanaga, et al. 1983. An experimental study of the combined effects of n-hexane and methyl ethyl ketone. Br. J. Ind. Med. 40: 199-203.

------<<< MEK >>>------

__VI.B. INHALATION RfD REFERENCES

None

------<<< MEK >>>------

__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

Douglas, G.R., E.R. Nestmann, J.L. Betts, et al. 1980. Mutagenic activity in pulp mill effuents. Water chlorination: Environ. Impact Health Effects. 3: 865-880.

Florin, I., L. Rutberg, M. Curvall and C.R. Enzell. 1980. Screening of tobacco smoke constituents for mutagenicity using the Ames test. Toxicology. 18: 219-232.

Horton, A.W., E.L. Bingham, M.J.G. Burton and R. Tye. 1965. Carcinogenesis of the skin. III. The contribution of elemental sulfur and of organic sulfur compounds. Cancer Res. 25: 1759-1763.

Mayer, V.W. and C.J. Goin. 1987. Effects of chemical combinations on the induction of aneuploidy in Saccharomyces cerevisiae. Mutat. Res. 187(1): 21-30.

U.S. EPA. 1985. Health and Environmental Effects Profile for Methyl Ethyl Ketone. 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. 1988. Updated Health Effects Assessment for Methyl Ethyl Ketone. 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.

Zimmermann, F.K., V.M. Mayer, I. Scheel and M.A. Resnick. 1985. Acetone, methyl ethyl ketone, ethyl acetate, acetonitrile and other polar aprotic

solvents are strong inducers of aneuploidy in Saccharomyces cerevisiae. Mutat. Res. 149(3): 339-351.

------<<< MEK >>>------

__VI.D. DRINKING WATER HA REFERENCES

None

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SYNONYMS

78-93-3
aethylmethylketon
2-butanone
butanone-2
ethyl methyl cetone
ethylmethylketon
ethyl methyl ketone
ketone, ethyl methyl
meetco
MEK
methyl acetone
Methyl Ethyl Ketone
metiletilchetone
metyloetyloketon
RCRA waste number U159
UN 1193
UN 1232

Enter keywords or Read or Scan or Mail
--108-88-3
Searching - Please wait...
1 Occurrences...

Enter keywords or Read or Scan or Mail
--read

N-Nitrosodiphenylamine; CASRN 86-30-6 (04/01/90)

Health risk assessment information on a chemical is included in IRIS only after a comprehensive review of chronic toxicity data by work groups composed of U.S. EPA scientists from several Program Offices. The summaries presented in Sections I and II represent a consensus reached in the review process. The other sections contain U.S. EPA information which is specific to a particular EPA program and has been subject to review procedures prescribed by that Program Office. The regulatory actions in Section IV may not be based on the most current risk assessment, or may be based on a current, but unreviewed, risk assessment, and may take into account factors other than health effects (e.g., treatment technology). When considering the use of regulatory action data for a particular situation, note the date of the regulatory action, the date of the most recent risk assessment relating to that action, and whether technological factors were considered. Background information and explanations of the methods used to derive the values given in IRIS are provided in the five Background Documents in Service Code 5, which correspond to Sections I through V of the chemical files.

STATUS OF DATA FOR N-Nitrosodiphenylamine

File On-Line 03/31/87

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	no data	
Inhalation RfD Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	on-line	03/01/88
Drinking Water Health Advisories (III.A.)	no data	
U.S. EPA Regulatory Actions (IV.)	on-line	03/01/88

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_I. CHRONIC HEALTH HAZARD ASSESSMENT FOR NONCARCINOGENIC EFFECTS

Substance Name -- N-Nitrosodiphenylamine
CASRN -- 86-30-6

Not available at this time

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_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- N-Nitrosodiphenylamine
CASRN -- 86-30-6
Last Revised -- 03/01/88

Section II provides information on three aspects of the carcinogenic risk assessment for the agent in question; the U.S. EPA classification, and quantitative estimates of risk from oral exposure and from inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen. 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. Background Document 2 (Service Code 5) provides details on the rationale and methods used to derive the carcinogenicity values found in IRIS. Users are referred to Section I for information on long-term toxic effects other than carcinogenicity.

<<< N-Nitrosodiphenylamine >>>

__II.A. EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

___II.A.1. WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification -- B2; probable human carcinogen

Basis -- Increased incidence of bladder tumors in male and female rats and reticulum cell sarcomas in mice, and structural relationship to carcinogenic nitrosamines

___II.A.2. HUMAN CARCINOGENICITY DATA

Inadequate. Human exposure to nitrosamines results from contact with mixtures containing these compounds (e.g., cutting oils, tobacco products). Because of potential confounding by the other substances in these mixtures, data are of limited use in the evaluation of carcinogenicity of individual nitrosamines.

<<< N-Nitrosodiphenylamine >>>

___II.A.3. ANIMAL CARCINOGENICITY DATA

N-nitrosodiphenylamine (98% pure containing two unspecified impurities) was administered at 0, 1000 or 4000 ppm in diet to groups of 50 F344 rats/sex. Matched controls consisted of 20 rats/sex. Dose-related mortality was noted in females. Statistically increased incidence of urinary bladder transitional cell carcinomas was observed in both sexes. Epithelial hyper-

plasia and squamous metaplasia also occurred, as did integumentary fibromas in males (NCI, 1979).

In the same study no increased tumor incidence was observed in B6C3F1 mice receiving dietary doses of 10,000 and 20,000 ppm (males) or 2475 and 6139 ppm (TWA, females). Likewise, no evidence of carcinogenicity was observed in BD rats administered 120 mg nitrosodiphenylamine/kg in water for 541 days or in male Wistar rats gavaged with 1.07 mg/day in 1.1% aqueous methylcellulose 5 days/week for 45 weeks (Druckrey et al., 1967; Argus and Hoch-Ligeti, 1961). Neither B6C3F1 nor B6AKF1 mice showed statistically significant increases in tumor incidence following gavage with 1000 mg/kg/day from day 7-28 of age followed by dietary exposure to 3769 ppm until weeks 77-79 of life (BRL, 1968; Innes et al., 1969). Weekly topical application of diphenylnitrosoamine for 20 weeks did not induce tumors in hr/hr Oslo mice, nor did weekly i.p. injection of 2.5 mg in PEG 400 (Iverson, 1980; Boyland et al., 1968). A single s.c. injection of 1000 mg/kg/day resulted in significantly increased incidence of reticulum cell sarcomas in male B6C3F1 mice, but not in females or B6AKF1 mice of either gender (BRL, 1968).

<<< N-Nitrosodiphenylamine >>>

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Nitrosodiphenylamine has produced mixed responses in genetic toxicology tests. It was negative in bacterial mutation assays, mutation assays in V79 and CHO and mouse lymphoma cells and SCE in CHO cells (IARC, 1982). Positive responses have been obtained for several endpoints in S. cerevisiae (de Serres and Hoffmann, 1981) and in DNA damage assays in rat hepatocytes (Althaus et al., 1982; Sina et al., 1983). N-nitrosodiphenylamine produced transformation of Syrian hamster embryo cells, BHK cells and F344 rat embryo cells infected with Rauscher murine leukemia viruses (Pienta and Kawalek, 1981; Daniel and Dehnel, 1981; Dunkel et al., 1981).

N-nitrosodiphenylamine is structurally related to carcinogenic nitrosamines.

------<<< N-Nitrosodiphenylamine >>>------

__II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

___II.B.1. SUMMARY OF RISK ESTIMATES

Oral Slope Factor -- 4.9E-3/mg/kg/day

Drinking Water Unit Risk -- 1.4E-7/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)	7E+2 ug/L
E-5 (1 in 100,000)	7E+1 ug/L
E-6 (1 in 1,000,000)	7E+0 ug/L

<<< N-Nitrosodiphenylamine >>>

___II.B.2. DOSE-RESPONSE DATA (CARCINOGENICITY, ORAL EXPOSURE)

Species/Strain Tumor Type	Dose Administered	Dose Human Equivalent	Tumor Incidence	Reference
Rat/F344, female; transitional cell carcinoma of the bladder	Route: Oral, diet			NCI, 1979
	ppm	mg/kg/day	mg/kg/day	
	0	0	0	0/18
	1000	50	7.7	0/48
	4000	200	30.6	40/49

___II.B.3. ADDITIONAL COMMENTS (CARCINOGENICITY, ORAL EXPOSURE)

The unit risk should not be used if the water concentration exceeds 7E+4 ug/L, since above this concentration the slope factor may differ from that stated.

___II.B.4. DISCUSSION OF CONFIDENCE (CARCINOGENICITY, ORAL EXPOSURE)

Adequate numbers of animals were treated and observed for their lifetime. Significant increases in tumor incidence were observed only in high-dose animals. NCI noted that the mechanism by which bladder tumors were induced (e.g., calculus formation or nitrosation of amines in feed) is not known.

------<<< N-Nitrosodiphenylamine >>>------

__II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

Not available.

------<<< N-Nitrosodiphenylamine >>>------

__II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

___II.D.1. EPA DOCUMENTATION

U.S. EPA. 1986. Health and Environmental Effects Profile for Nitrosamines. 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.

___II.D.2. REVIEW (CARCINOGENICITY ASSESSMENT)

The 1986 Health and Environmental Effects Profile for Nitrosoamines has received Agency review.

Agency Work Group Review: 02/11/87

Verification Date: 02/11/87

___II.D.3. U.S. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

James W. Cogliano / ORD -- (202)382-2575 / FTS 382-2575

Jim Holder / ORD -- (202)382-5721 / FTS 382-5721

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_III. HEALTH HAZARD ASSESSMENTS FOR VARIED EXPOSURE DURATIONS

Substance Name -- N-Nitrosodiphenylamine
CASRN -- 86-30-6

Not available at this time

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_IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- N-Nitrosodiphenylamine
CASRN -- 86-30-6
Last Revised -- 03/01/88

EPA risk assessments may be updated as new data are published and as assessment methodologies evolve. Regulatory actions are frequently not updated at the same time. Compare the dates for the regulatory actions in this section with the verification dates for the risk assessments in sections

I and II, as this may explain inconsistencies. Also note that some regulatory actions consider factors not related to health risk, such as technical or economic feasibility. Such considerations are indicated for each action. In addition, not all of the regulatory actions listed in this section involve enforceable federal standards. Please direct any questions you may have concerning these regulatory actions to the U.S. EPA contact listed for that particular action. Users are strongly urged to read the background information on each regulatory action in Background Document 4 in Service Code 5.

__IV.A. CLEAN AIR ACT (CAA)

No data available

------<<< N-Nitrosodiphenylamine >>>------

__IV.B. SAFE DRINKING WATER ACT (SDWA)

No data available

------<<< N-Nitrosodiphenylamine >>>------

__IV.C. CLEAN WATER ACT (CWA)

No data available

------<<< N-Nitrosodiphenylamine >>>------

__IV.D. FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT (FIFRA)

No data available

------<<< N-Nitrosodiphenylamine >>>------

__IV.E. TOXIC SUBSTANCES CONTROL ACT (TSCA)

No data available

------<<< N-Nitrosodiphenylamine >>>------

__IV.F. RESOURCE CONSERVATION AND RECOVERY ACT (RCRA)

___IV.F.1. RCRA APPENDIX IX, for Ground Water Monitoring

Status -- Listed

Reference -- 52 FR 25942 (07/09/87)

EPA Contact -- Jerry Garman / OSW / (202)382-4658 / FTS 382-4658

------<<< N-Nitrosodiphenylamine >>>------

__IV.G. SUPERFUND (CERCLA)

No data available

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_V. SUPPLEMENTARY DATA

Substance Name -- N-Nitrosodiphenylamine
CASRN -- 86-30-6

Not available at this time

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_VI. BIBLIOGRAPHY

Substance Name -- N-Nitrosodiphenylamine
CASRN -- 86-30-6
Last Revised -- 04/01/90

__VI.A. ORAL RfD REFERENCES

None

------<<< N-Nitrosodiphenylamine >>>------

__VI.B. INHALATION RfD REFERENCES

None

__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

Althaus, F.R., S.D. Lawrence, G.L. Sattler, D.G. Longfellow and H.C. Pitot. 1982. Chemical quantification of unscheduled DNA synthesis in cultured hepatocytes as an assay for the rapid screening of potential chemical carcinogens. Cancer Res. 42(8): 3010-3015.

Argus, M.F. and C. Hoch-Ligeti. 1961. Comparative study of the carcinogenic activity of nitrosamines. J. Natl. Cancer Inst. 27: 695-709.

Boyland, D., R.L. Carter, J.W. Gorrod and F.J.C. Roe. 1968. Carcinogenic properties of certain rubber additives. Eur. J. Cancer. 4(2): 233-239.

BRL (Bionetics Research Laboratory). 1968. Evaluation of carcinogenic, teratogenic and mutagenic activities of selected pesticides and industrial chemicals. Vol. 1, Carcinogenic study. NTIS PB 223-159.

Daniel, M.R. and J.M. Dehnel. 1981. Cell transformation test with baby hamster kidney cells. Prog. Mutat. Res. 1: 626-637.

de Serres, F.J. and G.R. Hoffmann. 1981. Summary report on the performance of yeast assays. Prog. Mutat. Res. 1: 68-76.

Druckrey, H., R. Preussmann, S. Ivankovic and D. Schmael. 1967. Organotropism and carcinogenic activities of 65 different N-Nitrosodi compounds on BD-rats. Z. Kerbsforsch. 69(2): 103-201.

Dunkel, V.C., R.J. Pienta, A. Sivak and K.A. Traul. 1981. Comparative neoplastic transformation responses of Balb/3T3 cells, Syrian hamster embryo cells, and Rauscher murine leukemia virus-infected Fischer 344 rat embryo cells to chemical carcinogens. J. Natl. Cancer Inst. 67(6): 1303-1315.

IARC (International Agency for Research on Cancer). 1982. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man N-Nitrosodiphenylamine. Some Aromatic Amines, Anthroquinones and Nitroso Compounds, and Inorganic Fluorides Used in Drinking Water and Dental Preparations. WHO, IARC, Vol. 27, Lyon, France. p. 213-225.

Innes, J.R.M., B.M. Ulland, M.G. Valeria, et al. 1969. Bioassay of pesticides and industrial chemicals for tumorigenicity in mice : A preliminary note. J. Natl. Cancer Inst. 42: 1101-1114.

Iverson, O.H. 1980. Tumorigenicity of N-nitroso-diaethyl, -dimethyl and -diphenyl-amines in skin painting experiments. A study utilizing the tetrazolium test and skin applications on hairless mice. Eur. J. Cancer. 16(5): 695-698.

NCI (National Cancer Institute). 1979. Bioassay of N-Nitrosodiphenylamine for Possible Carcinogenicity. NCI Carcinogenesis Technical Report Series No. 164. NIH 79-1720. NTIS PB 298-275.

Pienta, R.J. and J.C. Kawalek. 1981. Transformation of hamster embryo cells by aromatic amines. Natl. Cancer Inst. Monogr. 58: 243-251.

Sina, J.F., C.L. Bean, G.R. Dysart, V.I. Taylor and M.O. Bradley. 1983. Evaluation of the alkaline elution/rat hepatocyte assay as a predictor of carcinogenic/mutagenic potential. Mutat. Res. 113(5): 357-391.

U.S. EPA. 1980. Ambient Water Quality Criteria Document for Nitrosamines. 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 81-117756.

U.S. EPA. 1986. Health and Environmental Effects Profile for Nitrosamines. 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.

VI.D. DRINKING WATER HA REFERENCES

None

SYNONYMS

86-30-6
BENZENAMINE, N-NITROSO-N-PHENYL-
CURETARD A
DELAC J
DIPHENYLAMINE, N-NITROSO-
DIPHENYLNITROSAMIN
DIPHENYLNITROSAMINE
DIPHENYL N-NITROSOAMINE
NAUGARD TJB
NCI-C02880
NDPA
NDPhA
NITROSODIPHENYLAMINE
Nitrosodiphenylamine, N-
NITROUS DIPHENYLAMIDE
N,N-DIPHENYLNITROSAMINE
N-NITROSODIFENYLAMIN
N-Nitrosodiphenylamine
N-NITROSO-N-PHENYLANILINE
REDAX
RETARDER J
TJB

VULCALENT A
VULCATARD
VULCATARD A
VULKALENT A
VULTROL

Enter keywords or Read or Scan or Mail
--83-32-9
Searching - Please wait...
1 Occurrences...

Enter keywords or Read or Scan or Mail
--read

o-Cresol; CASRN 95-48-7 (10/01/90) (2-Methylphenol)

Health risk assessment information on a chemical is included in IRIS only after a comprehensive review of chronic toxicity data by work groups composed of U.S. EPA scientists from several Program Offices. The summaries presented in Sections I and II represent a consensus reached in the review process. The other sections contain U.S. EPA information which is specific to a particular EPA program and has been subject to review procedures prescribed by that Program Office. The regulatory actions in Section IV may not be based on the most current risk assessment, or may be based on a current, but unreviewed, risk assessment, and may take into account factors other than health effects (e.g., treatment technology). When considering the use of regulatory action data for a particular situation, note the date of the regulatory action, the date of the most recent risk assessment relating to that action, and whether technological factors were considered. Background information and explanations of the methods used to derive the values given in IRIS are provided in the five Background Documents in Service Code 5, which correspond to Sections I through V of the chemical files.

STATUS OF DATA FOR o-Cresol

File On-Line 09/07/88

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	09/01/90
Inhalation RfC Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	on-line	09/01/90
Drinking Water Health Advisories (III.A.)	no data	
U.S. EPA Regulatory Actions (IV.)	no data	
Supplementary Data (V.)	on-line	04/01/89

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_I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

__I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name -- o-Cresol
CASRN -- 95-48-7
Last Revised -- 09/01/90

The Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. 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 Background Document 1 in Service Code 5 for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of compounds which 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 when a review of that evaluation is completed.

<<< o-Cresol >>>

___I.A.1. ORAL RfD SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfD
Decreased body weights and neurotoxicity	NOAEL: 50 mg/kg/day	1000	1	5E-2 mg/kg/day
90-Day Oral Subchronic Neurotoxicity Study in Rats	LOAEL: 150 mg/kg/day			
U.S. EPA, 1986, 1987				

*Conversion Factors: None

<<< o-Cresol >>>

___I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

U.S. EPA. 1986. o, m, p-Cresol. 90-Day oral subchronic toxicity studies in rats. Office of Solid Waste, Washington, DC.

U.S. EPA. 1987. o, m, p-Cresol. 90-Day oral subchronic neurotoxicity study in rats. Office of Solid Waste, Washington, DC.

In a 90-day subchronic toxicity study (U.S. EPA, 1986), 30 Sprague-Dawley rats/sex/dose were gavaged daily with 0, 50, 175, or 600 mg/kg/day p-cresol. The following parameters were evaluated: body and organ weights, food consumption, mortality, clinical signs of toxicity, and clinical pathology. At sacrifice, animals were necropsied and tissues and organs were subjected to histopathological evaluation. At 600 mg/kg/day, o-cresol produced showed 47% combined mortality (9/30 males, 19/30 females), and a 30% reduction in body weight at week 1 and 10% at final sacrifice. Food consumption was also significantly reduced during weeks 1 through 6 and 9. Kidney-to-body weight ratio was 13% higher than that of the control value at the end of the study. In addition to the above effects, CNS effects such as lethargy, ataxia, coma, dyspnea, tremor, and convulsions were seen within 15 to 30 minutes after dosing; recovery occurred within 1 hour postgavage. At 450 mg/kg/day,

combined mortality was 20% (1/10 male, 1/10 female). In the 175 mg/kg/day group, two animals exhibited tremors on day 1 of the study during the hour following gavage administration, and one of these animals became comatose during that time. At 50 mg/kg/day, no significant adverse effects were observed.

In a 90-day neurotoxicity study (U.S. EPA, 1987), 10 Sprague-Dawley rats/sex/dose, were gavaged with o-cresol daily at 0, 50, 175, 450, or 600 mg/kg/day. In addition to the parameters evaluated in U.S. EPA (1986), the following were monitored for signs of neurotoxicity: salivation, urination, tremor, piloerection, diarrhea, pupil size, pupil response, lacrimation, hypothermia, vocalization, exophthalmia, palpebral closure, convulsions (type and severity), respiration (rate and type), impaired gait, positional passivity, locomotor activity, stereotypy, startle response, righting reflex, performance on a wire maneuver, forelimb strength, positive geotrophism, extensor thrust, limb rotation, tail pinch reflex, toe pinch reflex, and hind limb splay were also evaluated. The lowest dose of o-cresol (50 mg/kg/day) caused clinical signs of CNS-stimulation post dosing such a salivation, rapid respiration, and hypoactivity; however, these symptoms were low in incidence and sporadic in nature. Higher doses of o-cresol (greater than 450 mg/kg/day) produced significant neurological events, such as increased salivation, urination, tremors, lacrimation, palpebral closure, and rapid respiration. High dosed animals also showed abnormal patterns in the neurobehavioral tests. The NOAEL based on systemic toxicity was 50 mg/kg/day in rats.

<<< o-Cresol >>>

___I.A.3. UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

UF = 1000. 10 for interspecies and 10 for intraspecies variability and 10 for uncertainty in extrapolatlon of subchronic data to levels of chronic effects.

MF = 1.

<<< o-Cresol >>>

___I.A.4. ADDITIONAL COMMENTS (ORAL RfD)

In a series of subchronic inhalation studies, Uzhdavine et al. (1972) exposed rats and guinea pigs to o-cresol at a concentration of 9.0 (plus or minus 0.9) mg/cu.m. No effect was seen in guinea pigs. In rats, the authors reported various hematopoietic effects, respiratory tract irritation and sclerosis of lungs. Uzhdavine et al. (1972) also reported that humans exposed to 6 mg/cu.m cresol (duration unspecified) experienced nasopharyngeal irritation. Other studies support the findings (effects) reported in this study. Based on a review and assessment of the available literature, primarily Uzhdavine et al. (1972), NIOSH (1978) recommended a TLV-TWA of 10 mg/cu.m (0.05 mg/kg/day). An RfD of 0.05 mg/kg/day can also be derived from this value; this lends support to the RfD derived from the subchronic toxicity studies (U.S. EPA, 1986, 1987).
<<< o-Cresol >>>

___I.A.5. CONFIDENCE IN THE ORAL RfD

Study: High
Data Base: Medium
RfD: Medium

Confidence is the study is high because the critical studies provided adequate toxicological endpoints that included both general toxicity and neurotoxicity. The data base is medium because there are adequate supporting subchronic studies. Thus, until additional chronic toxicity studies and reproductive studies are available, medium confidence in the RfD is recommended.

<<< o-Cresol >>>

___I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

U.S. EPA. 1985. Health and Environmental Effects Profile for Cresols. 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.

The Health and Environmental Effects Profile has received an Agency-wide review with the help of two external scientists.

Agency RfD Work Group Review: 06/24/85, 07/08/85, 08/13/87

Verification Date: 08/13/87

___I.A.7. EPA CONTACTS (ORAL RfD)

Harlal Choudhury / ORD -- (513)569-7536 / FTS 684-7536

Christopher DeRosa / ORD -- (513)569-7534 / FTS 684-7534

__I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

Substance Name -- o-Cresol
CASRN -- 95-48-7

Not available at this time.

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_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- o-Cresol

CASRN -- 95-48-7
Last Revised -- 09/01/90

Section II provides information on three aspects of the carcinogenic risk assessment for the agent in question; the U.S. EPA classification, and quantitative estimates of risk from oral exposure and from inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen. 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. Background Document 2 (Service Code 5) provides details on the rationale and methods used to derive the carcinogenicity values found in IRIS. Users are referred to Section I for information on long-term toxic effects other than carcinogenicity.

<<< o-Cresol >>>

II.A. EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

II.A.1. WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification -- C; possible human carcinogen

Basis -- Based on an increased incidence of skin papillomas in mice in an initiation-promotion study. The three cresol isomers produced positive results in genetic toxicity studies both alone and in combination.

<<< o-Cresol >>>

II.A.2. HUMAN CARCINOGENICITY DATA

Inadequate. Only anecdotal data available. Garrett (1975) reported two cases of multifocal transitional cell carcinoma of the bladder following chronic occupational exposure to cresol and creosote. Wodyka (1964, as cited in U.S. EPA., 1979) described a squamous cell carcinoma of the vocal cords in a petroleum refinery worker with a long history of exposure to cresol, dichlorooctane, and chromic acid.

<<< o-Cresol >>>

II.A.3. ANIMAL CARCINOGENICITY DATA

Limited. Four skin application studies which had positive results are reported; however, the final two studies are of limited value due to the application of a mixture of chemicals. In a study by Boutwell and Bosch (1959), female Sutter mice (27-29/group; 2-3 months of age) received a single dermal application of 25 uL of 0.3% dimethylbenzanthracene (DMBA) in acetone as the initiator, followed 1 week later by 25 uL of 20% (v/v) o-, m- or p-cresol in benzene twice weekly for 12 weeks. Skin papillomas were evaluated

at 12 weeks. Many of the cresol-treated mice died, presumably of cresol toxicity. There was no mortality or evidence of skin papillomas in the benzene control group (benzene weekly after DMBA initiation). The numbers of surviving mice that developed skin papillomas at 12 weeks were as follows: 10/17, o-cresol; 7/14, m-cresol; and 7/20, p-cresol. None of the 12 mice in the benzene control group died or developed skin papillomas.

In another experiment, groups of 20 mice received a single dose (25 uL) of 0.3% DMBA in acetone, followed by twice weekly applications of 5.7% m-cresol in benzene or 5.7% p-cresol in benzene for 20 weeks. No skin papillomas were observed in the 18 surviving benzene control mice; 4/17 m-cresol- and 4/14 p-cresol-treated mice developed skin papillomas (Boutwell and Bosch, 1959). These two experiments indicate that cresols can serve as tumor promoters of a polycyclic aromatic hydrocarbon.

Kaiser (1977), using spectroscopic and gas chromatographic analysis, showed that o-, m-, and p-cresol were present in a phenolic fraction isolated from tea. Two groups of 15 Swiss mice (age and sex not specified) received a single dermal application of 1% benzo[a]pyrene in acetone. On alternate days one group received dermal applications of tea (1g/155 ml water, dose unspecified). The type of housing used in these studies was not specified. At the end of 110 days (55 total treatments), 6/15 mice had epithelial cell carcinomas and 9/15 had developed precarcinogenic or carcinogenic stages of squamous-cell tumors. Control mice, which received only the initial benzo[a]pyrene treatment, developed no pathologic lesions. Bock et al. (1971) used steam distillation to isolate subfractions of an acid fraction of cigarette smoke condensate; this fraction was previously shown to be a tumor promoter (Bock et al., 1969). Phenolic compounds including o-, m-, and p-cresol were detected in the steam distillate subfraction. A synthetic distillate with the same composition was prepared. Groups of fifty 14-week-old Swiss mice (gender unspecified) were administered 0.2 ml of the nonvolatile fraction of the distillate, the distillate, the synthetic distillate, or acetone (for the control group) by dermal application, 5 times per week for 61 weeks. Approximately 45% of the mice survived in each group. Skin tumors developed with the following incidence: 4/23, 4/26, 2/21, and 14/21 for the control group, the distillate application group, the synthetic distillate application group, and the nonvolatile fraction group, respectively. (The tumor type was not specified.) These studies are of limited value in determining the tumor-promoting activity of cresol, since both tea and cigarette smoke condensate contain numerous other compounds.

In an acute dermal toxicity study, technical grade o-, m-, and p-cresol caused severe skin damage on at least 2/6 shaved, female, albino New Zealand rabbits within 4 hours of application of 2000 mg/kg of technical grade cresol, 890 mg/kg of o-cresol, 2830 mg/kg of m-cresol, or 300 mg/kg p-cresol (Vernot et al. 1977).

<<< o-Cresol >>>

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Studies on the induction of unscheduled DNA synthesis showed p-cresol to be positive in human lung fibroblast cells in the presence of hepatic homogenates (Crowley and Margard, 1978), the mixture of the three isomers to

be weakly positive in primary rat hepatocytes (Litton Bionetics, 1980d), and o-cresol to be negative in rat hepatocytes (Litton Bionetics, 1981e).

In cell transformation assays using BALB/3T3 cells, a mixture of 3 cresol isomers was positive (Litton Bionetics, 1980d), and o-cresol was negative. Positive mutagenic responses were found at noncytotoxic doses (Litton Bionetics, 1980e). In another cell transformation assay using p-cresol, negative results were obtained with the mouse fibroblast cell line C3H10T1/2 (Crowley and Margard, 1978).

Cresols (o-, m- and p-) are not mutagenic for various strains of Salmonella typhimurium both in the presence and absence of mammalian liver homogenates (Crowley and Margard, 1978; Litton Bionetics, 1980a, 1981a; Florin et al., 1980; Douglas et al., 1980; Pool and Lin, 1982; Haworth et al., 1983).

A mixture of the three isomers was mutagenic in a mouse lymphoma forward mutation assay with mammalian liver homogenates, while o-cresol was not mutagenic both with and without liver homogenates (Litton Bionetics, 1980b, 1981b).

No isomer, when tested individually, induced sister chromatid exchanges (SCEs) in vivo, but the mixture of the three isomers induced SCEs in Chinese hamster ovary (CHO) cells in vitro (Litton Bionetics, 1980c). Only o-cresol induced SCEs in human lung fibroblasts (Cheng and Kligerman, 1984) and CHO cells (Litton Bionetics, 1981c).

In a screening test for putative carcinogens, infectious virus particles were produced from SV40-transformed weanling Syrian hamster kidney cells exposed to m-cresol (Moore and Coohill, 1983).

---------<<< o-Cresol >>>---------

__II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

None.

---------<<< o-Cresol >>>---------

__II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

None.

---------<<< o-Cresol >>>---------

__II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

___II.D.1. EPA DOCUMENTATION

U.S. EPA. 1979. The Carcinogen Assessment Group's Preliminary Risk Assessment on Cresols: Type 1 - Air Program. Prepared by the Office of Health and Environment Assessment for the Office of Air Quality Planning and Standards, Washington, DC.

U.S. EPA. 1985. Health and Environmental Effects Profiles for Cresols. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, for the Office of Solid Waste and Emergency Response, Washington, DC.

<<< o-Cresol >>>

___II.D.2. REVIEW (CARCINOGENICITY ASSESSMENT)

The 1985 Health and Environmental Effects Profile for Cresols is an external draft for review only and does not constitute Agency policy.

Agency Work Group Review: 07/11/88, 10/5/89

Verification Date: 10/5/89

___II.D.3. U.S. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

Herman Gibb / ORD -- (202)382-5720 / FTS 382-5720

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_III. HEALTH HAZARD ASSESSMENTS FOR VARIED EXPOSURE DURATIONS

__III.A. DRINKING WATER HEALTH ADVISORIES

Substance Name -- o-Cresol
CASRN -- 95-48-7

Not available at this time.

__III.B. OTHER ASSESSMENTS

Substance Name -- o-Cresol
CASRN -- 95-48-7

Content to be determined.

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_IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- o-Cresol
CASRN -- 95-48-7

Not available at this time.

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_V. SUPPLEMENTARY DATA

Substance Name -- o-Cresol
CASRN -- 95-48-7
Last Revised -- 04/01/89

The information contained in this section (subsections A and B) has been extracted from the EPA Chemical Profiles Database, which has been compiled from a number of secondary sources and has not undergone formal Agency review. The complete reference listings for the citations in this section are provided in Service Code 5. The user is urged to read Background Document 5 in Service Code 5 for further information on the sources and limitations of the data presented here.

<<< o-Cresol >>>

__V.A. ACUTE HEALTH HAZARD INFORMATION

Toxicity -- o-Cresol is rated as a very toxic compound with a probable oral lethal dose in humans of 50-500 mg/kg, or between 1 teaspoon and 1 ounce for a 70 kg (150 lb.) person (Gosselin, 1976). o-Cresol is a strong dermal irritant and frequently causes dermatitis. Serious or fatal poisoning may result if large areas of skin are wet with cresylic acid and the substance is not removed immediately (ACGIH, 1980). Ingestion of even a small amount may cause paralysis and coma (Merck, 1983). o-Cresol is corrosive to body tissues (NFPA, 1978, 49-32) with toxicity similar to phenol (Encyc Occupat Health and Safety, 1983, p. 569).

Medical Conditions Generally Aggravated by Exposure -- Not Found

Signs and Symptoms of Exposure -- Exposure to o-cresol may result in a burning pain in the mouth and throat; white necrotic lesions in the mouth, esophagus and stomach; abdominal pain, vomiting, diarrhea, paleness; sweating; weakness; headache; dizziness; ringing in ears; shallow respiration with "phenol" odor on the breath; scanty, dark-colored or "smoky" urine; and possibly delirium followed by unconsciousness. Convulsions are rarely seen, except in children (Gosselin, 1976). Hypersensitivity develops in certain

individuals (Clayton and Clayton, 1981-82, p. 2600).

---------<<< o-Cresol >>>---------

__V.B. PHYSICAL-CHEMICAL PROPERTIES

Chemical Formula -- C7H8O

Molecular Weight -- 108.15

Boiling Point -- 376F,, 191C (Weast, 1979)

Specific Gravity (H2O=1) -- 1.047 at 20C/4C (Merck, 1983)

Vapor Pressure (mmHg) -- 1 at 38.2C (Sax, 1979)

Melting Point -- 88F, 31C (Weast, 1979)

Vapor Density (AIR=1) -- 3.72 (Sax, 1979)

Evaporation Rate (Butyl acetate=1) -- Not Found

Solubility in Water -- Soluble in 40 parts water (Merck, 1983)

Appearance and Odor -- Colorless liquid (NFPA, 1978, p. 49-32), colorless crystalline compound (Clayton and Clayton, 1981-82) or white crystals (Hawley, 1981) with phenolic odor (Merck, 1983)

Flash Point (Method Used) -- 81-83C (Merck, 1983)

Flammable Limits:
LEL -- 1.4% at 300F (Sax, 1979)
UEL -- Not Found

Conditions and Materials to Avoid -- o-Cresol reacts violently with nitric acid, oleum, and chlorosulfonic acid (Sax, 1984, p. 814).

Hazardous Decomposition or Byproducts -- When heated to decomposition, o-cresol emits highly toxic fumes (Sax, 1979).

Use -- o-Cresol is an intermediate for phenolic and epoxy resins, sulfur chromium dyes, herbicides, magnet wire coatings, and pharmaceuticals. o-Cresol is also used as a disinfectant; a solvent; a fiber treatment agent, tanning agent, and a metal degreasing agent (SRI).

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_VI. BIBLIOGRAPHY

Substance Name -- o-Cresol

CASRN -- 95-48-7
Last Revised -- 09/01/90

__VI.A. ORAL RfD REFERENCES

NIOSH (National Institute for Occupational Safety and Health). 1978. Criteria for a recommended standard...Occupational exposure to cresol. U.S. DHEW, DHEW (NIOSH) Publ. No. 78-133.

U.S. EPA. 1985. Health and Environmental Effects Profile for Cresols. 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.

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U.S. EPA. 1987. o, m, p-Cresol. 90-Day oral subchronic neurotoxicity study in rats. Office of Solid Waste, Washington, DC.

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---------<<< o-Cresol >>>---------

__VI.B. INHALATION RfD REFERENCES

None

---------<<< o-Cresol >>>---------

__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

Bock, F.G., A.P. Swain and R.L. Stedman. 1969. Bioassay of major fractions of cigarette smoke condensate by an accelerated technic. Cancer Res. 29: 584-587.

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Boutwell, R.K. and D.K. Bosch. 1959. The tumor-promoting action of phenol and related compounds for mouse skin. Cancer Res. 19: 413-424.

Cheng, M. and A.O. Kligerman. 1984. Evaluation of the genotoxicity of

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Litton Bionetics. 1980c. Mutagenic evaluation of sample containing 33.3% each of ortho-, meta- and para-cresol in the sister chromatid exchange assay with Chinese hamster ovary cells. -- Final report. Unpublished data submitted by the Cresol Task Force to the Office of Toxic Substances, U.S. EPA. FYI-OTS-0780-0079.

Litton Bionetics. 1980d. Evaluation of sample containing 33.3% each of ortho-, meta- and para-cresol in the primary rat hepatocyte unscheduled DNA assay. Unpublished data submitted by the Cresol Task Force to the Office of Toxic Substances, U.S. EPA. FYI-OTS-0780-0079.

Litton Bionetics. 1980e. Evaluation of sample containing 33.3% each of ortho-, meta- and para-cresol in the in vitro transformation of BALB/3T3 cells assay with activation by primary rat hepatocytes -- Final report. Unpublished data submitted by the Cresol Task Force to the Office of Toxic Substances, U.S. EPA. FYI-OTS-0780-0079.

Litton Bionetics. 1981a. Mutagenic evaluation of N50C-81-3 [o-cresol] in the Ames Salmonella/microsome plate test -- Final report. Unpublished data

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Litton Bionetics. 1981d. Evaluation of N50C-81-3 [o-cresol] in the in vitro transformation of BALB/3T3 cells assay [without activation] -- Final report. Unpublished data submitted by the Cresol Task Force to the Office of Toxic Substances, U.S. EPA. FYI-OTS-0981-0126.

Litton Bionetics. 1981e. Evaluation of N50C-81-3 [o-cresol] in the primary rat hepatocyte unscheduled DNA synthesis assay -- Final report. Unpublished data submitted by the Cresol Task Force to the Office of Toxic Substances, U.S. EPA. FYI-OTS-0981-0126.

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Wodyka, J. 1964. Precancerous states of the larynx. Pol. Tyg. Ted. 19: 91-94. Reviewed in Albert, R.E. 1979. The Carcinogen Assessment Group's Preliminary Risk Assessment on Cresols. Type I - Air Program. U.S. EPA.

---------<<< o-Cresol >>>---------

__VI.D. DRINKING WATER HA REFERENCES

None

SYNONYMS

Substance Name -- o-Cresol
CASRN -- 95-48-7
Last Revised -- 09/07/88

95-48-7
o-Cresol
Cresol, ortho

Enter keywords or Read or Scan or Mail
--86-30-6
Searching - Please wait...
1 Occurrences...

Enter keywords or Read or Scan or Mail
--read

STATUS OF DATA FOR p-Cresol

File On-Line 08/22/88

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	09/01/90
Inhalation RfC Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	on-line	09/01/90
Drinking Water Health Advisories (III.A.)	no data	
U.S. EPA Regulatory Actions (IV.)	no data	
Supplementary Data (V.)	no data	

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_I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

__I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name -- p-Cresol
CASRN -- 106-44-5
Last Revised -- 09/01/90

The Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. 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 Background Document 1 in Service Code 5 for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of compounds which 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 when a review of that evaluation is completed.

<<< p-Cresol >>>

___I.A.1. ORAL RfD SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfD
Decreased body weights	NOAEL: 50 mg/kg/day	1000	1	5E-2

and neurotoxicity mg/kg/day

90-Day Oral Subchronic Neurotoxicity Study in Rats LOAEL: 150 mg/kg/day

U.S. EPA, 1986, 1987

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*Conversion Factors: None

<<< p-Cresol >>>

___I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

U.S. EPA. 1986. o, m, p-Cresol. 90-Day oral subchronic toxicity studies in rats. Office of Solid Waste, Washington, DC.

U.S. EPA. 1987. o, m, p-Cresol. 90-Day oral subchronic neurotoxicity study in rats. Office of Solid Waste, Washington, DC.

In a 90-day subchronic toxicity study (U.S. EPA, 1986), p-cresol was administered by gavage to 30 Sprague-Dawley rats/sex/dose at 0, 50, 175, or 600 mg/kg/day, once daily. The following parameters were evaluated: body and organ weights, food consumption, mortality, clinical signs of toxicity, and clinical pathology. At sacrifice, animals were necropsied and tissues and organs were subjected to histopathological evaluation. At 600 mg/kg/day of p-cresol, there was a significant reduction in weight gain (15% for females, 25% for males), significantly reduced food consumption at weeks 1 through 7 and 9 in males and significant increased incidence of CNS effects such as lethargy, excessive salivation, tremors, and diarrhea. Also, at 600 mg/kg/day the liver-to-body and kidney-to-body weight ratios were significantly increased, and there was a greater incidence of tracheal epithelial metaplasia compared with the animals in the control, low- or mid-dose groups. At the mid-dose group (175 mg/kg/day) the reduction in weight gain was 5 to 10% in males between weeks 1 and 3; liver-to-body weight ratio was elevated (though not statistically significant) in both sexes, and kidney-to-body weight ratio was significantly elevated in males. Although there was a slight reduction in weight gain and a small increase in kidney-to-body weight ratio at the 50 mg/kg/day level, these effects were not statistically significant.

In a 90-day neurotoxicity study (U.S. EPA, 1987), 10 Sprague-Dawley rats/sex/dose, were gavaged daily with 0, 50, 75, or 600 mg/kg/day p-cresol. In addition to the parameters evaluated by U.S. EPA (1986), the following were monitored for signs of neurotoxicity: salivation, urination, tremor, piloerection, diarrhea, pupil size, pupil response, lacrimation, hypothermia, vocalization, exophthalmia, palpebral closure, convulsions (type and severity), respiration (rate and type), impaired gait, positional passivity, locomotor activity, stereotypy, startle response, righting reflex, performance on a wire maneuver, forelimb strength, positive geotrophism, extensor thrust, limb rotation, tail pinch reflex, toe pinch reflex. and hind limb splay. The lowest dose (50 mg/kg/day) caused clinical signs of CNS-stimulation post dosing such a salivation, rapid respiration, and hypoactivity; however, they were low in incidence and sporadic in nature. The highest dose of p-cresol (600 mg/kg/day) produced significant neurological effects, such as increased

salivation and urination, tremors, lacrimation, palpebral closure, and rapid respiration. High-dose animals also showed abnormal patterns in the neurobehavioral tests. The NOAEL based on systemic toxicity was 50 mg/kg/day in rats.

<<< p-Cresol >>>

___I.A.3. UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

UF = 1000. 10 for interspecies and 10 for intraspecies variability and 10 for uncertainty in extrapolation of subchronic data to levels of chronic effects.

MF = 1.

<<< p-Cresol >>>

___I.A.4. ADDITIONAL COMMENTS (ORAL RfD)

In a series of subchronic inhalation studies, Uzhdavine et al. (1972) exposed rats and guinea pigs to o-cresol at a concentration of 9.0 (plus or minus 0.9) mg/cu.m. No effect was seen in guinea pigs. In rats, the authors reported various hematopoietic effects, respiratory tract irritation and sclerosis of lungs. Uzhdavine et al. (1972) also reported that humans exposed to 6 mg/cu.m cresol (duration unspecified) experienced nasopharyngeal irritation. Other studies support the findings (effects) reported in this study. Based on a review and assessment of the available literature, primarily Uzhdavine et al. (1972), NIOSH (1978) recommended a TLV-TWA of 10 mg/cu.m (0.05 mg/kg/day). An RfD of 0.05 mg/kg/day can also be derived from this value; this lends support to the RfD derived from the subchronic toxicity studies (U.S. EPA, 1986, 1987).

<<< p-Cresol >>>

___I.A.5. CONFIDENCE IN THE ORAL RfD

Study: High
Data Base: Medium
RfD: Medium

Confidence in the study is high because the critical studies provided adequate toxicological endpoints that included both general toxicity and neurotoxicity. The data base is medium because there are adequate supporting subchronic studies. Thus, until additional chronic toxicity studies and reproductive studies are available, medium confidence in the study, RfD is recommended.

<<< p-Cresol >>>

___I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

U.S. EPA. 1985. Health and Environmental Effects Profile for Cresols. 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.

The Health and Environmental Effects Profile has received an Agency-wide review with the help of two external scientists.

Agency RfD Work Group Review: 06/24/85, 07/08/85, 08/13/87

Verification Date: 08/13/87

___I.A.7. EPA CONTACTS (ORAL RfD)

Harlal Choudhury / ORD -- (513)569-7536 / FTS 684-7536

Christopher DeRosa / ORD -- (513)569-7534 / FTS 684-7536

__I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

Substance Name -- p-Cresol
CASRN -- 106-44-5

Not available at this time.

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_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- p-Cresol
CASRN -- 106-44-5
Last Revised -- 09/01/90

Section II provides information on three aspects of the carcinogenic risk assessment for the agent in question; the U.S. EPA classification, and quantitative estimates of risk from oral exposure and from inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen. 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. Background Document 2 (Service Code 5) provides details on the rationale and methods used to derive the carcinogenicity values found in IRIS. Users are referred to Section I for information on long-term toxic effects other than carcinogenicity.

<<< p-Cresol >>>

II.A. EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

II.A.1. WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification -- C; possible human carcinogen

Basis -- Based on an increased incidence of skin papillomas in mice in an initiation-promotion study. The three cresol isomers produced positive results in genetic toxicity studies both alone and in combination.

<<< p-Cresol >>>

II.A.2. HUMAN CARCINOGENICITY DATA

Inadequate. Only anecdotal data available. Garrett (1975) reported two cases of multifocal transitional cell carcinoma of the bladder following chronic occupational exposure to cresol and creosote. Wodyka (1964, as cited in U.S. EPA., 1979) described a squamous cell carcinoma of the vocal cords in a petroleum refinery worker with a long history of exposure to cresol, dichlorooctane, and chromic acid.

<<< p-Cresol >>>

II.A.3. ANIMAL CARCINOGENICITY DATA

Limited. Four skin application studies which had positive results are reported; however, the final two studies are of limited value due to the application of a mixture of chemicals. In a study by Boutwell and Bosch (1959), female Sutter mice (27-29/group; 2-3 months of age) received a single dermal application of 25 uL of 0.3% dimethylbenzanthracene (DMBA) in acetone as the initiator, followed 1 week later by 25 uL of 20% (v/v) o-, m- or p-cresol in benzene twice weekly for 12 weeks. Skin papillomas were evaluated at 12 weeks. Many of the cresol-treated mice died, presumably of cresol toxicity. There was no mortality or evidence of skin papillomas in the benzene control group (benzene weekly after DMBA initiation). The numbers of surviving mice that developed skin papillomas at 12 weeks were as follows: 10/17, o-cresol; 7/14, m-cresol; and 7/20, p-cresol. None of the 12 mice in the benzene control group died or developed skin papillomas.

In another experiment, groups of 20 mice received a single dose (25 uL) of 0.3% DMBA in acetone, followed by twice weekly applications of 5.7% m-cresol in benzene or 5.7% p-cresol in benzene for 20 weeks. No skin papillomas were observed in the 18 surviving benzene control mice; 4/17 m-cresol- and 4/14 p-cresol-treated mice developed skin papillomas (Boutwell and Bosch, 1959). These two experiments indicate that cresols can serve as tumor promoters of a polycyclic aromatic hydrocarbon.

Kaiser (1977), using spectroscopic and gas chromatographic analysis, showed that o-, m-, and p-cresol were present in a phenolic fraction isolated from tea. Two groups of 15 Swiss mice (age and sex not specified) received a single dermal application of 1% benzo[a]pyrene in acetone. On alternate days

one group received dermal applications of tea (1g/155 ml water, dose unspecified). The type of housing used in these studies was not specified. At the end of 110 days (55 total treatments), 6/15 mice had epithelial cell carcinomas and 9/15 had developed precarcinogenic or carcinogenic stages of squamous-cell tumors. Control mice, which received only the initial benzo[a]pyrene treatment, developed no pathologic lesions. Bock et al. (1971) used steam distillation to isolate subfractions of an acid fraction of cigarette smoke condensate; this fraction was previously shown to be a tumor promoter (Bock et al., 1969). Phenolic compounds including o-, m-, and p-cresol were detected in the steam distillate subfraction. A synthetic distillate with the same composition was prepared. Groups of fifty 14-week-old Swiss mice (gender unspecified) were administered 0.2 ml of the nonvolatile fraction of the distillate, the distillate, the synthetic distillate, or acetone (for the control group) by dermal application, 5 times per week for 61 weeks. Approximately 45% of the mice survived in each group. Skin tumors developed with the following incidence: 4/23, 4/26, 2/21, and 14/21 for the control group, the distillate application group, the synthetic distillate application group, and the nonvolatile fraction group, respectively. (The tumor type was not specified.) These studies are of limited value in determining the tumor-promoting activity of cresol, since both tea and cigarette smoke condensate contain numerous other compounds.

In an acute dermal toxicity study, technical grade o-, m-, and p-cresol caused severe skin damage on at least 2/6 shaved, female, albino New Zealand rabbits within 4 hours of application of 2000 mg/kg of technical grade cresol, 890 mg/kg of o-cresol, 2830 mg/kg of m-cresol, or 300 mg/kg p-cresol (Vernot et al. 1977).

<<< p-Cresol >>>

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Studies on the induction of unscheduled DNA synthesis showed p-cresol to be positive in human lung fibroblast cells in the presence of hepatic homogenates (Crowley and Margard, 1978), the mixture of the three isomers to be weakly positive in primary rat hepatocytes (Litton Bionetics, 1980d), and o-cresol to be negative in rat hepatocytes (Litton Bionetics, 1981e).

In cell transformation assays using BALB/3T3 cells, a mixture of 3 cresol isomers was positive (Litton Bionetics, 1980d), and o-cresol was negative. Positive mutagenic responses were found at noncytotoxic doses (Litton Bionetics, 1980e). In another cell transformation assay using p-cresol, negative results were obtained with the mouse fibroblast cell line C3H10T1/2 (Crowley and Margard, 1978).

Cresols (o-, m- and p-) are not mutagenic for various strains of Salmonella typhimurium both in the presence and absence of mammalian liver homogenates (Crowley and Margard, 1978; Litton Bionetics, 1980a, 1981a; Florin et al., 1980; Douglas et al., 1980; Pool and Lin, 1982; Haworth et al., 1983).

A mixture of the three isomers was mutagenic in a mouse lymphoma forward mutation assay with mammalian liver homogenates, while o-cresol was not mutagenic both with and without liver homogenates (Litton Bionetics, 1980b, 1981b).

No isomer, when tested individually, induced sister chromatid exchanges (SCEs) in vivo, but the mixture of the three isomers induced SCEs in Chinese hamster ovary (CHO) cells in vitro (Litton Bionetics, 1980c). Only o-cresol induced SCEs in human lung fibroblasts (Cheng and Kligerman, 1984) and CHO cells (Litton Bionetics, 1981c).

In a screening test for putative carcinogens, infectious virus particles were produced from SV40-transformed weanling Syrian hamster kidney cells exposed to m-cresol (Moore and Coohill, 1983).

---------<<< p-Cresol >>>---------

__II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

None.

---------<<< p-Cresol >>>---------

__II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

None.

---------<<< p-Cresol >>>---------

__II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

___II.D.1. EPA DOCUMENTATION

U.S. EPA. 1979. The Carcinogen Assessment Group's Preliminary Risk Assessment on Cresols: Type 1 - Air Program. Prepared by the Office of Health and Environment Assessment for the Office of Air Quality Planning and Standards, Washington, DC.

U.S. EPA. 1985. Health and Environmental Effects Profiles for Cresols. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, for the Office of Solid Waste and Emergency Response, Washington, DC.

<<< p-Cresol >>>

___II.D.2. REVIEW (CARCINOGENICITY ASSESSMENT)

The 1985 Health and Environmental Effects Profile for Cresols is an external draft for review only and does not constitute Agency policy.

Agency Work Group Review: 07/11/88, 10/5/89

Verification Date: 10/5/89

___II.D.3. U.S. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

Herman Gibb / ORD -- (202)382-5720 / FTS 382-5720

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_III. HEALTH HAZARD ASSESSMENTS FOR VARIED EXPOSURE DURATIONS

__III.A. DRINKING WATER HEALTH ADVISORIES

Substance Name -- p-Cresol
CASRN -- 106-44-5

Not available at this time.

__III.B. OTHER ASSESSMENTS

Substance Name -- p-Cresol
CASRN -- 106-44-5

Content to be determined.

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_IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- p-Cresol
CASRN -- 106-44-5

Not available at this time.

==========

_V. SUPPLEMENTARY DATA

Substance Name -- p-Cresol

CASRN -- 106-44-5

Not available at this time.

_VI. BIBLIOGRAPHY

Substance Name -- p-Cresol
CASRN -- 106-44-5
Last Revised -- 09/01/90

__VI.A. ORAL RfD REFERENCES

NIOSH (National Institute for Occupational Safety and Health). 1978. Criteria for a recommended standard...Occupational exposure to cresol. U.S. DHEW, DHEW (NIOSH) Publ. No. 78-133.

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---------<<< p-Cresol >>>---------

__VI.B. INHALATION RfD REFERENCES

None

---------<<< p-Cresol >>>---------

__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

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Litton Bionetics. 1980b. Mutagenic evaluation of ortho-, meta- and para-cresol 33.3% each in the mouse lymphoma forward mutation assay -- Final report. Unpublished data submitted by the Cresol Task Force to the Office of Toxic Substances, U.S. EPA. FYI-OTS-0780-0079.

Litton Bionetics. 1980c. Mutagenic evaluation of sample containing 33.3% each of ortho-, meta- and para-cresol in the sister chromatid exchange assay with Chinese hamster ovary cells. -- Final report. Unpublished data submitted by the Cresol Task Force to the Office of Toxic Substances, U.S. EPA. FYI-OTS-0780-0079.

Litton Bionetics. 1980d. Evaluation of sample containing 33.3% each of

ortho-, meta- and para-cresol in the primary rat hepatocyte unscheduled DNA assay. Unpublished data submitted by the Cresol Task Force to the Office of Toxic Substances, U.S. EPA. FYI-OTS-0780-0079.

Litton Bionetics. 1980e. Evaluation of sample containing 33.3% each of ortho-, meta- and para-cresol in the in vitro transformation of BALB/3T3 cells assay with activation by primary rat hepatocytes -- Final report. Unpublished data submitted by the Cresol Task Force to the Office of Toxic Substances, U.S. EPA. FYI-OTS-0780-0079.

Litton Bionetics. 1981a. Mutagenic evaluation of N50C-81-3 [o-cresol] in the Ames Salmonella/microsome plate test -- Final report. Unpublished data submitted by the Cresol Task Force to the Office of Toxic Substances, U.S. EPA. FYI-OTS-0981-0126.

Litton Bionetics. 1981b. Mutagenic evaluation of N50C-81-3 [o-cresol] in the mouse lymphoma forward mutation assay -- Final report. Unpublished data submitted by the Cresol Task Force to the Office of Toxic Substances, U.S. EPA. FYI-OTS-0981-0126.

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---------<<< p-Cresol >>>---------

__VI.D. DRINKING WATER HA REFERENCES

None

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SYNONYMS

Substance Name -- p-Cresol
CASRN -- 106-44-5
Last Revised -- 08/22/88

106-44-5
p-Cresol
Cresol, para

Enter keywords or Read or Scan or Mail
--quit

>off
Off At 10:40 01/17/91 EST
Time used: 00h 09m connect, 00m 09s CPU, 00m 01s I/O.
D64 DISCONNECTED 00 40 00:00:09:16 687 21

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Summary Page
3.9.2 (RfC)
DATI

Pentachlorophenol; CASRN 87-86-5 (08/01/90)

Health risk assessment information on a chemical is included in IRIS only after a comprehensive review of chronic toxicity data by work groups composed of U.S. EPA scientists from several Program Offices. The summaries presented in Sections I and II represent a consensus reached in the review process. The other sections contain U.S. EPA information which is specific to a particular EPA program and has been subject to review procedures prescribed by that Program Office. The regulatory actions in Section IV may not be based on the most current risk assessment, or may be based on a current, but unreviewed, risk assessment, and may take into account factors other than health effects (e.g., treatment technology). When considering the use of regulatory action data for a particular situation, note the date of the regulatory action, the date of the most recent risk assessment relating to that action, and whether technological factors were considered. Background information and explanations of the methods used to derive the values given in IRIS are provided in the five Background Documents in Service Code 5, which correspond to Sections I through V of the chemical files.

STATUS OF DATA FOR Pentachlorophenol

File On-Line 01/31/87

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	04/01/90
Inhalation RfC Assessment (I.B.)	pending	07/01/90
Carcinogenicity Assessment (II.)	pending	01/01/90
Drinking Water Health Advisories (III.A.)	on-line	08/01/90
U.S. EPA Regulatory Actions (IV.)	on-line	07/01/90
Supplementary Data (V.)	on-line	01/31/87

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_I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

__I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name -- Pentachlorophenol
CASRN -- 87-86-5
Last Revised -- 04/01/90

The Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. 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 Background Document 1 in Service Code 5 for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of compounds which 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 when a review of that evaluation is completed.

<<< Pentachlorophenol >>>

___I.A.1. ORAL RfD SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfD
Liver and kidney pathology	NOAEL: 3 mg/kg/day	100	1	3E-2 mg/kg/day
	LOAEL: 10 mg/kg/day			
Rat Oral Chronic Study				
Schwetz et al., 1978				

*Conversion Factors: none

<<< Pentachlorophenol >>>

___I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

Schwetz, B.A., J.F. Quast, P.A. Keelev, C.G. Humiston and R.J. Kociba. 1978. Results of 2-year toxicity and reproduction studies on pentachlorophenol in rats. In: Pentachlorophenol: Chemistry, Pharmacology and Environmental Toxicology, K.R. Rao, Ed. Plenum Press, NY. p. 301.

Only one chronic study regarding oral exposure (Schwetz et al., 1978) was located in the available literature. Twenty-five rats/sex were administered 1 of 3 doses in the diet. At the 30 mg/kg/day level of treatment, a reduced rate of body weight gain and increased specific gravity of the urine were observed in females. Pigmentation of the liver and kidneys was observed in females exposed at 10 mg/kg/day or higher levels and in males exposed to 30 mg/kg/day. The 3 mg/kg/day level of exposure was reported as a chronic NOAEL.

A number of studies that have investigated the teratogenicity of orally administered pentachlorophenol in rodents are available in the literature. Although these studies (Larsen et al., 1975; Schwetz and Gehring, 1973; Schwetz et al., 1978; Hinkle, 1973) did not reveal teratogenic effects, feto-maternal toxicity was seen at 30 mg/kg/day (Schwetz and Gehring, 1973). Since pentachlorophenol apparently does not cross the placental barrier, the observed fetotoxicity may be a reflection of maternal toxicity (Larsen et al.,

1975). The NOAEL in these studies was concluded to be 3.0 mg/kg/day (U.S. EPA, 1984), which is the same as for the chronic study reported earlier.

<<< Pentachlorophenol >>>

___I.A.3. UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

UF = 100. The 100-fold factor accounts for the expected intra- and inter-species variability to the toxicity of this chemical in lieu of specific data.

MF = 1.

<<< Pentachlorophenol >>>

___I.A.4. ADDITIONAL COMMENTS (ORAL RfD)

None.

<<< Pentachlorophenol >>>

___I.A.5. CONFIDENCE IN THE ORAL RfD

Study: High
Data Base: Medium
RfD: Medium

The confidence in the chosen study is rated high because a moderate number of animals/sex were used in each of three doses, a comprehensive analysis of parameters was conducted, and a reproductive study was also run. Confidence in the supporting data base is rated medium because only one chronic study is available. Other subchronic studies provide adequate but weaker supporting data. The confidence in the RfD is medium. More chronic/reproductive studies are needed to provide a higher confidence in the RfD.

<<< Pentachlorophenol >>>

___I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

U.S. EPA. 1984. Health Effects Assessment for Pentachlorophenol. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC.

Limited Peer Review and Agency-wide Internal Review, 1984.

U.S. EPA. 1985. Drinking Water Criteria Document for Pentachlorophenol. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC.

Two external peer reviews and an Agency internal review.

Agency RfD Work Group Review: 05/20/85

Verification Date: 05/20/85

___I.A.7. EPA CONTACTS (ORAL RfD)

Christopher T. DeRosa / ORD -- (513)569-7534 / FTS 684-7534

Michael L. Dourson / ORD -- (513)569-7544 / FTS 684-7544

__I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

Substance Name -- Pentachlorophenol
CASRN -- 87-86-5

A risk assessment for this substance/agent is under review by an EPA work group.

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_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Pentachlorophenol
CASRN -- 87-86-5

This substance/agent has been evaluated by the U.S. EPA for evidence of human carcinogenic potential. This does not imply that this chemical is necessarily a carcinogen. The evaluation for this chemical is under review by an inter-office Agency work group. A risk assessment summary will be included on IRIS when the review has been completed.

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_III. HEALTH HAZARD ASSESSMENTS FOR VARIED EXPOSURE DURATIONS

__III.A. DRINKING WATER HEALTH ADVISORIES

Substance Name -- Pentachlorophenol
CASRN -- 87-86-5
Last Revised -- 08/01/90

The Office of Drinking Water provides Drinking Water Health Advisories

(HAs) as technical guidance for the protection of public health. HAs are not enforceable Federal standards. HAs are concentrations of a substance in drinking water estimated to have negligible deleterious effects in humans, when ingested, for a specified period of time. Exposure to the substance from other media is considered only in the derivation of the lifetime HA. Given the absence of chemical-specific data, the assumed fraction of total intake from drinking water is 20%. The lifetime HA is calculated from the Drinking Water Equivalent Level (DWEL) which, in turn, is based on the Oral Chronic Reference Dose. Lifetime HAs are not derived for compounds which are potentially carcinogenic for humans because of the difference in assumptions concerning toxic threshold for carcinogenic and noncarcinogenic effects. A more detailed description of the assumptions and methods used in the derivation of HAs is provided in Background Document 3 in Service Code 5.

<<< Pentachlorophenol >>>

___III.A.1. ONE-DAY HEALTH ADVISORY FOR A CHILD

One-day HA -- 1E+0 mg/L

NOAEL -- 10 mg/kg/day
UF -- 100 (allows for interspecies and intrahuman variability with the use of a NOAEL from an animal study)
Assumptions -- 1 L/day water consumption for a 10-kg child

Principal Study -- Nishimura et al., 1982

Increased liver/body weight ratios were observed in male rats after single oral doses of sodium pentachlorophenate at levels greater than 10 mg/kg. The authors described the doses in terms of pentachlorophenol content.

<<< Pentachlorophenol >>>

___III.A.2. TEN-DAY HEALTH ADVISORY FOR A CHILD

Appropriate data for calculating a Ten-day HA are not available. It is recommended that the Longer-term HA for the 10-kg child of 0.30 mg/L be used as the Ten-day HA.

<<< Pentachlorophenol >>>

___III.A.3. LONGER-TERM HEALTH ADVISORY FOR A CHILD

Longer-term (Child) HA -- 3E-1 mg/L

NOAEL -- 3 mg/kg/day
UF -- 100 (allows for interspecies and intrahuman variability with the use of a NOAEL from an animal study)
Assumptions -- 1 L/day water consumption for a 10-kg child

Principal Study -- Johnson et al., 1973

Pentachlorophenol was fed to rats by diet at levels of 3, 10, or 30

mg/kg/day for 90 days. Increased liver and kidney weights were induced at the two higher doses, whereas increased liver and kidney weights were not evident at the 3-mg/kg/day feeding level.

<<< Pentachlorophenol >>>

___III.A.4. LONGER-TERM HEALTH ADVISORY FOR AN ADULT

Longer-term (Adult) HA -- 1.05E+0 mg/L

NOAEL -- 3 mg/kg/day
UF -- 100 (allows for interspecies and intrahuman variability with the use of a NOAEL from an animal study)
Assumptions -- 2 L/day water consumption for a 70-kg adult

Principal Study -- Johnson et al., 1973 (study described in III.A.3.)
<<< Pentachlorophenol >>>

___III.A.5. DRINKING WATER EQUIVALENT LEVEL / LIFETIME HEALTH ADVISORY

DWEL -- 1.05E+0 mg/L
Basis -- Derived from an oral chronic RfD of 3.0E-2 (unrounded); verification date - 05/20/85; Refer to Section I.A. for a discussion of the RfD.
Assumptions -- 2 L/day water consumption for a 70-kg adult

Lifetime Health Advisory -- 2E-1 mg/L
Assumptions -- 20% exposure by drinking water

Principal Study -- Schwetz et al., 1978 (This study was used in the derivation of the oral chronic RfD; see Section I.A.2.)

<<< Pentachlorophenol >>>

___III.A.6. ORGANOLEPTIC PROPERTIES

Odor perception threshold (water) -- 1600 ug/L.

Taste perception threshold (water) -- 30 ug/L.

<<< Pentachlorophenol >>>

___III.A.7. ANALYTICAL METHODS FOR DETECTION IN DRINKING WATER

Determination of pentachlorophenol is by a liquid-liquid extraction gas chromatographic procedure.

<<< Pentachlorophenol >>>

___III.A.8. WATER TREATMENT

Treatment techniques for removal of pentachlorophenol from drinking water pertain predominantly to adsorption. The use of air stripping also has been considered.

<<< Pentachlorophenol >>>

___III.A.9. DOCUMENTATION AND REVIEW OF HAs

U.S. EPA. 1985. Final Draft of the Drinking Water Criteria Document on Endrin. Office of Drinking Water, Washington, DC.

EPA review of HAs in 1985.

Public review of HAs following notification of availability in October, 1985.

Preparation date of this IRIS summary -- 06/17/87

___III.A.10. EPA CONTACTS

Jennifer Orme / ODW -- (202)382-7586 / FTS 382-7586

Edward V. Ohanian / ODW -- (202)382-7571 / FTS 382-7571

__III.B. OTHER ASSESSMENTS

Substance Name -- Pentachlorophenol
CASRN -- 87-86-5

Content to be determined.

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_IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- Pentachlorophenol
CASRN -- 87-86-5
Last Revised -- 07/01/90

EPA risk assessments may be updated as new data are published and as assessment methodologies evolve. Regulatory actions are frequently not updated at the same time. Compare the dates for the regulatory actions in this section with the verification dates for the risk assessments in sections I and II, as this may explain inconsistencies. Also note that some regulatory actions consider factors not related to health risk, such as technical or economic feasibility. Such considerations are indicated for each action. In addition, not all of the regulatory actions listed in this section involve enforceable federal standards. Please direct any questions you may have concerning these regulatory actions to the U.S. EPA contact listed for that

particular action. Users are strongly urged to read the background information on each regulatory action in Background Document 4 in Service Code 5.

<<< Pentachlorophenol >>>

__IV.A. CLEAN AIR ACT (CAA)

No data available

---------<<< Pentachlorophenol >>>---------

__IV.B. SAFE DRINKING WATER ACT (SDWA)

___IV.B.1. MAXIMUM CONTAMINANT LEVEL GOAL (MCLG) for Drinking Water

Value (status) -- 0.22 mg/L (Proposed, 1985)

Considers technological or economic feasibility? -- NO

Discussion -- An MCLG of 0.22 mg/L for pentachlorophenol is proposed based upon a DWEL of 1.1 mg/L and an assumed drinking water contribution of 20%. A DWEL of 1.1 mg/L was calculated from a NOAEL of 3 mg/kg/day for liver and kidney pigmentation and hepatic enzyme activity in rats (24-month feeding study) with an uncertainty factor of 100 and consumption of 2 L of water/per day.

Reference -- 50 FR 46936 Part IV (11/13/85)

EPA Contact -- Criteria and Standards Division, ODW / (202)382-7571 / FTS 382-7571; or Drinking Water Hotline / (800)426-4791

---------<<< Pentachlorophenol >>>---------

__IV.C. CLEAN WATER ACT (CWA)

___IV.C.1. AMBIENT WATER QUALITY CRITERIA, Human Health

Water and Fish Consumption: 1.01E+3 ug/L

Fish Consumption Only: None

Considers technological or economic feasibility? -- NO

Discussion -- The WQC necessary for the protection of public health is 1.01E+3 ug/L. Its basis is a NOAEL of 3 mg/kg in a mammalian study, a safety factor of 100, and an assumption of daily ingestion of 2 L of water and 6.5 g of fish. A WQC of 30.0 ug/L based upon organoleptic effects has also been derived. However, organoleptic endpoints have limited value in setting water

quality standards, since there is no demonstrated relationship between taste/odor effect and adverse health effects.

Reference -- 45 FR 79318 (11/28/80)

EPA Contact -- Criteria and Standards Division, OWRS
(202)475-7315 / FTS 475-7315

<<< Pentachlorophenol >>>

___IV.C.2. AMBIENT WATER QUALITY CRITERIA, Aquatic Organisms

Freshwater:

Acute -- 2.2E+1 ug/L (1 hour average)
Chronic -- 1.3E+1 ug/L (4 day average)

Marine:

Acute -- 1.3E+1 ug/L (1 hour average)
Chronic -- 7.9E+0 ug/L (4 day average)

Considers technological or economic feasibility? -- NO

Discussion -- The toxicity of pentachlorophenol is dependent on the pH of the ambient water. The value given is for a pH of 7.8. A more complete discussion can be found in the reference document.

Reference -- 51 FR 43665 (12/03/86)

EPA Contact -- Criteria and Standards Division, OWRS
(202)475-7315 / FTS 475-7315

---------<<< Pentachlorophenol >>>---------

__IV.D. FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT (FIFRA)

___IV.D.1. PESTICIDE ACTIVE INGREDIENT, Registration Standard

None

<<< Pentachlorophenol >>>

___IV.D.2. PESTICIDE ACTIVE INGREDIENT, Special Review

Action -- Final regulatory action - PD4 (1984)

Considers technological or economic feasibility? -- YES

Summary of regulatory action -- The basis for selection of the final regulatory option is presented in Position Document 4.

Reference -- 52 FR 2282 (01/21/87)

EPA Contact -- Special Review Branch, OPP / (703)557-7400 / FTS 557-7400

---------<<< Pentachlorophenol >>>---------

__IV.E. TOXIC SUBSTANCES CONTROL ACT (TSCA)

No data available

---------<<< Pentachlorophenol >>>---------

__IV.F. RESOURCE CONSERVATION AND RECOVERY ACT (RCRA)

___IV.F.1. RCRA APPENDIX IX, for Ground Water Monitoring

Status -- Listed

Reference -- 52 FR 25942 (07/09/87)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)382-3000 / FTS 382-3000

---------<<< Pentachlorophenol >>>---------

__IV.G. SUPERFUND (CERCLA)

___IV.G.1. REPORTABLE QUANTITY (RQ) for Release into the Environment

Value (status) -- 10 pounds (Proposed, 1987)

Considers technological or economic feasibility? -- NO

Discussion -- The proposed RQ is based on aquatic toxicity as assigned by Section 311(b)(4) of the Clean Water Act (40 CFR 117.3). Available data indicate a 96-hour Median Threshold Limit between 0.2 and 0.6 ppm, corresponding to an RQ of 10 pounds.

Reference -- 52 FR 8140 (03/16/87)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)382-3000 / FTS 382-3000

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V. SUPPLEMENTARY DATA

Substance Name -- Pentachlorophenol
CASRN -- 87-86-5
Last Revised -- 01/31/87

The information contained in this section (subsections A and B) has been extracted from the EPA Chemical Profiles Database, which has been compiled from a number of secondary sources and has not undergone formal Agency review. The complete reference listings for the citations in this section are provided in Service Code 5. The user is urged to read Background Document 5 in Service Code 5 for further information on the sources and limitations of the data presented here.

<<< Pentachlorophenol >>>

V.A. ACUTE HEALTH HAZARD INFORMATION

Toxicity -- Pentachlorophenol is poisonous if swallowed or inhaled (DOT, 1984). It is very toxic: the probable oral lethal dose being (human) 50-500 mg/kg (1 teaspoon to 1 ounce) for a 70 kg person (150 lbs.) (Gosselin et al., 1976). Lethal oral doses in humans have been reported at 29 mg/kg (NIOSH, 1985). It causes lung, liver, and kidney damage, and contact dermatitis (Merck, 1976). Inhalation results in acute poisoning centering in the circulatory system, with accompanying heart failure. Also, visual damage, scotoma, inflammation of conjunctiva, cornea opacity, cornea numbness, and slight pupil dilation are experienced (ACGIH, 1980).

Medical Conditions Generally Aggravated by Exposure -- Kidney and liver diseases (Clayton and Clayton, 1982).

Signs and Symptoms of Exposure -- Ingestion causes increased then decreased respiration, blood pressure, and urinary output; fever; increased bowel action; motor weakness; collapse with convulsions; and death (Merck, 1976). Inhalation of dust and mist causes violent sneezing and coughing (U.S. EPA, 1980). Liquid or solid dermal contact causes smarting of skin and first-degree burns on short exposure; it may cause secondary burns on long exposure (CHRIS, 1978).

---------<<< Pentachlorophenol >>>---------

V.B. PHYSICAL-CHEMICAL PROPERTIES

Chemical Formula --C6HCl5O

Molecular Weight -- 266.35

Boiling Point -- 588F, 309C

Specific Gravity (H2O=1) -- 1.978 at 22C/4C

Vapor Pressure (mmHg) -- 0.0002 at 20C

Melting Point -- 374F, 190C

Vapor Density (AIR=1) -- 9.20

Evaporation Rate (Butyl acetate=1) -- Not Found

Solubility in Water -- 0.002 g/100 mL at 30C

Flash Point [Method Used] -- Not Found

Flammable Limits -- This material may burn but does not ignite readily. Under normal conditions it is not flammable.

Appearance and Odor -- Needle-like crystals (Merck, 1983). Colorless crystals (pure); dark greyish powder or flakes (crude product) (Spencer, 1982). Phenolic odor (Spencer, 1982) and also a very pungent odor when hot (Merck, 1976).

Conditions or Materials to Avoid -- Prolonged heating above 200C produces trace amounts of octachlorodibenzo-para-dioxin (IARC, 1972-1985). Contact with strong oxidizers may cause fires or explosions (NIOSH/OSHA, 1981).

Hazardous Decomposition or Byproducts -- When heated to decomposition, pentachlorophenol emits highly toxic fumes of chlorides (Sax, 1975). Hydrogen chloride, chlorinated phenols, and carbon monoxide may be released upon decomposition (NIOSH/OSHA, 1981).

Use -- Pentachlorophenol is used as a wood preservative; as a soil fumigant for termites; as an herbicide, fungicide, slimicide, and algicide; and as an antibacterial agent in disinfectants and cleaners (SRI, 1983).

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_VI. BIBLIOGRAPHY

Substance Name -- Pentachlorophenol
CASRN -- 87-86-5
Last Revised -- 01/01/90

__VI.A. ORAL RfD REFERENCES

Hinkle, D.K. 1973. Fetotoxic effects of pentachlorophenol in the Golden Syrian Hamster. Toxicol. Appl. Pharmacol. 25: 445.

Larsen, R.V., G.S. Born, W.V. Kessler, S.M. Shaw and D.C. Van Sickle. 1975. Placental transfer and teratology of pentachlorophenol in rats. Environ. Lett. 10: 121-128.

Schwetz, B.A. and P.J. Gehring. 1973. The effect of tetrachlorophenol and pentachlorophenol on rat embryonal and fetal development. Toxicol. Appl. Pharmacol. 25: 455.

Schwetz, B.A., J.F. Quast, P.A. Keelev, C.G. Humiston and R.J. Kociba. 1978. Results of 2-year toxicity and reproduction studies on pentachlorophenol in rats. In: Pentachlorophenol: Chemistry, Pharmacology and Environmental Toxicology, K.R. Rao, Ed. Plenum Press, NY. p. 301.

U.S. EPA. 1984. Health Effects Assessment for Pentachlorophenol. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washiington, DC.

U.S. EPA. 1985. Drinking Water Criteria Document for Pentachlorophenol. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC.

---------<<< Pentachlorophenol >>>---------

__VI.B. INHALATION RfD REFERENCES

None

---------<<< Pentachlorophenol >>>---------

__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

None

---------<<< Pentachlorophenol >>>---------

__VI.D. DRINKING WATER HA REFERENCES

Nishimura, H., N. Nishimura and H. Oshima. 1982. Effects of pentachlorophenol on the levels of hepatic glycogen. Sangyo Isaku. 24(4):398-399.

Johnson, R.L., P.J. Gehring, R.J. Kociba and B.A. Schwetz. 1973. Chlorinated dibenzodioxins and pentachlorophenol. Environ. Health Perspect., Exp. Issue No. 5, September, 1973. p. 171.

Schwetz, B.A., J.F. Quast, P.A. Keelev, C.G. Humiston and R.J. Kociba. 1978. Results of 2-year toxicity and reproduction studies on pentachlorophenol in

rats. In: Pentachlorophenol: Chemistry, Pharmacology and Environmental Toxicology, K.R. Rao, Ed. Plenum Press, NY. p. 301.

U.S. EPA. 1985. Drinking Water Criteria Document for Endrin. Office of Drinking Water, Washington, DC. (Final Draft)

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SYNONYMS

Substance Name -- Pentachlorophenol
CASRN -- 87-86-5
Last Revised -- / /

87-86-5
Chem-Tol
Chlorophen
Cryptogil OL
Dowcide 7
Dowicide EC-7
DP-2, technical
Durotox
EP 30
Fungifen
Glazd penta
Grundier arbezol
1-Hydroxy- 2,3,4,5,6-pentachlorobenzene
Lauxtol
Lauxtol A
Liroprem
NCI-C54933
NCI-C55378
NCI-C55389
NCI-C56655
PCP
Penchlorol
Penta
Pentachloorfenol
Pentachlorofenol
Pentachlorofenolo
Pentachlorophenate
Pentachlorophenol
2,3,4,5,6-Pentachlorophenol.
Pentachlorphenol
Pentaclorofenolo
Pentacon
Penta-Kil
Pentasol
Penwar
Peratox
Permacide

Permagard
Permasan
Permatox
Permatox dp-2
Permatox penta
Permite
Phenol, pentachloro-
Preventol P
Priltox
Santobrite
Santophen
Santophen 20
Sinituho
Term-i-trol
WLN: QR BG CG DG EG FG

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Searching - Please wait...
1 Occurrences...

Enter keywords or Read or Scan or Mail
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Pentachlorophenol; CASRN 87-86-5 (03/01/91)

Health risk assessment information on a chemical is included in IRIS only after a comprehensive review of chronic toxicity data by work groups composed of U.S. EPA scientists from several Program Offices. The summaries presented in Sections I and II represent a consensus reached in the review process. The other sections contain U.S. EPA information which is specific to a particular EPA program and has been subject to review procedures prescribed by that Program Office. The regulatory actions in Section IV may not be based on the most current risk assessment, or may be based on a current, but unreviewed, risk assessment, and may take into account factors other than health effects (e.g., treatment technology). When considering the use of regulatory action data for a particular situation, note the date of the regulatory action, the date of the most recent risk assessment relating to that action, and whether technological factors were considered. Background information and explanations of the methods used to derive the values given in IRIS are provided in the five Background Documents in Service Code 5, which correspond to Sections I through V of the chemical files.

STATUS OF DATA FOR Pentachlorophenol

File On-Line 01/31/87

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	04/01/90
Inhalation RfC Assessment (I.B.)	pending	
Carcinogenicity Assessment (II.)	on-line	03/01/91
Drinking Water Health Advisories (III.A.)	on-line	08/01/90
U.S. EPA Regulatory Actions (IV.)	on-line	07/01/90
Supplementary Data (V.)	on-line	01/31/87

I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name -- Pentachlorophenol
CASRN -- 87-86-5
Last Revised -- 04/01/90

The Reference Dose (RfD) is based on the assumption that thresholds exist for

certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. 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 Background Document 1 in Service Code 5 for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of compounds which 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 when a review of that evaluation is completed.

<<< Pentachlorophenol >>>

___I.A.1. ORAL RfD SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfD
Liver and kidney pathology	NOAEL: 3 mg/kg/day	100	1	3E-2 mg/kg/day
	LOAEL: 10 mg/kg/day			
Rat Oral Chronic Study				
Schwetz et al., 1978				

*Conversion Factors: none

<<< Pentachlorophenol >>>

___I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

Schwetz, B.A., J.F. Quast, P.A. Keelev, C.G. Humiston and R.J. Kociba. 1978. Results of 2-year toxicity and reproduction studies on pentachlorophenol in rats. In: Pentachlorophenol: Chemistry, Pharmacology and Environmental Toxicology, K.R. Rao, Ed. Plenum Press, NY. p. 301.

Only one chronic study regarding oral exposure (Schwetz et al., 1978) was located in the available literature. Twenty-five rats/sex were administered 1 of 3 doses in the diet. At the 30 mg/kg/day level of treatment, a reduced rate of body weight gain and increased specific gravity of the urine were observed in females. Pigmentation of the liver and kidneys was observed in females exposed at 10 mg/kg/day or higher levels and in males exposed to 30 mg/kg/day. The 3 mg/kg/day level of exposure was reported as a chronic NOAEL.

A number of studies that have investigated the teratogenicity of orally administered pentachlorophenol in rodents are available in the literature. Although these studies (Larsen et al., 1975; Schwetz and Gehring, 1973; Schwetz et al., 1978; Hinkle, 1973) did not reveal teratogenic effects, feto-maternal toxicity was seen at 30 mg/kg/day (Schwetz and Gehring, 1973). Since pentachlorophenol apparently does not cross the placental barrier, the observed fetotoxicity may be a reflection of maternal toxicity (Larsen et al., 1975). The NOAEL in these studies was concluded to be 3.0 mg/kg/day (U.S.

EPA, 1984), which is the same as for the chronic study reported earlier.

<<< Pentachlorophenol >>>

___I.A.3. UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

UF = 100. The 100-fold factor accounts for the expected intra- and inter-species variability to the toxicity of this chemical in lieu of specific data.

MF = 1.

<<< Pentachlorophenol >>>

___I.A.4. ADDITIONAL COMMENTS (ORAL RfD)

None.

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___I.A.5. CONFIDENCE IN THE ORAL RfD

Study: High
Data Base: Medium
RfD: Medium

The confidence in the chosen study is rated high because a moderate number of animals/sex were used in each of three doses, a comprehensive analysis of parameters was conducted, and a reproductive study was also run. Confidence in the supporting data base is rated medium because only one chronic study is available. Other subchronic studies provide adequate but weaker supporting data. The confidence in the RfD is medium. More chronic/reproductive studies are needed to provide a higher confidence in the RfD.

<<< Pentachlorophenol >>>

___I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

U.S. EPA. 1984. Health Effects Assessment for Pentachlorophenol. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC.

Limited Peer Review and Agency-wide Internal Review, 1984.

U.S. EPA. 1985. Drinking Water Criteria Document for Pentachlorophenol. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC.

Two external peer reviews and an Agency internal review.

Agency RfD Work Group Review: 05/20/85

Verification Date: 05/20/85

___I.A.7. EPA CONTACTS (ORAL RfD)

Christopher T. DeRosa / ORD -- (513)569-7534 / FTS 684-7534

Michael L. Dourson / ORD -- (513)569-7544 / FTS 684-7544

__I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

Substance Name -- Pentachlorophenol
CASRN -- 87-86-5

A risk assessment for this substance/agent is under review by an EPA work group.

_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Pentachlorophenol
CASRN -- 87-86-5
Last Revised -- 03/01/91

Section II provides information on three aspects of the carcinogenic risk assessment for the agent in question; the U.S. EPA classification, and quantitative estimates of risk from oral exposure and from inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen. 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. Background Document 2 (Service Code 5) provides details on the rationale and methods used to derive the carcinogenicity values found in IRIS. Users are referred to Section I for information on long-term toxic effects other than carcinogenicity.

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__II.A. EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

___II.A.1. WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification -- B2; probable human carcinogen

Basis -- The classification is based on inadequate human data and sufficient evidence of carcinogenicity in animals: statistically significant increases in the incidences of multiple biologically significant tumor types (hepatocellular adenomas and carcinomas, adrenal medulla pheochromocytomas and malignant pheochromocytomas, and/or hemangiosarcomas and hemangiomas) in one or both sexes of B6C3F1 mice using two different preparations of pentachlorophenol (PeCP). In addition, a high incidence of two uncommon tumors (adrenal medulla pheochromocytomas and hemangiomas/hemangiosarcomas) was observed with both preparations. This classification is supported by mutagenicity data, which provides some indication that PeCP has clastogenic potential.

<<< Pentachlorophenol >>>

___II.A.2. HUMAN CARCINOGENICITY DATA

Inadequate. Gilbert et al. (1990) attempted to study the effects of exposure to PeCP and other chemical preservatives among a cohort of 182 men employed in the wood treating industry in Hawaii. The study included both current and former workers who had experienced a minimum of 3 months of continuous employment treating wood between 1960 and November 1981. The first part of the study consisted of a cross-sectional clinical assessment of 88 workers (66 current, 22 former) and 58 nonexposed men employed in other occupations. Significantly elevated levels of urinary PeCP were found among the wood treaters but this was not related to any morbidity or mortality endpoint.

In part two of the study, the authors attempted to compare the mortality experience of the cohort with that expected in Hawaiian males of the same age. Only deaths that occurred in Hawaii were ascertained. Six deaths were observed compared with eight expected. Overall, the authors concluded that their results do not suggest any clinically significant adverse health effects nor any increased cancer morbidity or mortality from exposure to PeCP and other wood preserving chemicals. These conclusions must be seriously questioned based on the following: inadequate detail of selection for participation, particularly among the 58 unexposed "controls"; only 50% of eligible workers participated in the clinical portion which creates the potential for selection bias; employment eligibility criteria were different for current versus former workers; the clinical examiner was not blinded as to the exposure status of participants which raises questions about the presence of observation bias; the clinical data were presented and analyzed in a nonstandard way; no details are given about methods used to compute mortality "rates"; and, failure to ascertain deaths occurring outside of Hawaii. With over 30% of the original cohort apparently lost to follow-up, the study is of questionable validity. It cannot be used as evidence of no effect of the exposures but instead must be viewed as uninformative.

<<< Pentachlorophenol >>>

___II.A.3. ANIMAL CARCINOGENICITY DATA

Sufficient. Two different 90% pure preparations of PeCP were tested in

2-year bioassays in B6C3F1 mice (NTP, 1989). Typical impurities present in both preparations included tri- and tetrachlorophenol, hexachlorobenzene, polychlorinated dibenzo-p-dioxins, and polychlorinated dibenzofurans. Technical grade PeCP (TG-PeCP) is a composite that consisted of equal proportions of product from Monsanto, Reichold and Vulcan. These specific products are no longer being produced. The second 90% pure preparation of PeCP, EC-7 PeCP, differed from TG-PeCP in the level and nature of impurities present (e.g., EC-7 PeCP contained lower levels of dioxins and dibenzofurans). TG-PeCP was administered daily in the feed at dose levels of 0, 100, and 200 ppm to groups of 50 male and 50 female B6C3F1 mice for 2 years. The average doses of TG-PeCP were approximately 17-18 or 35 mg/kg for males and females, respectively. Two groups of control mice (35/sex) were fed basal diets. Survival of the mice did not appear to be affected by exposure to TG-PeCP at any dose level tested. However, it should be noted that survival of the male control mice (12/35) was low compared with historical control values. The early deaths were found to be due to urinary tract infections resulting from injuries sustained during fighting among the group-housed control male mice. After month 16 of the study, the male mice were singly housed to reduce the incidence of fighting and consequent high mortality. The incidences of hepatocellular adenomas and/or carcinomas were significantly increased in male mice exposed to TG-PeCP when compared with controls; the incidences were 7/32, 26/47 and 37/48 in control, low-dose and high-dose male mice, respectively. The incidences of benign and malignant pheochromocytomas of the adrenal medulla were also significantly greater in dosed male mice than in controls; the incidences were 0/31 in controls, 10/45 in low-dose animals and 23/45 in the high-dose animals. There was no significant increase in the numbers of liver tumors or pheochromocytomas in female mice exposed to TG-PeCP. However, the nonsignificant increase in liver tumors in TG-PeCP exposed females was considered biologically significant. TG-PeCP- and EC-7 PeCP-exposed females showed comparable responses in the 100- and 200-ppm dose groups with a marked increase observed only at 600 ppm in the EC-7 PeCP females. The liver tumor incidences for TG-PeCP exposed females was 3/33, 9/49 and 9/50, respectively. Vascular tumors (hemangiomas and/or hemangiosarcomas) were observed in female mice but not in male mice. Incidences of the hemangiosarcoma tumors were statistically significantly increased when compared to controls and all were malignant (0/30, 3/48, 6/46 in the control, low-dose and high-dose females, respectively).

EC-7 PeCP was administered daily in the feed at dose levels of 0, 100, 200, and 600 ppm (NTP, 1989). The average daily doses of EC-7 PeCP were approximately 17-18, 34-37, and 114-118 mg/kg, for the low-, mid-, and high-dose groups, respectively. Two groups of control mice (35/sex) were fed basal diets. Survival did not appear to be affected by exposure to EC-7 PeCP at any of the dose levels tested. The incidences of hepatocellular adenomas and/or carcinomas were significantly increased in dosed male mice exposed to EC-7 PeCP when compared with controls (6/35, 19/48, 21/48, 34/49 in the control, low-, mid-, and high-dose males, respectively). The incidences of benign and malignant pheochromocytomas of the adrenal medulla in males were also significantly greater in treated males than in the controls (1/34, 4/48, 21/48, 45/49 in the control, low-, mid-, and high-dose males, respectively). There was a significant increase in liver tumors (adenomas and/or carcinomas) (1/34, 4/50, 6/49 and 31/48 in the control, low-, mid-, and high-dose females, respectively) and benign and malignant pheochromocytomas in female mice exposed to EC-7 PeCP at the high-dose only (0/35, 2/49, 2/46, 38/49 in the

control, low-, mid-, and high-dose females, respectively). Vascular tumors (hemangiomas and/or hemangiosarcomas) were observed in female mice but not in male mice. The incidence of these latter tumors was statistically significantly elevated in the high-dose group when compared with controls and all but one of the tumors was malignant (0/34, 1/50, 3/48, 9/47 in the control, low-, mid-, and high-dose females, respectively).

In a study reported by BRL (1968) and Innes et al. (1969), 18 male and 18 female crossbred mice were administered 46.4 mg/kg EC-7 PeCP in gelatin by gavage on days 7 through 28 after birth, followed by administration of 130 ppm (17 mg/kg/day) EC-7 PeCP in the diet for 18 months. It is not possible to ascertain whether the EC-7 PeCP used in this study is the same as the EC-7 used in the NTP (1989) study, since the level and nature of the impurities present in the preparation were not reported by Innes or BRL. Groups of mice from each strain served as negative or vehicle controls. Results indicated that there was no difference between the incidence of tumors in the PeCP-treated group and the control groups. Only tumor incidences were reported, so it is not known what other toxic effects (if any) may have occurred. This study is limited for drawing conclusions concerning the carcinogenicity of PeCP, however, because only one dose level was used. Furthermore, an insufficient number of animals (according to current guidelines) was studied.

In a chronic oral study on a different species conducted by Schwetz et al. (1978), groups of 25 Sprague-Dawley rats/sex were fed diets of 0, 8, 23, 77, or 231 ppm PeCP for 22 (for male) or 24 (for female) months (equivalent to 1, 3, 10, or 30 mg PeCP/kg/day). The PeCP preparation used in this study was reported to be 90% pure, and representative of the commercially available Dowicide EC-7 PeCP used in the NTP (1989) study. Results from the experiment indicated that in the high-dose group a reduced rate of body weight gain (i.e., a 12% lower mean monthly body weight during the last 12 months of the study) and an increased specific gravity of the urine were observed in females. Pigmentation of the liver and kidneys was observed in females exposed at 10 mg/kg/day or higher levels and in males exposed to 30 mg/kg/day. There was no significant increase in tumor incidence as compared with controls. A slight increase in pheochromocytomas of the adrenal medulla was noted at the lower dose levels. Survival was reported to be unaffected by treatment. Since the high dose (30 mg/kg/day) elicited signs of only mild toxicity, NTP suggested that the MTD had been reached but not exceeded in this study.

Catilina et al. (1981) also found no evidence of carcinogenicity in Wistar rats following subcutaneous administration of purified and technical grades of PeCP (6 mg/kg/dose). Test compounds were administered 3 times/week for 40 weeks followed by a 3-month post-treatment observation period. The use of only one dose, the use of an inappropriate route of administration, the relatively short exposure time, and excessive mortality limit the usefulness of this study for drawing conclusions concerning the carcinogenicity of PeCP.

In another study, Boutwell and Bosch (1959) applied a 20% solution of commercial grade PeCP in benzene to the shaved skin of Sutter mice twice weekly for 13 weeks following an initial exposure with 0.3% DMBA in benzene. Because of the dose level, frequency and duration of exposure in this study, only limited conclusions concerning the effectiveness of PeCP as a complete carcinogen can be made; these results, however, are sufficient to conclude

that PeCP was not a tumor promoter in this assay.

<<< Pentachlorophenol >>>

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Results from cytogenetic studies provide evidence for the clastogenic potential of PeCP. In cytogenicity studies with cultured CHO cells, TG-PeCP produced an increase in chromosomal aberrations in the presence but not the absence of S9 hepatic homogenate activation. Conversely, SCEs were induced only in the absence of S9 hepatic homogenate (NTP, 1989).

---------<<< Pentachlorophenol >>>---------

__II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

___II.B.1. SUMMARY OF RISK ESTIMATES

Oral Slope Factor -- 1.2E-1 per (mg/kg)/day

Drinking Water Unit Risk -- 3E-6 per (ug/L)

Extrapolation Method -- Linearized multistage procedure

Drinking Water Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	3E+1 ug/L
E-5 (1 in 100,000)	3E+0 ug/L
E-6 (1 in 1,000,000)	3E-1 ug/L

<<< Pentachlorophenol >>>

___II.B.2. DOSE-RESPONSE DATA (CARCINOGENICITY, ORAL EXPOSURE)

Tumor Type -- hepatocellular adenoma/carcinoma, pheochromocytoma/malignant pheochromocytoma, hemangiosarcoma/hemangioma (pooled incidence)
Test Animals -- mouse/B6C3F1, female
Route -- oral (in feed)
Reference -- NTP, 1989

---- Dose -----			
Administered (ppm)	(mg/kg/day)	Human Equivalent (mg/kg/day)	Pooled Hepatocellular and Hemangiosarcoma Tumor Incidence

Technical grade pentachlorophenol

0	0	0	5/31
100	17	1.4	12/48
200	35	2.7	15/46

			Pooled Hepatocellular, Hemangiosarcoma and Pheochromocytoma Tumor Incidence
Dowicide EC-7 pentachlorophenol			
0	0	0	1/34
100	17	1.3	6/49
200	34	2.7	9/46
600	114	8.7	42/49

<<< Pentachlorophenol >>>

___II.B.3. ADDITIONAL COMMENTS (CARCINOGENICITY, ORAL EXPOSURE)

Two different pentachlorophenol preparations induced liver tumors, pheochromocytomas and hemangiosarcomas in female mice and liver tumors and pheochromocytomas in male mice. All three tumor types are considered related to the administration of pentachlorophenol. The hemangiosarcomas, however, are considered to be the tumor of greatest concern; the EPA Science Advisory Board found that "these tumors were related to the administration of the pentachlorophenol formulations tested, occurred in a dose-response manner in the treated animals, and are morphologically related to known fatal human cancers that are induced by xenobiotics." Hemangiosarcomas were found only in female mice. To give preference to the data on hemangiosarcomas and because some male groups experienced significant early loss, only the female mice are used in the quantitative risk assessment.

In developing these estimates, benign and malignant tumors are combined; the liver tumors and pheochromocytomas were mostly benign. The pooled incidence counts animals with any of the three tumor types. Animals dying before the first tumor was observed are not considered to be at risk and are not included in the totals. Equivalent human doses are calculated using a surface-area adjustment. There are no pharmacokinetic data on pentachlorophenol. The slope factor is calculated as the geometric mean of the slope factors for each pentachlorophenol preparation.

<<< Pentachlorophenol >>>

___II.B.4. DISCUSSION OF CONFIDENCE (CARCINOGENICITY, ORAL EXPOSURE)

For purposes of comparison, a slope factor of 0.05 can be derived from the incidence of hemangiosarcomas alone. Also for comparison, a slope factor of 0.5 can be derived from the pooled incidence of liver tumors and pheochromocytomas in male B6C3F1 mice.

The carcinogenicity assessment is based on results in a single animal species.

---------<<< Pentachlorophenol >>>---------

__II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

Not available.

---------<<< Pentachlorophenol >>>---------

__II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

___II.D.1. EPA DOCUMENTATION

Source Document -- This assessment is not presented in any existing U.S. EPA document.

<<< Pentachlorophenol >>>

___II.D.2. REVIEW (CARCINOGENICITY ASSESSMENT)

Agency Work Group Review: 11/10/87, 09/22/88, 10/19/88, 12/06/89, 02/08/90, 08/02/90

Verification Date: 08/02/90

___II.D.3. U.S. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

James Cogliano / ORD -- (202)245-3843 / FTS 245-3843

Rita Schoeny / ORD -- (513)569-7544 / FTS 684-7544

_III. HEALTH HAZARD ASSESSMENTS FOR VARIED EXPOSURE DURATIONS

__III.A. DRINKING WATER HEALTH ADVISORIES

Substance Name -- Pentachlorophenol
CASRN -- 87-86-5
Last Revised -- 08/01/90

The Office of Drinking Water provides Drinking Water Health Advisories (HAs) as technical guidance for the protection of public health. HAs are

not enforceable Federal standards. HAs are concentrations of a substance in drinking water estimated to have negligible deleterious effects in humans, when ingested, for a specified period of time. Exposure to the substance from other media is considered only in the derivation of the lifetime HA. Given the absence of chemical-specific data, the assumed fraction of total intake from drinking water is 20%. The lifetime HA is calculated from the Drinking Water Equivalent Level (DWEL) which, in turn, is based on the Oral Chronic Reference Dose. Lifetime HAs are not derived for compounds which are potentially carcinogenic for humans because of the difference in assumptions concerning toxic threshold for carcinogenic and noncarcinogenic effects. A more detailed description of the assumptions and methods used in the derivation of HAs is provided in Background Document 3 in Service Code 5.

<<< Pentachlorophenol >>>

___III.A.1. ONE-DAY HEALTH ADVISORY FOR A CHILD

One-day HA -- 1E+0 mg/L

NOAEL -- 10 mg/kg/day
UF -- 100 (allows for interspecies and intrahuman variability with the use of a NOAEL from an animal study)
Assumptions -- 1 L/day water consumption for a 10-kg child

Principal Study -- Nishimura et al., 1982

Increased liver/body weight ratios were observed in male rats after single oral doses of sodium pentachlorophenate at levels greater than 10 mg/kg. The authors described the doses in terms of pentachlorophenol content.

<<< Pentachlorophenol >>>

___III.A.2. TEN-DAY HEALTH ADVISORY FOR A CHILD

Appropriate data for calculating a Ten-day HA are not available. It is recommended that the Longer-term HA for the 10-kg child of 0.30 mg/L be used as the Ten-day HA.

<<< Pentachlorophenol >>>

___III.A.3. LONGER-TERM HEALTH ADVISORY FOR A CHILD

Longer-term (Child) HA -- 3E-1 mg/L

NOAEL -- 3 mg/kg/day
UF -- 100 (allows for interspecies and intrahuman variability with the use of a NOAEL from an animal study)
Assumptions -- 1 L/day water consumption for a 10-kg child

Principal Study -- Johnson et al., 1973

Pentachlorophenol was fed to rats by diet at levels of 3, 10, or 30 mg/kg/day for 90 days. Increased liver and kidney weights were induced at the

two higher doses, whereas increased liver and kidney weights were not evident at the 3-mg/kg/day feeding level.

<<< Pentachlorophenol >>>

___III.A.4. LONGER-TERM HEALTH ADVISORY FOR AN ADULT

Longer-term (Adult) HA -- 1.05E+0 mg/L

NOAEL -- 3 mg/kg/day
UF -- 100 (allows for interspecies and intrahuman variability with the use of a NOAEL from an animal study)
Assumptions -- 2 L/day water consumption for a 70-kg adult

Principal Study -- Johnson et al., 1973 (study described in III.A.3.)

<<< Pentachlorophenol >>>

___III.A.5. DRINKING WATER EQUIVALENT LEVEL / LIFETIME HEALTH ADVISORY

DWEL -- 1.05E+0 mg/L
Basis -- Derived from an oral chronic RfD of 3.0E-2 (unrounded); verification date - 05/20/85; Refer to Section I.A. for a discussion of the RfD.
Assumptions -- 2 L/day water consumption for a 70-kg adult

Lifetime Health Advisory -- 2E-1 mg/L
Assumptions -- 20% exposure by drinking water

Principal Study -- Schwetz et al., 1978 (This study was used in the derivation of the oral chronic RfD; see Section I.A.2.)

<<< Pentachlorophenol >>>

___III.A.6. ORGANOLEPTIC PROPERTIES

Odor perception threshold (water) -- 1600 ug/L.

Taste perception threshold (water) -- 30 ug/L.

<<< Pentachlorophenol >>>

___III.A.7. ANALYTICAL METHODS FOR DETECTION IN DRINKING WATER

Determination of pentachlorophenol is by a liquid-liquid extraction gas chromatographic procedure.

<<< Pentachlorophenol >>>

___III.A.8. WATER TREATMENT

Treatment techniques for removal of pentachlorophenol from drinking water pertain predominantly to adsorption. The use of air stripping also has been considered.

<<< Pentachlorophenol >>>

___III.A.9. DOCUMENTATION AND REVIEW OF HAs

U.S. EPA. 1985. Final Draft of the Drinking Water Criteria Document on Endrin. Office of Drinking Water, Washington, DC.

EPA review of HAs in 1985.

Public review of HAs following notification of availability in October, 1985.

Preparation date of this IRIS summary -- 06/17/87

___III.A.10. EPA CONTACTS

Jennifer Orme / ODW -- (202)382-7586 / FTS 382-7586

Edward V. Ohanian / ODW -- (202)382-7571 / FTS 382-7571

__III.B. OTHER ASSESSMENTS

Substance Name -- Pentachlorophenol
CASRN -- 87-86-5

Content to be determined.

_IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- Pentachlorophenol
CASRN -- 87-86-5
Last Revised -- 07/01/90

EPA risk assessments may be updated as new data are published and as assessment methodologies evolve. Regulatory actions are frequently not updated at the same time. Compare the dates for the regulatory actions in this section with the verification dates for the risk assessments in sections I and II, as this may explain inconsistencies. Also note that some regulatory actions consider factors not related to health risk, such as technical or economic feasibility. Such considerations are indicated for each action. In addition, not all of the regulatory actions listed in this section involve enforceable federal standards. Please direct any questions you may have concerning these regulatory actions to the U.S. EPA contact listed for that

particular action. Users are strongly urged to read the background information on each regulatory action in Background Document 4 in Service Code 5.

<<< Pentachlorophenol >>>

__IV.A. CLEAN AIR ACT (CAA)

No data available

---------<<< Pentachlorophenol >>>---------

__IV.B. SAFE DRINKING WATER ACT (SDWA)

___IV.B.1. MAXIMUM CONTAMINANT LEVEL GOAL (MCLG) for Drinking Water

Value (status) -- 0.22 mg/L (Proposed, 1985)

Considers technological or economic feasibility? -- NO

Discussion -- An MCLG of 0.22 mg/L for pentachlorophenol is proposed based upon a DWEL of 1.1 mg/L and an assumed drinking water contribution of 20%. A DWEL of 1.1 mg/L was calculated from a NOAEL of 3 mg/kg/day for liver and kidney pigmentation and hepatic enzyme activity in rats (24-month feeding study) with an uncertainty factor of 100 and consumption of 2 L of water/per day.

Reference -- 50 FR 46936 Part IV (11/13/85)

EPA Contact -- Criteria and Standards Division, ODW / (202)382-7571 / FTS 382-7571; or Drinking Water Hotline / (800)426-4791

---------<<< Pentachlorophenol >>>---------

__IV.C. CLEAN WATER ACT (CWA)

___IV.C.1. AMBIENT WATER QUALITY CRITERIA, Human Health

Water and Fish Consumption: 1.01E+3 ug/L

Fish Consumption Only: None

Considers technological or economic feasibility? -- NO

Discussion -- The WQC necessary for the protection of public health is 1.01E+3 ug/L. Its basis is a NOAEL of 3 mg/kg in a mammalian study, a safety factor of 100, and an assumption of daily ingestion of 2 L of water and 6.5 g of fish. A WQC of 30.0 ug/L based upon organoleptic effects has also been derived. However, organoleptic endpoints have limited value in setting water

quality standards, since there is no demonstrated relationship between taste/odor effect and adverse health effects.

Reference -- 45 FR 79318 (11/28/80)

EPA Contact -- Criteria and Standards Division, OWRS
(202)475-7315 / FTS 475-7315

<<< Pentachlorophenol >>>

___IV.C.2. AMBIENT WATER QUALITY CRITERIA, Aquatic Organisms

Freshwater:

Acute -- 2.2E+1 ug/L (1 hour average)
Chronic -- 1.3E+1 ug/L (4 day average)

Marine:

Acute -- 1.3E+1 ug/L (1 hour average)
Chronic -- 7.9E+0 ug/L (4 day average)

Considers technological or economic feasibility? -- NO

Discussion -- The toxicity of pentachlorophenol is dependent on the pH of the ambient water. The value given is for a pH of 7.8. A more complete discussion can be found in the reference document.

Reference -- 51 FR 43665 (12/03/86)

EPA Contact -- Criteria and Standards Division, OWRS
(202)475-7315 / FTS 475-7315

---------<<< Pentachlorophenol >>>---------

__IV.D. FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT (FIFRA)

___IV.D.1. PESTICIDE ACTIVE INGREDIENT, Registration Standard

None

<<< Pentachlorophenol >>>

___IV.D.2. PESTICIDE ACTIVE INGREDIENT, Special Review

Action -- Final regulatory action - PD4 (1984)

Considers technological or economic feasibility? -- YES

Summary of regulatory action -- The basis for selection of the final regulatory option is presented in Position Document 4.

Reference -- 52 FR 2282 (01/21/87)

EPA Contact -- Special Review Branch, OPP / (703)557-7400 / FTS 557-7400

---------<<< Pentachlorophenol >>>---------

__IV.E. TOXIC SUBSTANCES CONTROL ACT (TSCA)

No data available

---------<<< Pentachlorophenol >>>---------

__IV.F. RESOURCE CONSERVATION AND RECOVERY ACT (RCRA)

___IV.F.1. RCRA APPENDIX IX, for Ground Water Monitoring

Status -- Listed

Reference -- 52 FR 25942 (07/09/87)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)382-3000 / FTS 382-3000

---------<<< Pentachlorophenol >>>---------

__IV.G. SUPERFUND (CERCLA)

___IV.G.1. REPORTABLE QUANTITY (RQ) for Release into the Environment

Value (status) -- 10 pounds (Proposed, 1987)

Considers technological or economic feasibility? -- NO

Discussion -- The proposed RQ is based on aquatic toxicity as assigned by Section 311(b)(4) of the Clean Water Act (40 CFR 117.3). Available data indicate a 96-hour Median Threshold Limit between 0.2 and 0.6 ppm, corresponding to an RQ of 10 pounds.

Reference -- 52 FR 8140 (03/16/87)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)382-3000 / FTS 382-3000

_V. SUPPLEMENTARY DATA

Substance Name -- Pentachlorophenol
CASRN -- 87-86-5
Last Revised -- 01/31/87

The information contained in this section (subsections A and B) has been extracted from the EPA Chemical Profiles Database, which has been compiled from a number of secondary sources and has not undergone formal Agency review. The complete reference listings for the citations in this section are provided in Service Code 5. The user is urged to read Background Document 5 in Service Code 5 for further information on the sources and limitations of the data presented here.

<<< Pentachlorophenol >>>

__V.A. ACUTE HEALTH HAZARD INFORMATION

Toxicity -- Pentachlorophenol is poisonous if swallowed or inhaled (DOT, 1984). It is very toxic: the probable oral lethal dose being (human) 50-500 mg/kg (1 teaspoon to 1 ounce) for a 70 kg person (150 lbs.) (Gosselin et al., 1976). Lethal oral doses in humans have been reported at 29 mg/kg (NIOSH, 1985). It causes lung, liver, and kidney damage, and contact dermatitis (Merck, 1976). Inhalation results in acute poisoning centering in the circulatory system, with accompanying heart failure. Also, visual damage, scotoma, inflammation of conjunctiva, cornea opacity, cornea numbness, and slight pupil dilation are experienced (ACGIH, 1980).

Medical Conditions Generally Aggravated by Exposure -- Kidney and liver diseases (Clayton and Clayton, 1982).

Signs and Symptoms of Exposure -- Ingestion causes increased then decreased respiration, blood pressure, and urinary output; fever; increased bowel action; motor weakness; collapse with convulsions; and death (Merck, 1976). Inhalation of dust and mist causes violent sneezing and coughing (U.S. EPA, 1980). Liquid or solid dermal contact causes smarting of skin and first-degree burns on short exposure; it may cause secondary burns on long exposure (CHRIS, 1978).

---------<<< Pentachlorophenol >>>---------

__V.B. PHYSICAL-CHEMICAL PROPERTIES

Chemical Formula --C6HCl5O

Molecular Weight -- 266.35

Boiling Point -- 588F, 309C

Specific Gravity (H2O=1) -- 1.978 at 22C/4C

Vapor Pressure (mmHg) -- 0.0002 at 20C

Melting Point -- 374F, 190C

Vapor Density (AIR=1) -- 9.20

Evaporation Rate (Butyl acetate=1) -- Not Found

Solubility in Water -- 0.002 g/100 mL at 30C

Flash Point [Method Used] -- Not Found

Flammable Limits -- This material may burn but does not ignite readily. Under normal conditions it is not flammable.

Appearance and Odor -- Needle-like crystals (Merck, 1983). Colorless crystals (pure); dark greyish powder or flakes (crude product) (Spencer, 1982). Phenolic odor (Spencer, 1982) and also a very pungent odor when hot (Merck, 1976).

Conditions or Materials to Avoid -- Prolonged heating above 200C produces trace amounts of octachlorodibenzo-para-dioxin (IARC, 1972-1985). Contact with strong oxidizers may cause fires or explosions (NIOSH/OSHA, 1981).

Hazardous Decomposition or Byproducts -- When heated to decomposition, pentachlorophenol emits highly toxic fumes of chlorides (Sax, 1975). Hydrogen chloride, chlorinated phenols, and carbon monoxide may be released upon decomposition (NIOSH/OSHA, 1981).

Use -- Pentachlorophenol is used as a wood preservative; as a soil fumigant for termites; as an herbicide, fungicide, slimicide, and algicide; and as an antibacterial agent in disinfectants and cleaners (SRI, 1983).

_VI. BIBLIOGRAPHY

Substance Name -- Pentachlorophenol
CASRN -- 87-86-5
Last Revised -- 03/01/91

__VI.A. ORAL RfD REFERENCES

Hinkle, D.K. 1973. Fetotoxic effects of pentachlorophenol in the Golden Syrian Hamster. Toxicol. Appl. Pharmacol. 25: 445.

Larsen, R.V., G.S. Born, W.V. Kessler, S.M. Shaw and D.C. Van Sickle. 1975. Placental transfer and teratology of pentachlorophenol in rats. Environ. Lett. 10: 121-128.

Schwetz, B.A. and P.J. Gehring. 1973. The effect of tetrachlorophenol and pentachlorophenol on rat embryonal and fetal development. Toxicol. Appl. Pharmacol. 25: 455.

Schwetz, B.A., J.F. Quast, P.A. Keelev, C.G. Humiston and R.J. Kociba. 1978. Results of 2-year toxicity and reproduction studies on pentachlorophenol in rats. In: Pentachlorophenol: Chemistry, Pharmacology and Environmental Toxicology, K.R. Rao, Ed. Plenum Press, NY. p. 301.

U.S. EPA. 1984. Health Effects Assessment for Pentachlorophenol. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washiington, DC.

U.S. EPA. 1985. Drinking Water Criteria Document for Pentachlorophenol. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC.

---------<<< Pentachlorophenol >>>---------

__VI.B. INHALATION RfD REFERENCES

None

---------<<< Pentachlorophenol >>>---------

__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

Boutwell, R.K. and D.K. Bosch. 1959. The tumor-promoting action of phenol and related compounds for mouse skin. Cancer Res. 19: 413-424.

BRL (Bionetics Research Laboratories). 1968. Evaluation of the carcinogenic, teratogenic and mutagenic activities of selected pesticides and industrial chemicals, Vol. 1. Carcinogenic Study. Prepared for the National Cancer Institute, Bethesda, MD. NTIS PB-223-159. p. 393.

Catilina, P., A. Chamoux, M.J. Catilina and J. Champeix. 1981. Study of the pathogenic properties of substances used as wood protectives: Pentachlorophenol. Arch. Mal. Prof. Med. Trav. Secur. Soc. 42(6): 334-337. (Fre.)

Gilbert, F., C. Minn, R. Duncan and J. Wilkinson. 1990. Effects of pentachlorophenol and other chemical preservatives on the health of wood-treating workers in Hawaii. Arch. Environ. Contam. Toxicol. 19(4): 603-609.

Innes, J.R.M., B.M. Ulland, M.G. Valerio, et al. 1969. Bioassay of pesticides and industrial chemicals for tumorigenicity in mice. A preliminary

note. J. Natl. Cancer Inst. 42: 1101-1114.

NTP (National Toxicology Program). 1989. Technical Report on the Toxicology and Carcinogenesis Studies of Pentachlorophenol (CAS No. 87-86-5) in B6C3F1 mice (Feed Studies). NTP Tech. Report No. 349. NIH Publ. No. 89-2804.

Schwetz, B.A., J.F. Quast, P.A. Keeler, C.G. Humiston and R.J Kociba. 1978. Results of two-year toxicity and reproduction studies on pentachlorophenol in rats. In: Pentachlorophenol: Chemistry, Pharmacology and Environmental Toxicology, K.R. Rao, Ed. Plenum Press, NY. p. 301-309.

---------<<< Pentachlorophenol >>>---------

__VI.D. DRINKING WATER HA REFERENCES

Nishimura, H., N. Nishimura and H. Oshima. 1982. Effects of pentachlorophenol on the levels of hepatic glycogen. Sangyo Isaku. 24(4):398-399.

Johnson, R.L., P.J. Gehring, R.J. Kociba and B.A. Schwetz. 1973. Chlorinated dibenzodioxins and pentachlorophenol. Environ. Health Perspect., Exp. Issue No. 5, September, 1973. p. 171.

Schwetz, B.A., J.F. Quast, P.A. Keelev, C.G. Humiston and R.J. Kociba. 1978. Results of 2-year toxicity and reproduction studies on pentachlorophenol in rats. In: Pentachlorophenol: Chemistry, Pharmacology and Environmental Toxicology, K.R. Rao, Ed. Plenum Press, NY. p. 301.

U.S. EPA. 1985. Drinking Water Criteria Document for Endrin. Office of Drinking Water, Washington, DC. (Final Draft)

SYNONYMS

Substance Name -- Pentachlorophenol
CASRN -- 87-86-5
Last Revised -- 01/31/87

87-86-5
Chem-Tol
Chlorophen
Cryptogil OL
Dowcide 7
Dowicide EC-7
DP-2, technical
Durotox
EP 30

Fungifen
Glazd penta
Grundier arbezol
1-Hydroxy- 2,3,4,5,6-pentachlorobenzene
Lauxtol
Lauxtol A
Liroprem
NCI-C54933
NCI-C55378
NCI-C55389
NCI-C56655
PCP
Penchlorol
Penta
Pentachloorfenol
Pentachlorofenol
Pentachlorofenolo
Pentachlorophenate
Pentachlorophenol
2,3,4,5,6-Pentachlorophenol.
Pentachlorphenol
Pentaclorofenolo
Pentacon
Penta-Kil
Pentasol
Penwar
Peratox
Permacide
Permagard
Permasan
Permatox
Permatox dp-2
Permatox penta
Permite
Phenol, pentachloro-
Preventol P
Priltox
Santobrite
Santophen
Santophen 20
Sinituho
Term-i-trol
WLN: QR BG CG DG EG FG

Phenol; CASRN 108-95-2 (11/01/90)

Health risk assessment information on a chemical is included in IRIS only after a comprehensive review of chronic toxicity data by work groups composed of U.S. EPA scientists from several Program Offices. The summaries presented in Sections I and II represent a consensus reached in the review process. The other sections contain U.S. EPA information which is specific to a particular EPA program and has been subject to review procedures prescribed by that Program Office. The regulatory actions in Section IV may not be based on the most current risk assessment, or may be based on a current, but unreviewed, risk assessment, and may take into account factors other than health effects (e.g., treatment technology). When considering the use of regulatory action data for a particular situation, note the date of the regulatory action, the date of the most recent risk assessment relating to that action, and whether technological factors were considered. Background information and explanations of the methods used to derive the values given in IRIS are provided in the five Background Documents in Service Code 5, which correspond to Sections I through V of the chemical files.

STATUS OF DATA FOR Phenol

File On-Line 01/31/87

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	02/01/90
Inhalation RfC Assessment (I.B.)	message	07/01/90
Carcinogenicity Assessment (II.)	on-line	11/01/90
Drinking Water Health Advisories (III.A.)	no data	
U.S. EPA Regulatory Actions (IV.)	on-line	06/01/90
Supplementary Data (V.)	on-line	01/31/87

==========

_I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

__I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name -- Phenol
CASRN -- 108-95-2
Last Revised -- 02/01/90

The Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. 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 Background Document 1 in Service Code 5 for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of compounds which 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 when a review of that evaluation is completed.

<<< Phenol >>>

___I.A.1. ORAL RfD SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfD
Reduced fetal body weight in rats	NOAEL: 60 mg/kg/day LOAEL: 120 mg/kg/day	100	1	6E-1 mg/kg/day
Rat Oral Developmental Study				
NTP, 1983				

*Conversion Factors: none

<<< Phenol >>>

___I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

NTP (National Toxicology Program). 1983. Teratologic evaluation of phenol in CD rats and mice. Report prepared by Research Triangle Institute, Research Triangle Park, NC. NTIS PB83-247726. Gov. Rep. Announce. Index. 83(25): 6247.

Developmental effects of phenol were evaluated in timed-pregnant CD rats. Phenol was administered by gavage at 0, 30, 60, and 120 mg/kg/day in distilled water on gestational days 6 to 15. Females were weighed daily during treatment and observed for clinical signs of toxicity. A total of 20 to 22 females/group were confirmed to be pregnant at sacrifice on gestational day 20. Detailed teratological evaluations were conducted at sacrifice. Results of this study did not show any dose-related signs of maternal toxicity or any clinical symptoms of toxicity related to phenol treatment. The number of implantation sites per litter was approximately the same in all groups, as was the number of live fetuses per litter. However, since implantations in this strain take place prior to gestational day 6 (prior to dosing), no relationships between treatment and number of implantation sites can be established. The most important finding, however, was a highly significant

reduction in fetal body weights in the high-dose group. The highest fetal NOAEL in this study was 60 mg/kg/day.

<<< Phenol >>>

___I.A.3. UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

UF = 100. Uncertainty factor included 10 for interspecies extrapolation and 10 for sensitive human population.

MF = 1.

<<< Phenol >>>

___I.A.4. ADDITIONAL COMMENTS (ORAL RfD)

In NCI (1980) rat and mice 90-day subchronic studies, 10 animals/sex/group were exposed to 0, 100, 300, 1000, 3000, or 10,000 ppm phenol in water. Decreased water intake and body weight gain were noted for both sexes of rats and mice and rats exposed to the high dose (780 mg/kg/day for rats and 1700 mg/kg/day for mice). Lower doses of phenol exposure did not cause any adverse effects in either rats or mice (234 and 510 mg/kg/day, respectively). The LOAEL for this study was 10,000 ppm.

In a subchronic oral study (Dow, 1945), 10 rats/group were gavaged 5 days/week with 0, 50, or 100 mg/kg (0, 35.7 or 71.4 mg/kg/day) phenol until 135 or 136 doses were administered. Rats in the high-dose group showed a more marked drop in body weight gain than did other groups, but the group rapidly recovered. Rats in both dosage groups showed some degree of unspecific kidney damage yielding a LOAEL of 50 mg/kg, or 5000 ppm, for this study. This difference between the LOAELs of the NCI (1980) and Dow (1945) studies may be attributed to differences in mode of administration, with the Dow gavage study showing the lower LOAEL (possibly explained as a bolus dosage effect).

The Dow research also indicates that the 100% lethal acute dose of phenol is 700 mg/kg (Dow, 1945). In contrast, in a well-designed dose selection study (NCI, 1980) conducted prior to the 2-year bioassay, all rats exposed to 10,000 ppm (780 mg/kg/day) phenol in the drinking water survived a 90-day exposure period. The Dow (1945) study contained several deficiencies, such as limited sample size, lack of details of pertinent experimental design, incomplete histopathological evaluations and unspecific high mortality rate in control and exposed rats during early stages of the study. Therefore, the Dow (1945) study is not considered the best available study for risk assessment.

Other studies indicate no effects on water consumption and weight gain at phenol concentrations as high as 1600 mg/L (1600 ppm) (Deichmann and Oesper, 1940).

In a chronic drinking water study conducted by NCI (1980), rats (F344) and mice (B6C3F1) were dosed with 0, 2500, and 5000 ppm phenol (rats: 0, 153, 344 mg/kg/day; mice: 0, 313, 500 mg/kg/day) in the drinking water for 103 weeks. All the animals were sacrificed 2 weeks after dosing ceased; detailed histopathological and carcinogenic evaluations of target organs were

conducted. Results of this bioassay indicated a dose-related depression in mean body weight gain in both sexes of mice and rats. Animals exposed to both dose levels of phenol showed a significant drop in water consumption (water consumption in mice was severely depressed) resulting in significant body weight depression in the high-dose animals. This study also reported an increased incidence of chronic kidney inflammation in all dosed female rats and in the 5000-ppm male rats. The incidence of this lesion in females was: 7/50 (control); 13/50 (2500 ppm); 37/50 (5000 ppm), whereas in male rats the incidence was: 37/50 (control); 37/50 (2500 ppm) and 48/50 (5000 ppm). However, historical control data (Armed Forces Institute of Pathology, 1980) in the F344 rat indicated nephropathy that approaches an incidence of 100%. These rats were the same (comparable) age as the rats killed at the completion of this 2-year NCI (1980) study. In the absence of other toxicological parameters, such as mortality, percent survival, clinical signs of toxicity, and morphological alterations in target organs, the reduction in body weight in both high-dose mice and rats could be related to depressed water intake resulting from phenol exposure. Based on the body weight depression in both exposed mice and rats, the LOAELs in mice and rats, respectively, were 313 and 344 mg/kg/day and the NOAEL in rats was 153 mg/kg/day. A NOAEL for mice was not observed.

Heller and Pursell (1938) reported normal growth and reproduction at phenol concentrations up to 5000 mg/L (400 mg/kg/day) in a multi-generation rat reproduction study.

In a mouse developmental toxicity study (NTP, 1983). phenol was administered by gavage at 0, 70, 140, or 280 mg/kg/day on gestational days 6 to 15. At the highest dose, 4/36 mice died; no deaths occurred^Pin any other groups. Average maternal body weight gain and weight gain in survivors also were significantly reduced at the highest dose; significant clinical signs of toxicity (tremors) also were seen at that dose level. As in the rat study, there was a highly significant dose-related for reduced fetal body weight, statistically different from controls at the highest dose level. An increased incidence of cleft palate was also reported at the highest dose level. The highest NOAEL in this study was 140 mg/kg/day.

In an unpublished developmental toxicity study, Kavlock (1987) gavaged SD rats with phenol at doses of 0, 667, and 1000 mg/kg on gestational day 11; the females were allowed to deliver and postnatal weight, viability, and function were evaluated. Pup body weights at weaning was decreased in the 1000 mg/kg/day group; kidney weight decreased only in female pups at weaning (667 and 1000 mg/kg groups). On days 8 and 9 postnatally, pup kidney weights were increased at both dosages of phenol, while urine osmolality was decreased and urine volume was increased at 1000 mg/kg. The most striking findings were limb abnormalities (paralysis and palsy) produced by phenol (667 and 1000 mg/kg groups) that were evident 10-14 days after birth. The LOAEL in this study was 667 mg/kg/day.

In summary, the evaluations of subchronic, chronic and reproductive/ developmental studies indicated that phenol administered to pregnant rats at 120 mg/kg/day caused significant depression in fetal body weights, establishing this endpoint as the critical effect. Therefore, it is inappropriate to use NOAELs of 140 mg/kg/day for mice (NTP, 1983) or 153 mg/kg/day for rats (NCI, 1980). The LOAEL for fetotoxicity was established at

120 mg/kg/day and the highest NOAEL at 60 mg/kg/day (NTP, 1983).

<<< Phenol >>>

___I.A.5. CONFIDENCE IN THE ORAL RfD

Study: Low
Data Base: Medium
RfD: Low

Confidence in the study is low because of the gavage nature of the dose administration. The data base contains several supporting studies (subchronic, chronic, and reproductive/developmental); thus, a medium confidence is recommended. Low-to-medium confidence in the RfD follows.

<<< Phenol >>>

___I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

U.S. EPA. 1985. Health and Environmental Effects Profile for Phenol. Errata, 1986. 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.

Agency RfD Work Group Review: 08/05/85, 10/28/86, 11/16/88, 03/22/89

Verification Date: 11/16/88

___I.A.7. EPA CONTACTS (ORAL RfD)

Harlal Choudhury / ORD -- (513)569-7536 / FTS 684-7536

Christopher DeRosa / ORD -- (513)569-7534 / FTS 684-7534

__I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

Substance Name -- Phenol
CASRN -- 108-95-2

Data for this substance/agent have been reviewed by an EPA work group and have been judged to be inadequate for purposes of quantitative risk assessment.

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_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Phenol
CASRN -- 108-95-2
Last Revised -- 11/01/90

Section II provides information on three aspects of the carcinogenic risk assessment for the agent in question; the U.S. EPA classification, and quantitative estimates of risk from oral exposure and from inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen. 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. Background Document 2 (Service Code 5) provides details on the rationale and methods used to derive the carcinogenicity values found in IRIS. Users are referred to Section I for information on long-term toxic effects other than carcinogenicity.

<<< Phenol >>>

II.A. EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

II.A.1. WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification -- D; not classifiable as to human carcinogencity

Basis -- Based on no human carcinogenicity data and inadequate animal data.

<<< Phenol >>>

II.A.2. HUMAN CARCINOGENICITY DATA

None.

<<< Phenol >>>

II.A.3. ANIMAL CARCINOGENICITY DATA

Inadequate. In carcinogenicity bioassays conducted by the National Cancer Institute (NCI, 1980), B6C3F1 mice (50/sex/dose) and F344 rats (50/sex/dose) were administered analytical grade phenol (approximately 98.5% pure) in the drinking water at concentrations of 0, 2500 or 5000 ppm for 103 weeks. Dose-related decreases in weight gain in treated mice were attributed to decreased water consumption. No other clinical signs of toxicity were observed, and mortality rates (approximately 14%) were comparable between experimental and control groups. Histopathological examination and statistical analyses revealed no phenol-related toxic or carcinogenic effects in mice.

At the end of the study the survival rate of male rats was comparable among the three groups (approximately 52%) and the survival rate among the female rat groups was comparable (approximately 76%). No trends in cancer

incidence were seen when compared with controls, however, low-dose male rats had, by pair-wise comparison, a statistically significant increase in the incidences of pheochromocytomas of the adrenal medulla (13/50, 22/50 and 9/50 in the control, low-, and high-dose groups, respectively), interstitial cell tumors of the testes (42/48, 49/50 and 47/50), and leukemias or lymphomas (18/50, 31/50 and 25/50). There was no significant increase in tumor incidence in any tissue in female rats. Based on a high spontaneous tumor rate in matched controls, comparable survival patterns with no major fall off, and the lack of a positive association between phenol administration and tumor incidence in high-dose male rats, NCI concluded that, under these conditions, phenol was not carcinogenic in mice or rats (NCI, 1980).
<<< Phenol >>>

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Studies indicate that phenol may be a promoter and/or weak skin carcinogen in specially inbred sensitive mouse strains. Boutwell and Bosch (1959) demonstrated that repeated dermal applications of phenol promoted the development of skin papillomas and carcinomas in Sutter, Holtzman, CHF1, and C3H mouse strains exposed to a single dermal application of an initiator, 7,12-dimethylbenz[a]anthracene (DMBA, 75 ug). In this series of studies, groups of 23 to 30 mice/sex were treated twice a week for up to 72 weeks with equivalent volumes of benzene- or acetone-based solutions containing 10% phenol. Housing conditions were not described. Papillomas first appeared at 6 weeks and a 95% response had occurred by week 13; carcinomas first appeared at 19 weeks with a 73% response by week 42. In mice receiving only the 10% phenol treatments (no initiator), 4% of the mice had papillomas at week 12 and 36% had papillomas at week 32. The incidence of carcinomas was not reported. In the same series of studies, groups of 30 female mice/dose received twice-weekly dermal applications of 5, 10 or 20% phenol in benzene after an initial treatment of benzene (control) or benzene with 75 ug DMBA. In the noninitiated groups (those receiving only the dermal phenol applications) the percentage of mice bearing papillomas was 74, 100 and 100% in the 5, 10 and 20% phenol treatment groups, respectively, and in the groups receiving the initial DMBA application, 56, 95 and 90% of the mice bore papillomas in the 5, 10 and 20% treatment groups, respectively. Papillomas occurred in 11% of the mice treated with benzene alone. The percentage of mice bearing carcinomas (between weeks 38 and 40) in the noninitiated groups was 26, 93 and 70% in the 5, 10 and 20% phenol groups. In the groups receiving the initial DMBA application, the percentage of mice bearing carcinomas was 12, 68 and 65% in the 5, 10 and 20% phenol groups. No carcinomas were reported in the group receiving only benzene.

Similar results were obtained by Salaman and Glendenning (1957). "S" strain albino mice (20 mice/group) showed strong tumor-promoting activity after initiation with 0.15% DMBA and subsequent, repeated weekly applications of 5 or 20% phenol (w/v in acetone) for 24 to 32 weeks. At the 20% level, phenol induced ulceration of the skin and had a strong promoting effect on tumor induction. At the 0.5% level, no ulceration was found; phenol had a moderate promoting effect but did not act as an initiator. Housing conditions of the animals were not indicated.

Analytical grade phenol (99.9% pure) (up to 10 mg/plate) was not mutagenic in Salmonella typhumurium strains TA98, TA100, TA1535, TA1537, or TA1538 with

or without addition of rat liver homogenates (Florin et al., 1980; Pool and Lin, 1982; Haworth et al., 1983). However, Gocke et al. (1981) reported that phenol was mutagenic in TA98 with hepatic homogenates. Phenol was not mutagenic in Neurospora crassa (Dickey et al., 1949) and was not positive in the micronucleus test on mouse bone marrow from male and female NMRI mice treated in vivo (Gocke et al., 1981). In a study by Demerec et al. (1951), phenol exhibited mutagenic activity in Escherichia coli but only at highly toxic concentrations (0.1-0.2%).

---------<<< Phenol >>>---------

__II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

None.

---------<<< Phenol >>>---------

__II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

None.

---------<<< Phenol >>>---------

__II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

___II.D.1. EPA DOCUMENTATION

U.S. EPA. 1988. Updated Health Effects Assessment for Phenol. Prepared by the Office of Health and Environment Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

<<< Phenol >>>

___II.D.2. REVIEW (CARCINOGENICITY ASSESSMENT)

The 1988 Health Effects Assessment for Phenol has received Agency review.

Agency Work Group Review: 08/02/89

Verification Date: 08/02/89

___II.D.3. U.S. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

Charli Hiremath / ORD -- (202)382-5725 / FTS 382- 5725

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_III. HEALTH HAZARD ASSESSMENTS FOR VARIED EXPOSURE DURATIONS

__III.A. DRINKING WATER HEALTH ADVISORIES

Substance Name -- Phenol
CASRN -- 108-95-2

Not available at this time.

__III.B. OTHER ASSESSMENTS

Substance Name -- Phenol
CASRN -- 108-95-2

Content to be determined.

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_IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- Phenol
CASRN -- 108-95-2
Last Revised -- 06/01/90

EPA risk assessments may be updated as new data are published and as assessment methodologies evolve. Regulatory actions are frequently not updated at the same time. Compare the dates for the regulatory actions in this section with the verification dates for the risk assessments in sections I and II, as this may explain inconsistencies. Also note that some regulatory actions consider factors not related to health risk, such as technical or economic feasibility. Such considerations are indicated for each action. In addition, not all of the regulatory actions listed in this section involve enforceable federal standards. Please direct any questions you may have concerning these regulatory actions to the U.S. EPA contact listed for that particular action. Users are strongly urged to read the background information on each regulatory action in Background Document 4 in Service Code 5.

<<< Phenol >>>

__IV.A. CLEAN AIR ACT (CAA)

___IV.A.1. CAA REGULATORY DECISION

Action -- Decision not to regulate

Considers technological or economic feasibility? -- NO

Discussion -- The U.S. EPA concluded that the available health information on phenol at concentrations measured or estimated to occur in the ambient air is insufficient to warrant specific Federal regulation of routine phenol emissions under the CAA at this time.

Reference -- 51 FR 22854 (06/23/86)

EPA Contact -- Emissions Standards Division, OAQPS
(919)541-5571 / FTS 629-5571

---------<<< Phenol >>>---------

__IV.B. SAFE DRINKING WATER ACT (SDWA)

No data available

---------<<< Phenol >>>---------

__IV.C. CLEAN WATER ACT (CWA)

___IV.C.1. AMBIENT WATER QUALITY CRITERIA, Human Health

Water and Fish Consumption: 3E+2 ug/L

Fish Consumption Only: None

Considers technological or economic feasibility? -- NO

Discussion -- The WQC of 3E+2 ug/L is based upon organoleptic effects (taste and odor thresholds). However, organoleptic endpoints have limited value in setting water quality standards, since there is no demonstrated relationship between taste/odor effect and adverse health effects. If there is significant chlorination of water containing phenol, reference should be made to the criteria for 2-chlorophenol and 2,4-dichlorophenol.

Reference -- 45 FR 79318 (11/28/80)

EPA Contact -- Criteria and Standards Division, OWRS
(202)475-7315 / FTS 475-7315

<<< Phenol >>>

___IV.C.2. AMBIENT WATER QUALITY CRITERIA, Aquatic Organisms

Freshwater:

Acute LEC -- 1.02E+4 ug/L
Chronic LEC -- 2.56E+3 ug/L

Marine:

Acute LEC -- 5.8E+3 ug/L
Chronic -- None

Considers technological or economic feasibility? -- NO

Discussion -- The values that are indicated as "LEC" are not criteria, but are the lowest effect levels found in the literature. LECs are given when the minimum data required to derive water quality criteria are not available.

Reference -- 45 FR 79318 (11/28/80)

EPA Contact -- Criteria and Standards Division, OWRS
(202)475-7315 / FTS 475-7315

---------<<< Phenol >>>---------

__IV.D. FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT (FIFRA)

No data available

---------<<< Phenol >>>---------

__IV.E. TOXIC SUBSTANCES CONTROL ACT (TSCA)

No data available

---------<<< Phenol >>>---------

__IV.F. RESOURCE CONSERVATION AND RECOVERY ACT (RCRA)

___IV.F.1. RCRA APPENDIX IX, for Ground Water Monitoring

Status -- Listed

Reference -- 52 FR 25942 (07/09/87)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)382-3000 / FTS 382-3000

---------<<< Phenol >>>---------

__IV.G. SUPERFUND (CERCLA)

___IV.G.1. REPORTABLE QUANTITY (RQ) for Release into the Environment

Value (status) -- 1000 pounds (Final, 1986)

Considers technological or economic feasibility? -- NO

Discussion-- The final RQ takes into account the natural biodegradation and photolysis of this hazardous substance. The biological oxygen demand in 5 days (BOD5) is between 58-83% of the theoretcial oxygen demand. The lowest primary RQ adjustment criteria for phenol (100 pounds based on chronic toxicity composite score of 35) has been adjusted upward one RQ level.

Reference -- 51 FR 34534 (09/29/86)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)382-3000 / FTS 382-3000

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_V. SUPPLEMENTARY DATA

Substance Name -- Phenol
CASRN -- 108-95-2
Last Revised -- 01/31/87

The information contained in this section (subsections A and B) has been extracted from the EPA Chemical Profiles Database, which has been compiled from a number of secondary sources and has not undergone formal Agency review. The complete reference listings for the citations in this section are provided in Service Code 5. The user is urged to read Background Document 5 in Service Code 5 for further information on the sources and limitations of the data presented here.

<<< Phenol >>>

__V.A. ACUTE HEALTH HAZARD INFORMATION

Toxicity -- Phenol's toxic hazard rating is very toxic. The probable oral lethal dose (human) is 50-500 mg/kg (Gosselin et al., 1976). Ingestion of 1 gram has been lethal to humans (Encyc. Occupat. Health and Safety, 1971). Lethal amounts may be absorbed through skin or inhaled (NFPA, 1978).

Medical Conditions Generally Aggravated by Exposure -- Persons affected with hepatic or kidney diseases are at a greater risk (Clayton and Clayton, 1981-82).

Signs and Symptoms of Exposure -- Symptoms include burning pain in the mouth and throat, bloody diarrhea, pallor, sweating, weakness, headache, dizziness, ringing in the ears, shock, and profound fall in body temperature. Oral exposure signs and symptoms include sonorous breathing, and frothing at the mouth and nose. Skin exposure may cause pain followed by numbness (Gosselin et al., 1976).

---------<<< Phenol >>>---------

__V.B. PHYSICAL-CHEMICAL PROPERTIES

Chemical Formula -- C6H6O

Molecular Weight -- 94.11

Boiling Point -- 359.1F, 181.75C

Specific Gravity (H2O=1) -- 1.0722 at 20/4C

Vapor Pressure (mmHg) -- 0.3513 at 25C

Melting Point -- 109F, 43C

Vapor Density (AIR=1) -- 3.24

Evaporation Rate (Butyl acetate=1) -- Not Found

Solubility in Water -- 93 g/L at 25C

Flash Point [Method Used] -- 79C (CC)

Flammable Limits:
    LEL -- 1.7%
    UEL -- 8.6%

Appearance and Odor -- Colorless crystals or white crystalline mass (Merck, 1976), with aromatic, somewhat sickening sweet and acrid odor (Clayton and Clayton, 1981-82). Phenol is liquefied by mixing with about 8% water (Merck, 1983, p. 1043).

Conditions or Materials to Avoid -- Phenol decomposes slowly on air contact (Merck, 1976). Avoid contact with strong oxidizing agents (CHRIS, 1978), aluminum chloride/nitrobenzene mixture, peroxodisulfuric acid, and peroxomonosulfuric acid (Bretherick, 1979).

Hazardous Decomposition or Byproducts -- Not Found

Use -- Used as a disinfectant, antiseptic, and bactericide (Merck, 1976); as a chemical intermediate for phenolic resins, medicinals, and many other chemicals; and as a solvent for petroleum refining (SRI).

_VI. BIBLIOGRAPHY

Substance Name -- Phenol
CASRN -- 108-95-2
Last Revised -- 11/01/90

__VI.A. ORAL RfD REFERENCES

Deichmann, W. and P. Oesper. 1940. Ingestion of phenol-effects on the albino rat. Ind. Med. 9: 296.

Dow Chemical Co. 1945. The toxicity of phenol. Biochem. Res. Lab. Unpublished report dated 04/12/45.

Heller, V.G. and L. Pursell. 1938. J. Pharmacol. Exp. Ther. 63: 99. (Cited in Deichmann and Oesper, 1940)

Kavlock, R.J. 1987. Interim Report on Structure-Activity Relationships in the Developmental Toxicity of Substituted Phenols. Health Effects Research Laboratory, Research Triangle Park, NC.

NCI (National Cancer Institute). 1980. Bioassay of phenol for possible carcinogenicity in F344 rats and B6C3F1 mice. NIH Publ. No. 80-1759. August 1980.

NTP (National Toxicology Program). 1983. Teratologic evaluation of phenol in CD rats and mice. Report prepared by Research Triangle Institute, Research Triangle Park, NC. NTIS PB83-247726. Gov. Rep. Announce. Index. 83(25): 6247.

U.S. EPA. 1985. Health and Environmental Effects Profile for Phenol. Errata, 1986. 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.

---------<<< Phenol >>>---------

__VI.B. INHALATION RfD REFERENCES

None

---------<<< Phenol >>>---------

__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

Boutwell, R.K. and D.K. Bosch. 1959. The tumor-promoting action of phenol and related compounds for mouse skin. Cancer Res. 19: 413-424.

Demerec, M., G. Bertani and J. Flint. 1951. A survey of chemicals for mutagenic action on E. coli. Am. Natur. 85(821): 119-135.

Dickey, F.H., G.H. Cleland and C. Lotz. 1949. The role of organic peroxides in the induction of mutations. Proc. Natl. Acad. Sci. 35: 581-586.

Florin, I., L. Rutberg, M. Curvall and C.R. Enzell. 1980. Screening of tobacco smoke constituents for mutagenicity using the Ames test. Toxicology. 18: 219-232.

Gocke, E., M.-T. King, K. Eckhardt and D. Wild. 1981. Mutagenicity of cosmetics ingredients licensed by the European communities. Mutat. Res. 90: 91-109.

Haworth, S., T. Lawlor, K. Mortelmans, W. Speck and E. Zeiger. 1983. Salmonella mutagenicity test results for 250 chemicals. Environ. Mutagen.1Suppl. 1: 3-142.

NCI (National Cancer Institute). 1980. Bioassay of phenol for possible carcinogenicity. Prepared by the National Cancer Institute, Bethesda, MD for the National Toxicology Program, Research Triangle Park, NC. NCI-CG-TR-203, DHHS/PUB/NIH80-1759.

Pool, B.L. and P.Z. Lin. 1982. Mutagenicity testing in the Salmonella typhimurium assay of phenolic compounds and phenolic fractions obtained from smokehouse smoke condensates. Food Chem. Toxicol. 20: 383-391.

Salaman, M.H. and O.M. Glendenning. 1957. Tumor promotion in mouse skin by sclerosing agents. Br. J. Cancer. 11: 434-444.

U.S. EPA. 1988. Updated Health Effects Assessment for Phenol. Prepared by the Office of Health and Environment Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

---------<<< Phenol >>>---------

VI.D. DRINKING WATER HA REFERENCES

None

SYNONYMS

Substance Name -- Phenol
CASRN -- 108-95-2
Last Revised -- 01/31/87

108-95-2
Benzenol
Carbolic Acid
Hydroxybenzene
Izal
Monohydroxybenzene
Monophenol
NCI-C50124
Oxybenzene
Phenic Acid
Phenol
Phenyl Alcohol
Phenyl Hydrate
Phenyl Hydroxide
Phenylic Acid
Phenylic Alcohol

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STATUS OF DATA FOR Polychlorinated biphenyls (PCBs)

File On-Line 05/01/89

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	no data	
Inhalation RfD Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	on-line	01/01/90
Drinking Water Health Advisories (III.A.)	no data	
U.S. EPA Regulatory Actions (IV.)	no data	

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_I. CHRONIC HEALTH HAZARD ASSESSMENT FOR NONCARCINOGENIC EFFECTS

Substance Name -- Polychlorinated biphenyls (PCBs)
CASRN -- 1336-36-3

Not available at this time

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_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Polychlorinated biphenyls (PCBs)
CASRN -- 1336-36-3
Last Revised -- 01/01/90

Section II provides information on three aspects of the carcinogenic risk assessment for the agent in question; the U.S. EPA classification, and quantitative estimates of risk from oral exposure and from inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen. 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. Background Document 2 (Service Code 5) provides details on the rationale and methods used to derive the carcinogenicity values found in IRIS. Users are referred to Section I for information on long-term toxic effects other than carcinogenicity.

<<< PCBs >>>

II.A. EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

II.A.1. WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification -- B2; probable human carcinogen

Basis -- hepatocellular carcinomas in three strains of rats and two strains of mice and inadequate yet suggestive evidence of excess risk of liver cancer in humans by ingestion and inhalation or dermal contact.

<<< PCBs >>>

II.A.2. HUMAN CARCINOGENICITY DATA

Inadequate. Although there are many studies, the data are inadequate due to confounding exposures or lack of exposure quantification. The first documentation of carcinogenicity associated with PCB exposure was reported at a New Jersey petrochemical plant involving 31 research and development employees and 41 refinery workers (Bahn et al., 1976, 1977). Although a statistically significant increase in malignant melanomas was reported, the two studies failed to report a quantified exposure level and to account for the presence of other potential or known carcinogens. In an expanded report of these studies, NIOSH (1977) concurred with the Bahn et al. (1976) findings. Brown and Jones (1981) reported a retrospective cohort mortality study on 2567 workers who had completed at least 3 months of employment at one or two capacitor manufacturing plants. Exposure levels were 24-393 mg/cu.m at plant A and 318-1260 mg/cu.m at plant B. No excess risk of cancer was observed. In a 7-year follow-up study, Brown (1987) reported a statistically significant excess risk of liver and biliary cancer, with four of the five liver cancers in female workers at plant B. A review of the pathology reports indicated that two of the liver tumors counted in the follow-up study were not primary liver tumors. When these tumors are excluded the elevation in incidence is not statistically significant. The results also may be confounded by population differences in alcohol consumption, dietary habits, and ethnic composition.

Bertazzi et al. (1987) conducted a mortality study of 544 male and 1556 female employees of a capacitor-making facility in Northern Italy. Aroclor 1254 and Pyralene 1476 were used in this plant until 1964. These were progressively replaced by Pyralenes 3010 and 3011 until 1970, after which lower chlorinated Pyralenes were used exclusively. In 1980 the use of PCBs was abandoned. Some employees also used trichloroethylene but, according to the authors, were presumed to be protected by efficient ventilation. Air samples were collected and analyzed for PCBs in 1954 and 1977 because of reports of chloracne in workers. Quantities of PCBs on workers' hands and workplace surfaces also were measured in 1977. In 18 samples, levels ranged from 0.2-159.0 ug/sq.m on workplace surfaces and 0.3-9.2 ug/sq.m on workers' hands.

The authors compared observed mortality with that expected between 1946 and 1982 based on national and local Italian mortality rates. With vital

status ascertainment 99.5% complete, relatively few deaths were reported by 1982 [30 males (5.5%) and 34 females (2.2%)]. In cohort males, the number of deaths from malignant tumors was significantly higher than expected compared with local or national rates, as was the number of deaths from cancer of the GI tract (6 observed vs. 1.7 national expected and 2.2 local expected). Of the six GI cancer deaths, one was due to liver cancer and one to biliary tract cancer. Deaths from hematologic neoplasms in males were also higher than expected, but the excess was not statistically significant. Total cancer deaths in females were significantly elevated in comparison to local rates (12 observed vs. 5.3 expected). None of these were liver or biliary cancers. The number of deaths from hematologic neoplasms in females was higher than expected when compared with lo<1 rates (4 observed vs. 1.1 expected). This study is limited by several factors, particularly the small number of deaths that occurred by the cut-off period. The power of the study is insufficient to detect an elevated risk of site-specific cancer. In addition, the authors stated, after an examination of the individual cases, that interpretation of the increase in GI tract cancer in males was limited, as it appeared likely that some of these individuals had only limited PCB exposure. Confounding factors may have included possible contamination of the PCBs by dibenzofurans and exposure of some of the workers to trichloroethylene, alkylbenzene, and epoxy resins.

Two occurrences of ingestion of PCB-contaminated rice oil have been reported: the Yusho incident of 1968 in Japan and the Yu-Cheng incident of 1979 in Taiwan. Amano et al. (1984) completed a 16-year retrospective cohort mortality study of 581 male and 505 female victims of the Yusho incident. A consistently high risk of liver cancer in females over the entire 16 years was observed; liver cancer in males was also significantly increased. Several serious limitations are evident in this study. There was a lack of information regarding job histories or the influence of alcoholism or smoking. The information concerning the diagnosis of liver cancer was obtained from the victims' families, and it is not clear whether this information was independently verified by health professionals. For some of the cancers described, the latency period is shorter than would be expected. Furthermore, the contaminated oils contained polychlorinated dibenzofurans and polychlorinated quinones as well as PCBs, and the study lacks data regarding exposure to the first two classes of compounds. There is strong evidence indicating that the health effects seen in Yusho victims were due to ingestion of polychlorinated dibenzofurans, rather than to PCBs themselves (reviewed in EPA, 1988). The results of the Amano et al. study can, therefore, be considered as no more than suggestive of carcinogenicity of PCBs.

<<< PCBs >>>

___II.A.3. ANIMAL CARCINOGENICITY DATA

Sufficient. PCB mixtures assayed in the following studies were commercial preparations and may not be the same as mixtures of isomers found in the environment. Although animal feeding studies demonstrate the carcinogenicity of commercial PCB preparations, it is not known which of the PCB congeners in such preparations are responsible for these effects, or if decomposition products, contaminants or metabolites are involved in the toxic response. Early bioassays with rats (Kimura and Baba, 1973; Ito et al., 1974) were inadequate to assess carcinogenicity due to the small number of animals and

short duration of exposure to PCB. A long-term bioassay of Aroclor 1260 reported by Kimbrough et al. (1975) produced hepatocellular carcinomas in female Sherman rats when 100 ppm was administered for 630 days to 200 animals. Hepatocellular carcinomas and neoplastic nodules were observed in 14 and 78%, respectively, of the dosed animals, compared with 0.58 and 0%, respectively, of the controls.

The NCI (1978) reported results for 24 male and 24 female Fischer 344 rats treated with Aroclor 1254 at 25, 50, or 100 ppm for 104 to 105 weeks. Although carcinomas of the gastrointestinal tract were observed among the treated animals only, the incidence was not statistically significantly elevated. An apparent dose-related incidence of hepatic nodular hyperplasia in both sexes as well as hepatocellular carcinomas among mid- to high-dose treated males was reported (4-12%, compared to 0% in controls).

Norback and Weltman (1985) fed 70 male and 70 female Sprague-Dawley rats a diet containing Aroclor 1260 in corn oil at 100 ppm for 16 months, followed by a 50 ppm diet for an additional 8 months, then a basal diet for 5 months. Control animals (63 rats/sex) received a diet containing corn oil for 18 months, then a basal diet alone for 5 months. Among animals that survived for at least 18 months, females exhibited a 91% incidence (43/47) of hepatocellular carcinoma. An additional 4% (2/47) had neoplastic nodules. In males corresponding incidences were 4% (2/46) for carcinoma and 11% (5/46) for neoplastic nodules. Concurrent liver morphology studies were carried out on tissue samples obtained by partial hepatectomies of three animals/group at eight time points. These studies showed the sequential progression of liver lesions to hepatocellular carcinomas.

Orally administered PCB resulted in increased incidences of hepatocellular carcinomas in two mouse strains. Ito et al. (1973) treated male dd mice (12/group) with Kanechlors 500, 400 and 300 each at dietary levels of 100, 250 or 500 ppm for 32 weeks. The group fed 500 ppm of Kanechlor 500 had a 41.7% incidence of hepatocellular carcinomas and a 58.3% incidence of nodular hyperplasia. Hepatocelluar carcinomas and nodular hyperplasia were not observed in mice fed 100 or 250 ppm of Kanechlor 500, nor among those fed Kanechlors 400 or 300 at any concentrations.

Schaeffer et al. (1984) fed male Wistar rats diets containing 100 ppm of the PCB mixtures Clophen A 30 (30% chlorine by weight) or Clophen A 60 (60% chlorine by weight) for 800 days. The PCB mixtures were reported to be free of furans. Clophen A 30 was administered to 152 rats, Clophen A 60 to 141 rats, and 139 rats received a standard diet. Mortality and histologic lesions were reported for animals necropsied during each 100-day interval for all three groups. Of the animals that survived the 800-day treatment period, 1/53 rats (2%) in the control group, 3/87 (3%) in the Clophen A 30 group and 52/85 (61%) in the Clophen A 60 group had developed hepatocellular carcinoma. The incidence in the Clophen A 60 group was significantly elevated in comparison to the control group. Neoplastic nodules were reported in 2/53 control, 35/87 Clophen A 30, and 34/85 Clophen A 60-treated animals. The incidence of nodules was significantly increased in both treatment groups in comparison to the control group. Neoplastic liver nodules and hepatocellular carcinomas appeared earlier and at higher incidence in the Clophen A 60 group relative to the Clophen A 30 group. The authors interpreted the results as indicative of a carcinogenic effect related to the degree of chlorination of the PCB

mixture. The authors also suggested that these findings support those of others, including Ito et al. (1973) and Kimbrough et al. (1975), in which hepatocellular carcinomas were produced by more highly chlorinated mixtures.

Kimbrough and Linder (1974) dosed groups of 50 male BALB/cJ mice (a strain with a low spontaneous incidence of hepatoma) with Aroclor 1254 at 300 ppm in the diet for 11 months or 6 months, followed by a 5-month recovery period. Two groups of 50 mice were fed a control diet for 11 months. The incidence of hepatomas in survivors fed Aroclor 1254 for 11 months was 10/22. One hepatoma was observed in the 24 survivors fed Aroclor 1254 for 6 months.

<<< PCBs >>>

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Most genotoxicity assays of PCBs have been negative. The majority of microbial assays of PCB mixtures and various congeners showed no evidence of mutagenic effects (Schoeny et al., 1979; Schoeny, 1982; Wyndham et al., 1976). Of various tests on the clastogenic effect of PCBs (Heddle and Bruce, 1977; Green et al., 1975), only Peakall et al. (1972) reported results indicative of a possible clastogenic action by PCBs in dove embryos.

Chlorinated dibenzofurans (CDFs), known contaminants of PCBs, and chlorinated dibenzodioxins (CDDs) are structurally related to and produce certain biologic effects similar to those of PCB congeners. While the CDDs are known to be carcinogenic, the carcinogenicity of CDFs is still under evaluation.

__II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE
<<< PCBs >>>

___II.B.1. SUMMARY OF RISK ESTIMATES

Oral Slope Factor -- 7.7/mg/kg/day

Drinking Water Unit Risk -- 2.2E-4/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)	5E-1 ug/L
E-5 (1 in 100,000)	5E-2 ug/L
E-6 (1 in 1,000,000)	5E-3 ug/L

<<< PCBs >>>

___II.B.2. DOSE-RESPONSE DATA (CARCINOGENICITY, ORAL EXPOSURE)

Tumor Type -- trabecular carcinoma/adenocarcinoma, neoplastic nodule
Test Animals -- Rat/Sprague-Dawley, female
Route -- oral, diet
Reference -- Norback and Weltman, 1985

Dose		Tumor
Administered (mg/kg/day) (TWA)	Human Equivalent (mg/kg/day)	Incidence
0	0	1/49
3.45	0.59	45/47

<<< PCBs >>>

___II.B.3. ADDITIONAL COMMENTS (CARCINOGENICITY, ORAL EXPOSURE)

Human equivalent dosage assumes a TWA daily dose of 3.45 mg/kg/day. This reflects the dosing schedule of 5 mg/kg/day (assuming the rat consumes an amount equal to 5% of its bw/day) for the first 16 months, 2.5 mg/kg/day for the next 8 months, and no dose for the last 5 months.

A slope factor of 3.9/mg/kg/day was based on data from the Kimbrough et al. (1975) study of female Sherman rats fed Aroclor 1260. The estimate based on the data of Norback and Weltman (1985) is preferred because Sprague-Dawley rats are known to have low incidence of spontaneous hepatocellular neoplasms. Moreover, the latter study spanned the natural life of the animal, and concurrent morphologic liver studies showed the sequential progression of liver lesions to hepatocellular carcinomas.

Although it is known that PCB congeners vary greatly as to their potency in producing biological effects, for purposes of this carcinogenicity assessment Aroclor 1260 is intended to be representative of all PCB mixtures. There is some evidence that mixtures containing more highly chlorinated biphenyls are more potent inducers of hepatocellular carcinoma in rats than mixtures containing less chlorine by weight (reviewed in Kimbrough, 1987 and Schaeffer et al., 1984).

The unit risk should not be used if the water concentration exceeds 50 ug/L, since above this concentration the slope factor may differ from that stated.

<<< PCBs >>>

___II.B.4. DISCUSSION OF CONFIDENCE (CARCINOGENICITY, ORAL EXPOSURE)

The Norback and Weltman study used an adequate number of animals, observed for their normal lifespan. Only one non-zero test dose was used. A second risk estimate was also calculated based on the numbers of malignant tumors alone, as called for in the EPA's guidelines for carcinogen risk assessment. The slope factor thus derived is 5.7/mg/kg/day, which is 26% less than that

derived using combined malignant tumors and neoplastic nodules. This risk estimate is supported by one based on data of Kimbrough et al. (1975).

PCB mixtures in drinking water may not be the same as the mixtures introduced or used for testing carcinogenicity in animals.

__II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

Not available.

------<<< PCBs >>>------

__II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

___II.D.1. EPA DOCUMENTATION

U.S. EPA. 1988. Drinking Water Criteria Document for Polychlorinated Biphenyls (PCBs). Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC.

___II.D.2. REVIEW (CARCINOGENICITY ASSESSMENT)

The 1988 Drinking Water Criteria Document for PCBs has received OHEA review.

Agency Work Group Review: 04/22/87

Verification Date: 04/22/87

___II.D.3. U.S. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

Charli Hiremath / ORD -- (202)382-5725/ FTS 382-5725

Debdas Mukerjee / ORD -- (513)569-7572/ FTS 684-7572

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_III. HEALTH HAZARD ASSESSMENTS FOR VARIED EXPOSURE DURATIONS

Substance Name -- Polychlorinated biphenyls (PCBs)

CASRN -- 1336-36-3

Not available at this time

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_IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- Polychlorinated biphenyls (PCBs)
CASRN -- 1336-36-3

Not available at this time

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_V. SUPPLEMENTARY DATA

Substance Name -- Polychlorinated biphenyls (PCBs)
CASRN -- 1336-36-3

Not available at this time

==========

_VI. BIBLIOGRAPHY

Substance Name -- Polychlorinated biphenyls (PCBs)
CASRN -- 1336-36-3
Last Revised -- 01/01/90

__VI.A. ORAL RfD REFERENCES

None

------<<< PCBs >>>------

__VI.B. INHALATION RfD REFERENCES

None

VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

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NIOSH (National Institute for Occupational Safety and Health). 1977. Criteria for a Recommended Standard . . . Occupational Exposure to Polychlorinated Biphenyls (PCBs). U.S. DHEW, PHS, CDC, Rockville, Md. Publ. No. 77-225.

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------<<< PCBs >>>------

__VI.D. DRINKING WATER HA REFERENCES

None

SYNONYMS

1336-36-3
AROCLOR
AROCLOR 1221
AROCLOR 1232
AROCLOR 1242
AROCLOR 1248
AROCLOR 1254
AROCLOR 1260
AROCLOR 1262
AROCLOR 1268
AROCLOR 2565
AROCLOR 4465
AROCLOR 5442
BIPHENYL, POLYCHLORO-
CHLOPHEN
CHLOREXTOL
CHLORINATED BIPHENYL
CHLORINATED DIPHENYL
CHLORINATED DIPHENYLENE
CHLORO BIPHENYL
CHLORO 1,1-BIPHENYL
CLOPHEN
DYKANOL
FENCLOR
INERTEEN
KANECHLOR
KANECHLOR 300
KANECHLOR 400
MONTAR
NOFLAMOL
PCB
PCBs
PHENOCHLOR
PHENOCLOR
POLYCHLORINATED BIPHENYL
Polychlorinated Biphenyls
POLYCHLOROBIPHENYL
PYRALENE
PYRANOL
SANTOTHERM
SANTOTHERM FR
SOVOL
THERMINOL FR-1
UN 2315

Soil/Sediment
3.9 E (soil)
DOE

STATUS OF DATA FOR Pyrene

File On-Line 09/01/90

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	09/01/90
Inhalation RfC Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	pending	
Drinking Water Health Advisories (III.A.)	no data	
U.S. EPA Regulatory Actions (IV.)	no data	
Supplementary Data (V.)	on-line	09/01/90

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_I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

__I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name -- Pyrene
CASRN -- 129-00-0
Last Revised -- 09/01/90

The Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. 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 Background Document 1 in Service Code 5 for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of compounds which 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 when a review of that evaluation is completed.

<<< Pyrene >>>

___I.A.1. ORAL RfD SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfD
Kidney effects (renal	NOAEL: 75 mg/kg/day	3000	1	3E-2

tubular pathology, decreased kidney weights) LOAEL: 125 mg/kg/day mg/kg/day

Mouse Subchronic Oral Bioassay

U.S. EPA, 1989

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*Conversion Factors: None

<<< Pyrene >>>

___I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

U.S. EPA. 1989. Mouse Oral Subchronic Toxicity of Pyrene. Study conducted by Toxicity Research Laboratories, Muskegon, MI for the Office of Solid Waste, Washington, DC.

Male and female CD-1 mice (20/sex/group) were gavaged with 0, 75, 125, or 250 mg/kg/day pyrene in corn oil for 13 weeks. The toxicological parameters examined in this study included body weight changes, food consumption, mortality, clinical pathological evaluations of major organs and tissues, and hematology and serum chemistry. Nephropathy, characterized by the presence of multiple foci of renal tubular regeneration, often accompanied by interstitial lymphocytic infiltrates and/or foci of interstitial fibrosis, was present in 4, 1, 1, and 9 male mice in the control, low-, medium-, and high-dose groups, respectively. Similar lesions were seen in 2, 3, 7, and 10 female mice in the 0, 75, 125, and 250 mg/kg treatment groups. The kidney lesions were described as minimal or mild in all dose groups. Relative and absolute kidney weights were reduced in the two higher dosage groups. Based on the results of this study, the low dose (75 mg/kg/day) was considered the NOAEL and 125 mg/kg/day the LOAEL for nephropathy and decreased kidney weights.

<<< Pyrene >>>

___I.A.3. UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

UF = 3000. An uncertainty factor of 3000 reflects 10 each for intra- and interspecies variability, 10 for the use of a subchronic study for chronic RfD derivation, and an additional 3 to account for the lack of both toxicity studies in a second species and developmental/reproductive studies.

MF = 1.
<<< Pyrene >>>

___I.A.4. ADDITIONAL COMMENTS (ORAL RfD)

White and White (1939) fed six male rats (unspecified strain) a diet containing 2000 mg pyrene/kg for 40 days. The average reported food intake for two animals was 6.1 g/day, and the average body weight for these two animals was 94.3 g. A decrease in body weight gain was observed in two animals. The authors stated that this body weight gain was representative of the whole group; although there was no change in food intake. White and White

(1939) also observed enlarged livers and increased hepatic lipid content in animals treated with pyrene, benzpyrene or methylcholanthrene in the diet; however, incidence data were not reported and it is unclear whether this effect occurred in the pyrene treated rats. Interpretation of this study is further complicated by the lack of experimental controls and statistical analysis, small sample size, and incomplete reporting of histopathology results.

<<< Pyrene >>>

___I.A.5. CONFIDENCE IN THE ORAL RfD

Study: Medium
Data Base: Low
RfD: Low

Confidence in the principal study is medium, as it was a well-designed experiment that examined a variety of toxicological endpoints and identified both a NOAEL and LOAEL for the critical effect. Confidence in the data base is low, due to the lack of supporting subchronic, chronic, and developmental/reproductive studies. Accordingly, confidence in the RfD is low.

<<< Pyrene >>>

___I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

Source Document -- This assessment is not presented in any existing U.S. EPA document.

Agency RfD Work Group Review: 11/15/89

Verification Date: 11/15/89

___I.A.7. EPA CONTACTS (ORAL RfD)

John Risher / ORD -- (513)569-7633 / FTS 684-7633

Harlal Choudhury / ORD -- (513)569-7536 / FTS 684-7536

__I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

Substance Name -- Pyrene
CASRN -- 129-00-0

Not available at this time.

_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Pyrene
CASRN -- 129-00-0

This substance/agent has been evaluated by the U.S. EPA for evidence of human carcinogenic potential. This does not imply that this chemical is necessarily a carcinogen. The evaluation for this chemical is under review by an inter-office Agency work group. A risk assessment summary will be included on IRIS when the review has been completed.

_III. HEALTH HAZARD ASSESSMENTS FOR VARIED EXPOSURE DURATIONS

__III.A. DRINKING WATER HEALTH ADVISORIES

Substance Name -- Pyrene
CASRN -- 129-00-0

Not available at this time.

__III.B. OTHER ASSESSMENTS

Substance Name -- Pyrene
CASRN -- 129-00-0

Content to be determined.

_IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- Pyrene
CASRN -- 129-00-0

Not available at this time.

_V. SUPPLEMENTARY DATA

Substance Name -- Pyrene
CASRN -- 129-00-0
Last Revised -- 09/01/90

The information contained in this section (subsections A and B) has been extracted from the EPA Chemical Profiles Database, which has been compiled from a number of secondary sources and has not undergone formal Agency review. The complete reference listings for the citations in this section are provided in Service Code 5. The user is urged to read Background Document 5 in Service Code 5 for further information on the sources and limitations of the data presented here.

<<< Pyrene >>>

__V.A. ACUTE HEALTH HAZARD INFORMATION

Toxicity -- Pyrene is absorbed by the skin and is a skin irritant (Hawley, 1981, p. 872). Workers exposed to 3 to 5 mg/m3 of pyrene exhibited some teratogenic effects (Clayton and Clayton, 1981-82, p. 3361). Pyrene is a polycyclic aromatic hydrocarbon (PAH). The acute toxicity of pure PAHs appears low when administered orally or dermally to rats or mice (Encyc Occupat Health and Safety, 1983, p. 1758). Human exposure to PAHs is almost exclusively via the gastrointestinal and respiratory tracts, and approximately 99 percent is ingested in the diet. Despite the high concentrations of pyrene to which humans may be exposed through food, there is currently little information available to implicate diet-derived PAHs as the cause of serious health effects (NRC, 1983, p. ES-6).

Medical Conditions Generally Aggravated by Exposure -- Not Found

Signs and Symptoms of Exposure -- Not Found

---------<<< Pyrene >>>---------

__V.B. PHYSICAL-CHEMICAL PROPERTIES

Chemical Formula: C16H10

Molecular Weight: 202.26

Boiling Point: 759F, 404C (Merck, 1976) (SUSPECT)

Specific Gravity (H2O=1): 1.27 at 23C (Merck, 1976)

Vapor Pressure (mmHg): Not Found

Melting Point: 313F, 156C (Merck, 1976)

Vapor Density (AIR=1): Not Found

Evaporation Rate (Butyl acetate=1): Not Found

Solubility in Water: 0.135 mg/liter in water (MacKay, 1977)

Appearance and Odor: Colorless solid (Sax, 1984, p. 2324); solid and solutions have a slight blue fluorescence (Merck, 1983, p. 1149)

Flash Point [Method Used]: Not Found

Flammable Limits -- Not Found

Conditions or Materials to Avoid -- Not Found

Hazardous Decomposition or Byproducts -- When heated to decomposition, pyrene emits acrid smoke and fumes (Sax, 1984, p. 2324).

Use -- Biochemical research (Hawley, 1981, p. 872).

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_VI. BIBLIOGRAPHY

Substance Name -- Pyrene
CASRN -- 129-00-0
Last Revised -- 09/01/90

__VI.A. ORAL RfD REFERENCES

U.S. EPA. 1989. Mouse Oral Subchronic Toxicity with Pyrene. Study conducted by Toxicity Research Laboratories, Muskegon, MI for the Office of Solid Waste, Washington, DC.

White, J. and A. White. 1939. Inhibition of growth of the rat by oral administration of methylcholanthrene, benzpyrene, or pyrene and the effects of various dietary supplements. J. Biol. Chem. 131: 149-161.

---------<<< Pyrene >>>---------

__VI.B. INHALATION RfD REFERENCES

None

---------<<< Pyrene >>>---------

__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

None

---------<<< Pyrene >>>---------

__VI.D. DRINKING WATER HA REFERENCES

None

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SYNONYMS

Substance Name -- Pyrene
CASRN -- 129-00-0
Last Revised -- 09/01/90

129-00-0
BENZO(DEF)PHENANTHRENE
HSDB 4023
NSC 17534
PYREN [GERMAN]
PYRENE
BETA-PYRENE

Enter keywords or Read or Scan or Mail
--7440-38-2
Searching - Please wait...
1 Occurrences...

Enter keywords or Read or Scan or Mail
--read

Sullivan's Ledge
3.9.2 (AK)
DOE

STATUS OF DATA FOR Toluene

File On-Line 01/31/87

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	08/01/90
Inhalation RfC Assessment (I.B.)	pending	07/01/90
Carcinogenicity Assessment (II.)	on-line	08/01/90
Drinking Water Health Advisories (III.A.)	on-line	09/01/90
U.S. EPA Regulatory Actions (IV.)	on-line	03/01/88
Supplementary Data (V.)	no data	

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_I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

__I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name -- Toluene
CASRN -- 108-88-3
Last Revised -- 08/01/90

The Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. 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 Background Document 1 in Service Code 5 for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of compounds which 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 when a review of that evaluation is completed.

<<< Toluene >>>

___I.A.1. ORAL RfD SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfD
Changes in liver and	NOAEL = 312 mg/kg	1000	1	2E-1

kidney weights	converted to 223 mg/kg/day	mg/kg/day
13-Week Rat Gavage Study	LOAEL = 625 mg/kg converted to 446	
NTP, 1989	mg/kg/day	

*Conversion Factors: Dose adjusted for gavage schedule of 5 days/week.

<<< Toluene >>>

___I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

NTP (National Toxicology Program). 1989. Toxicology and Carcinogenesis Studies of toluene in F344/N rats and B6C3F1 mice. Technical Report Series No. 371. Research Triangle Park, NC.

The oral toxicity of toluene was investigated in this subchronic gavage study in F344 rats. Groups of 10 rats/sex/group were administered toluene in corn oil at dosage levels of 0, 312, 625, 1250, 2500, or 5000 mg/kg for 5 days/week for 13 weeks. All animals receiving 5000 mg/kg died within the first week. One female and 8 males in the 2500 mg/kg group died, but 2 of these were due to gavage errors. No deaths occurred at lower doses. Several toxic effects were noted at doses greater than or equal to 2500 mg/kg, including prostration, hypoactivity, ataxia, piloerection, lacrimation, excessive salivation, and body tremors. No signs of biologic significance were seen in groups receiving less than or equal to 1250 mg/kg. The only significant change in body weight was a decrease ($p<0.05$) for males in the 2500 mg/kg group. There were no toxicologically significant changes in hematology or urinalysis for any group of animals. Biochemical changes, including a significant increase ($p<0.05$) in SGOT in 2500 males and a dose-related increase in cholinesterase in females receiving 2500 and 5000 mg/kg, were not considered to be biologically significant. There were several pathologic findings and organ weight changes in the liver, kidney, brain, and urinary bladder. In males, absolute and relative weights of both the liver and kidney were significantly increased ($p<0.05$) at doses greater than or equal to 625 mg/kg. In females, absolute and relative weights of the liver, kidney, and heart were all significantly increased at doses greater than or equal to 1250 mg/kg ($p<0.01$ for all comparisons except $p<0.05$ for absolute kidney and heart weights at 1250 mg/kg). Histopathologic lesions in the liver consisted of hepatocellular hypertrophy, occurring at greater than or equal to 2500 mg/kg. Nephrosis was observed in rats that died, and damage to the tubular epithelia of the kidney occurred in terminally sacrificed rats. Histopathologic changes were also noted in the brain and urinary bladder. In the brain, mineralized foci and necrosis of neuronal cells were observed in males and females at 2500 mg/kg and males at 1250 mg/kg. In the bladder, hemorrhage of the muscularis was seen in males and females at 5000 mg/kg and males at 2500 mg/kg. The NOAEL for this study is 312 mg/kg/day based on liver and kidney weight changes in male rats at 625 mg/kg. The toxicologic significance of these organ weight changes is strengthened by the occurrence of histopathologic changes in both the liver and kidney at higher doses. Because the exposure was for 5 days/week, this dose is converted to 312 x 5/7 = 223 mg/kg/day. The LOAEL is 625 mg/kg, which is 446 mg/kg/day when converted.

NTP (1989) also conducted a 13-week gavage study in B6C3F1 mice, following the same regimen described above. All mice receiving 5000 mg/kg died and 8/20 receiving 2500 mg/kg also died. Signs of toxicity seen in animals receiving greater than or equal to 2500 mg/kg included subconvulsive jerking, prostration, impaired grasping reflex, bradypnea, hypothermia, ataxia, and hypoactivity. By week 13, the mean body weight of 2500 mg/kg males was significantly ($p<0.05$) lower than controls. No other significant changes were reported for any group, including macroscopic observation, organ weight means, or clinical pathology parameters. The NOAEL for mice in this study was 1250 mg/kg.

The subchronic study by Wolf et al. (1956) is supportive of the NTP studies. Groups of 10 female Wistar rats were administered gavage doses of 0, 118, 354, or 590 mg/kg toluene dissolved in olive oil. A total of 138 doses were administered over 193 days, resulting in average doses of approximately 0, 84, 253, or 422 mg/kg/day. Hematologic, behavioral, gross and histopathologic examinations were conducted with no toxic effects being reported at any dose. Therefore, the highest dose of 422 mg/kg/day is considered to be the NOAEL for this study. However, this study is not used as the basis for the RfD because the LOAEL of 446 mg/kg/day identified by NTP (1989) is too close to the NOAEL identified by Wolf et al. (1956). Also, the NTP study indicated that male rats are more sensitive to toluene and the Wolf study utilized only female rats.

<<< Toluene >>>

___I.A.3. UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

UF = 1000. An uncertainty factor of 1000 was applied to account for inter- and intraspecies extrapolations, for subchronic-to-chronic extrapolation and for limited reproductive and developmental toxicity data.

MF = 1.

<<< Toluene >>>

___I.A.4. ADDITIONAL COMMENTS (ORAL RfD)

Kostas and Hotchin (1981) exposed NYLAR mice pre- and post-natally to toluene provided in the drinking water at concentrations of 0, 16, 80, or 400 ppm. Effects were noted in all dosed groups on rotorod performance, measured at 45 to 55 days of age, but there was an inverse dose-response relationship. No effects of toluene exposure were seen on maternal fluid consumption, offspring mortality rate, development of eye or ear openings, or surface-righting response. This study is not suitable for use in risk assessment because only 6 to 9 pregnancies/dose group were obtained, and because the dose-response relationship was inverse.

In an abstract providing limited information, Nawrot and Staples (1979) reported an increase in embryonic lethality in mice exposed to toluene from days 6 to 15 of gestation. Pregnant CD-1 dams were administered 0.3, 0.5, or 1.0 mL/kg bw, 3 times/day (equivalent to approximately 780, 1300, or 2600 mg/kg/day). Maternal toxicity was not observed at any dose level, but toluene was shown to be teratogenic at the high dose and embryolethal at the low dose.

These levels are higher than the NOAEL demonstrated by the NTP (1989) study.

Several subchronic and chronic inhalation studies have been performed on toluene but are not considered to be suitable for deriving an oral RfD. These studies are summarized nicely in the introduction to the 2-year inhalation bioassay by NTP, 1989. The studies identify the following potential target organs: kidney (male rat); hematologic effects (mice); central nervous system (rats, mice, primates); developmental toxicity (rats, rabbits). It is beyond the scope of this oral RfD summary sheet to describe each of these studies, but the two chronic (2 year) inhalation studies are summarized briefly below.

In a 2-year inhalation study by NTP (1989), F344 rats (60/sex/group) were exposed to 0, 600, or 1200 ppm toluene and B6C3F1 mice (60/sex/group) to 0, 120, 600, or 1200 ppm toluene for 6.5 hours/day, 5 days/week. Ten animals/group (except male mice) were removed at 15 months for toxicologic evaluation. At 15 months, there was an increased incidence and severity of nonneoplastic lesions of the nasal cavity of exposed rats. Minimal hyperplasia of the bronchial epithelium was seen in 4/10 female mice at 1200 ppm. There were no significant differences in survival among any group of animals during the 2-year study. Mean body weights were generally similar for all groups throughout the study. Nephropathy was seen in almost all rats with the severity somewhat increased in exposed rats. There were also effects on the olfactory and respiratory epithelia of exposed rats. No biologically important lesions were seen in any groups of mice. There was no evidence of carcinogenicity for any group of animals in this study.

A chronic inhalation study in rats performed by CIIT (1980) failed to produce an adverse effect. Groups of 40 F344 rats/sex were exposed to 30, 100, or 300 ppm toluene for 6 hours/day, 5 days/week for 24 months. An unexposed group of 120 rats/sex served as a control. Clinical chemistry, hematology, and urinalysis testing were conducted at 18 and 24 months. All parameters measured at the termination of the study were normal except for a dose-related reduction in hematocrit values in females exposed to 100 and 300 ppm toluene. The highest dose of 300 ppm was considered to be a NOAEL.

<<< Toluene >>>

___I.A.5. CONFIDENCE IN THE ORAL RfD

Study: High
Data Base: Medium
RfD: Medium

Confidence in the principal study is high because a sufficient number of animals/sex were tested in each of six dose groups (including vehicle controls) and many parameters were studied. The same protocol was tested in both mice and rats, with rats being identified as the more sensitive species. The data base is rated medium because it is supported by a 6-month oral study. It is not higher than medium because there is no reproductive study. Also, the oral studies are all subchronic, with the critical study being only 13 weeks in duration. Medium confidence in the RfD follows.

<<< Toluene >>>

___I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

Source Document -- This assessment is not presented in any existing U.S. EPA document.

Agency RfD Work Group Review: 05/20/85, 08/05/85, 08/05/86, 05/17/90, 06/20/90

Verification Date: 06/20/90

___I.A.7. EPA CONTACTS (ORAL RfD)

Sue Velazquez / ORD -- (513)569-7571 / FTS 684-7571

Krishan Khanna / ODW -- (202)382-7588 / FTS 382-7588

__I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

Substance Name -- Toluene
CASRN -- 108-88-3

A risk assessment for this substance/agent is under review by an EPA work group.

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_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Toluene
CASRN -- 108-88-3
Last Revised -- 08/01/90

Section II provides information on three aspects of the carcinogenic risk assessment for the agent in question; the U.S. EPA classification, and quantitative estimates of risk from oral exposure and from inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen. 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. Background Document 2 (Service Code 5) provides details on the rationale and methods used to derive

the carcinogenicity values found in IRIS. Users are referred to Section I for information on long-term toxic effects other than carcinogenicity.

<<< Toluene >>>

II.A. EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

II.A.1. WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification -- D; not classified

Basis -- No human data and inadequate animal data. Toluene did not produce positive results in the majority of genotoxic assays.

<<< Toluene >>>

II.A.2. HUMAN CARCINOGENICITY DATA

None.

<<< Toluene >>>

II.A.3. ANIMAL CARCINOGENICITY DATA

A chronic (106-week) bioassay of toluene in F344 rats of both sexes reported no carcinogenic responses (CIIT, 1980). A total of 960 rats were exposed by inhalation for 6 hours/day, 5 days/week to toluene at 0, 30, 100, or 300 ppm. Groups of 20/sex/dose were sacrificed at 18 months. Gross and microscopic examination of tissues and organs identified no increase in neoplastic tissue or tumor masses among treated rats when compared with controls. The study is considered inadequate because the highest dose administered was well below the MTD for toluene and because of the high incidence of lesions and pathological changes in the control animals.

Several studies have examined the carcinogenicity of toluene following repeated dermal applications. Toluene (dose not reported) applied to shaved interscapular skin of 54 male mice (strains A/He, C3HeB, SWR) throughout their lifetime (3 times weekly) produced no carcinogenlc response (Poel, 1963). One drop of toluene (about 6 mL) applied to the dorsal skin of 20 random-bred albino mice twice weekly for 50 weeks caused no skin papillomas or carcinomas after a 1-year latency period was allowed (Coombs et al., 1973). No increase in the incidence of skin or systemic tumors was demonstrated in male or female mice of three strains (CF, C3H, or CBaH) when toluene was applied to the back of 25 mice of each sex of each strain at 0.05-0.1 mL/mouse, twice weekly for 56 weeks (Doak et al., 1976). One skin papilloma and a single skin carcinoma were reported among a group of 30 mice treated dermally with one drop of 0.2% (w/v) solution toluene twice weekly, administered from droppers delivering 16-20 uL per drop for 72 weeks (Lijinsky and Garcia, 1972). It is not reported whether evaporation of toluene from the skin was prevented during these studies.

<<< Toluene >>>

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Toluene was found to be nonmutagenic in reverse mutation assays with S. typhimurium (Mortelmans and Riccio, 1980; Nestmann et al., 1980; Bos et al., 1981; Litton Bionetics, Inc., 1981; Snow et al., 1981) and E. coli (Mortelmans and Riccio, 1980), with and without metabolic activation. Toluene did not induce mitotic gene conversion (Litton Bionetics, Inc., 1981; Mortelmans and Riccio, 1980) or mitotic crossing over (Mortelmans and Riccio, 1980) in S. cerevisiae. Although Litton Bionetics, Inc. (1981) reported that toluene did not cause increased chromosomal aberrations in bone marrow cells, several Russian studies (Dobrokhotov, 1972; Lyapkalo, 1973) report toluene as effective in causing chromosal damage in bone marrow cells of rats. There was no evidence of chromosomal aberrations in blood lymphocytes of workers exposed to toluene only (Maki-Paakkanen et al., 1980; Forni et al., 1971), although a slight increase was noted in workers exposed to toluene and benzene (Forni et al., 1971; Funes-Craviota et al., 1977). This finding is supported by studies of cultured human lymphocytes exposed to toluene in vitro; no elevation of chromosomal aberrations or sister chromatid exchanges was observed (Gerner-Smidt and Friedrich, 1978).

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__II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

Not available.

---------<<< Toluene >>>---------

__II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

Not available.

---------<<< Toluene >>>---------

__II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

___II.D.1. EPA DOCUMENTATION

U.S. EPA. 1987. Drinking Water Criteria Document for Toluene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. ECAO-CIN-408.

<<< Toluene >>>

___II.D.2. REVIEW (CARCINOGENICITY ASSESSMENT)

The values in the 1987 Drinking Water Criteria Document for Toluene have received peer and administrative review.

Agency Work Group Review: 09/15/87

Verification Date: 09/15/87

___II.D.3. U.S. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

Dharm V. Singh / ORD -- (202)382-5958 / FTS 382-5958

Robert E. McGaughy / ORD -- (202)382-5898 / FTS 382-5898

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_III. HEALTH HAZARD ASSESSMENTS FOR VARIED EXPOSURE DURATIONS

__III.A. DRINKING WATER HEALTH ADVISORIES

Substance Name -- Toluene
CASRN -- 108-88-3
Last Revised -- 09/01/90

The Office of Drinking Water provides Drinking Water Health Advisories (HAs) as technical guidance for the protection of public health. HAs are not enforceable Federal standards. HAs are concentrations of a substance in drinking water estimated to have negligible deleterious effects in humans, when ingested, for a specified period of time. Exposure to the substance from other media is considered only in the derivation of the lifetime HA. Given the absence of chemical-specific data, the assumed fraction of total intake from drinking water is 20%. The lifetime HA is calculated from the Drinking Water Equivalent Level (DWEL) which, in turn, is based on the Oral Chronic Reference Dose. Lifetime HAs are not derived for compounds which are potentially carcinogenic for humans because of the difference in assumptions concerning toxic threshold for carcinogenic and noncarcinogenic effects. A more detailed description of the assumptions and methods used in the derivation of HAs is provided in Background Document 3 in Service Code 5.

<<< Toluene >>>

___III.A.1. ONE-DAY HEALTH ADVISORY FOR A CHILD

One-day HA -- 2E+1 mg/L

NOAEL -- 21.5 mg/kg/day

UF -- 10 (allows for intrahuman variability with the use of a NOAEL from a human study)
Assumptions -- 1 L/day water consumption for a 10-kg child

Principal Study -- Gamberale and Hultengren, 1972

This study reported that a 20-minute exposure to 100 ppm toluene was a no-effect level when determined by perceptual speed and reaction time tests in human volunteers. At 200 ppm, toluene was noted as clearly causing toxic effects such as incoordination, exhilaration, and prolonged reaction time. These and other data support the selection of 100 ppm (377 mg/cu.m) toluene as the NOAEL in humans exposed for up to 8 hours. Based on the conditions of exposure and an assumed absorption rate of 60%, this level is equivalent to 21.5 mg/kg/day.

<<< Toluene >>>

___III.A.2. TEN-DAY HEALTH ADVISORY FOR A CHILD

No information was found in the available literature that was suitable for determination of a Ten-day HA value. It is, therefore, recommended that the DWEL, adjusted for a 10-kg child (3 mg/L) be used as the Ten-day HA value.

<<< Toluene >>>

___III.A.3. LONGER-TERM HEALTH ADVISORY FOR A CHILD

No information was found in the available literature that was suitable for determination of a Longer-term HA value. It is, therefore, recommended that the DWEL, adjusted for a 10-kg child (3 mg/L) be used as the Longer-term HA value for a child.

<<< Toluene >>>

___III.A.4. LONGER-TERM HEALTH ADVISORY FOR AN ADULT

No information was found in the available literature that was suitable for determination of a Longer-term HA value. It is, therefore, recommended that the DWEL, adjusted for a 70-kg adult (10 mg/L) be used as the Longer-term HA value for an adult.

<<< Toluene >>>

___III.A.5. DRINKING WATER EQUIVALENT LEVEL / LIFETIME HEALTH ADVISORY

DWEL -- 7E-0 mg/L

Assumptions -- 2 L/day water consumption for a 70-kg adult

RfD Verification Date -- 06/20/90

Lifetime HA -- 1E-0 mg/L

Assumptions -- 20% exposure by drinking water

Principal Study -- NTP, 1989 (This study was used in the derivation of the chronic oral RfD; see Section I.A.2.)

<<< Toluene >>>

___III.A.6. ORGANOLEPTIC PROPERTIES

Taste threshold in water is reported as 0.04 and 1 mg/L. Odor threshold in water is reported as 0.04 and 1 mg/L.

<<< Toluene >>>

___III.A.7. ANALYTICAL METHODS FOR DETECTION IN DRINKING WATER

Analysis of toluene is by a purge-and-trap gas chromatographic procedure used for the determination of volatile aromatic and unsaturated organic compounds in water.

<<< Toluene >>>

___III.A.8. WATER TREATMENT

Treatment options for removing toluene form drinking water sources include air stripping and adsorption onto granular activated carbon.

<<< Toluene >>>

___III.A.9. DOCUMENTATION AND REVIEW OF HAs

U.S. EPA. 1990. Final Draft of the Drinking Water Criteria Document for Toluene. Office of Drinking Water, Washington, DC.

EPA review of HAs in 1986.

Public review of HAs in 1987.

Science Advisory Board review to be determined.

Preparation date of this IRIS summary -- 08/20/90

___III.A.10. EPA CONTACTS

Krishan Khanna / ODW -- (202)475-9568 / FTS 475-9568

Edward V. Ohanian / ODW -- (202)382-7571 / FTS 382-7571

__III.B. OTHER ASSESSMENTS

Substance Name -- Toluene
CASRN -- 108-88-3

Content to be determined.

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_IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- Toluene
CASRN -- 108-88-3
Last Revised -- 03/01/88

EPA risk assessments may be updated as new data are published and as assessment methodologies evolve. Regulatory actions are frequently not updated at the same time. Compare the dates for the regulatory actions in this section with the verification dates for the risk assessments in sections I and II, as this may explain inconsistencies. Also note that some regulatory actions consider factors not related to health risk, such as technical or economic feasibility. Such considerations are indicated for each action. In addition, not all of the regulatory actions listed in this section involve enforceable federal standards. Please direct any questions you may have concerning these regulatory actions to the U.S. EPA contact listed for that particular action. Users are strongly urged to read the background information on each regulatory action in Background Document 4 in Service Code 5.

<<< Toluene >>>

__IV.A. CLEAN AIR ACT (CAA)

___IV.A.1. CAA REGULATORY DECISION

Action -- Decision not to regulate

Considers technological or economic feasibility? -- NO

Discussion -- The U.S. EPA concluded that current information does not indicate that toluene endangers public health at ambient concentrations (excluding emergency releases), and thus no regulation directed specifically at toluene is necessary at this time under the CAA.

Reference -- 45 FR 22195 (05/25/84)

EPA Contact -- Emissions Standards Division, OAQPS
(919)541-5571 / FTS 629-5571

---------<<< Toluene >>>---------

__IV.B. SAFE DRINKING WATER ACT (SDWA)

___IV.B.1. MAXIMUM CONTAMINANT LEVEL GOAL (MCLG) for Drinking Water

Value (status) -- 2.0 mg/L (Proposed, 1985)

Considers technological or economic feasibility? -- NO

Discussion -- An MCLG of 2.0 mg/L for toluene is proposed based on a DWEL of 10.1 mg/L and an assumed contribution of 20% from drinking water. A DWEL of 10.1 mg/L was calculated from a NOAEL of 1130 mg/cu.m (highest dose tested) for
lung effects in rats (2-year inhalation study), with an uncertainty factor of 100 applied and an assumed 50% pulmonary absorption rate.

Reference -- 50 FR 46936 Part IV (11/13/85)

EPA Contact -- Krishan Khanna / Criteria and Standards Division, ODW / (202)382-7571 / FTS 382-7571; or Drinking Water Hotline / (800)426-4791

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__IV.C. CLEAN WATER ACT (CWA)

___IV.C.1. AMBIENT WATER QUALITY CRITERIA, Human Health

Water and Fish Consumption: 14.3 mg/L

Fish Consumption Only: 424 mg/L

Considers technological or economic feasibility? -- NO

Discussion -- The WQC of 14.3 mg/L is based on consumption of contaminated aquatic organisms and water. A WQC of 424 mg/L has also been established based on consumption of contaminated aquatic organisms alone.

Reference -- 45 FR 79318 (11/28/80)

EPA Contact -- Criteria and Standards Division / OWRS / (202)475-7315 / FTS 475-7315

<<< Toluene >>>

___IV.C.2. AMBIENT WATER QUALITY CRITERIA, Aquatic Organisms

Freshwater:

Acute -- 17,500 ug/L (LEL)
Chronic -- None

Marine:

Acute -- 6300 ug/L (LEL)
Chronic -- 5000 ug/L (LEL)

Considers technological or economic feasibility? -- NO

Discussion -- Water quality criteria for the protection of aquatic life are derived from a minimum data base of acute and chronic tests on a variety of aquatic organisms. The "(LEL)" after the value indicates that the minimum data were not available and the concentration given is not a criteria value but the lowest effect level found in the literature.

Reference -- 45 FR 79318 (11/28/80)

EPA Contact -- Criteria and Standards Division / OWRS /
(202)475-7315 / FTS 475-7315

---------<<< Toluene >>>---------

__IV.D. FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT (FIFRA)

No data available

---------<<< Toluene >>>---------

__IV.E. TOXIC SUBSTANCES CONTROL ACT (TSCA)

No data available

---------<<< Toluene >>>---------

__IV.F. RESOURCE CONSERVATION AND RECOVERY ACT (RCRA)

___IV.F.1. RCRA APPENDIX IX, for Ground Water Monitoring

Status -- Listed

Reference -- 52 FR 25942 (07/09/87)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)382-3000 / FTS 382-3000

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__IV.G. SUPERFUND (CERCLA)

___IV.G.1. REPORTABLE QUANTITY (RQ) for Release into the Environment

Value (status) -- 1000 pounds (Final, 1985)

Considers technological or economic feasibility? -- NO

Discussion -- The final RQ is based on aquatic toxicity, as established under Section 311(b)(4) of the Clean Water Act, ignitability, and chronic toxicity. Available data indicate that the aquatic 96-Hour Median Threshold Limit for Toluene is between 10 and 100 ppm. Its closed-cup flash point is less than 100F and its boiling point is >100F. RQ assignments based on chronic toxicity reflect two primary attributes of the hazardous substance, the minimum effective dose (MED) levels for chronic exposure (mg/day for a 70-kg person) and the type of effect (liver necrosis, teratogenicity, etc). A composite score is determined from an evaluation of these two attributes. Toluene was determined to have a composite score between 6 and 20, corresponding to a chronic toxicity RQ of 1000 pounds.

Reference -- 50 FR 13456 (04/04/85)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)382-3000 / FTS 382-3000

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_V. SUPPLEMENTARY DATA

Substance Name -- Toluene
CASRN -- 108-88-3

Not available at this time.

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_VI. BIBLIOGRAPHY

Substance Name -- Toluene
CASRN -- 108-88-3
Last Revised -- 09/01/90

__VI.A. ORAL RfD REFERENCES

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toluene. CIIT, Research Triangle Park, NC.

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__VI.B. INHALATION RfD REFERENCES

None

---------<<< Toluene >>>---------

__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

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Poel, W.E. 1963. Skin as a test site for the bioassay of carcinogens and carcinogen precursors. Natl. Cancer Inst. Monogr. 10: 611-625.

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__VI.D. DRINKING WATER HA REFERENCES

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SYNONYMS

Substance Name -- Toluene
CASRN -- 108-88-3
Last Revised -- 01/31/87

108-88-3
ANTISAL 1a
BENZENE, METHYL
METHACIDE
METHYL-BENZENE
METHYLBENZOL
NCI-C07272
PHENYL-METHANE
RCRA WASTE NUMBER U220
TOLUEEN
TOLUEN
Toluene
TOLUOL
TOLUOLO
TOLU-SOL
UN 1294

Enter keywords or Read or Scan or Mail
--67-66-3
Searching - Please wait...
4 Occurrences...

Enter keywords or Read or Scan or Mail
--scan