Hexachlorocyclopentadiene (HCCPD); CASRN 77-47-4

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

STATUS OF DATA FOR Hexachlorocyclopentadiene (HCCPD)

File First On-Line 01/31/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	07/05/2001
Inhalation RfC (I.B.)	yes	07/05/2001
Carcinogenicity Assessment (II.)	yes	07/05/2001

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

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

Substance Name — Hexachlorocyclopentadiene (HCCPD)
CASRN — 77-47-4
Last Revised — 07/05/2001

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

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

I.A.1. Oral RfD Summary

The current RfD for hexachlorocyclopentadiene (HCCPD) is a reevaluation of an assessment placed on-line on 01/31/1987. Although the current assessment used benchmark dose modeling for the dose-response analysis, the resulting RfD is similar to that reported in the 1987 assessment.

Critical Effect	Experimental Doses*	UF	MF	RfD
Chronic irritation **Rat subchronic gavage bioassay** **Abdo et al., 1984**	$BMDL_{10}$: 6 mg/kg/day BMD_{10}: 11 mg/kg/day	1,000	1	6E-3 mg/kg/day

$BMDL_{10}$ - 95% lower confidence limit on the maximum likelihood estimate of the dose corresponding to 10% risk.
BMD_{10} - Maximum likelihood estimate of the dose corresponding to 10% risk.

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

There are no chronic oral human studies or animal studies available for dose-response assessment. There were two subchronic oral studies in rodents. One is a gavage study in rats and mice by Abdo et al. (1984) and the other is a dietary study by Industrial Bio-test Laboratories (1975b). Athough gavage administration is not ideal for extrapolation to human exposure, there are two main reasons for choosing Abdo et al. (1984) as the principal study: (1) no effects were observed in the Industrial Bio-test Studies, and (2) effects were noted at lower doses than those given in the Industrial Bio-test Laboratories (1975b) study. Although dietary administration is more relevant to human exposure, there are two main reasons not to choose Industrial Bio-test Laboratories (1975b) as the principal study: (1) the quality of the data is suspect because the study was performed during a time when critical errors were committed at Industrial Bio-test Laboratories, and (2) it was not published in the peer-

reviewed literature. See Section 4.2.2.2 of U.S. EPA (2001) for a summary of the subchronic study conducted by Industrial Bio-test Laboratories (1975b).

Abdo, KM; Montgomery, CA; Kluwe, WM; et al. (1984) Toxicity of hexachlorocyclopentadiene: subchronic (13-week) administration by gavage to F344 rats and B6C3F1 mice. J Appl Toxicol 4:75-81.

Young adult F344 rats (10/sex/dose) were administered 0, 10, 19, 38, 75, or 150 mg HCCPD/kg via corn oil gavage 5 days/week for 13 weeks. Young adult B6C3F1 mice were treated on the same regimen, but at doses of 0, 19, 38, 75, 150, or 300 mg/kg. Stability of the gavage mixture, or the frequency of preparation, was not reported. Standard bioassay data including body weights, organ weights, pathology, and histopathology were collected.

Mortality attributed to HCCPD occurred in six male rats in the 150 mg/kg group and in one male rat in the 75 mg/kg group. Other deaths were associated with gavage error, but the authors suggested that HCCPD may have been a contributor. A dose-related increase in the incidence of forestomach lesions started occurring in female rats at 19 mg/kg and in males at 38 mg/kg. Lesions were characterized by hyperplasia, acanthosis, and hyperkeratosis of the epithelial surface of the forestomach and increased mitotic activity in the basal layer of the epithelium. The forestomach lesions ranged from minimal to marked in severity and were focal to diffuse in distribution. Toxic nephrosis was noted in both sexes at 38 mg/kg and higher. Kidney lesions were predominantly limited to the terminal portion of the proximal convoluted tubules in the inner cortex and were characterized by dilated tubules and epithelial changes consisting of cytomegaly, karyomegaly, and anisokaryosis with nuclear and cytoplasmic vacuolization. Decreased body weights were noted in males at 38 mg/kg and in females at 75 mg/kg.

Mortality was observed in mice at 300 mg/kg and was greater for males (10/10) than for females (3/10). Forestomach lesions were found in both sexes at 38 mg/kg. Lesions progressed to black foci, red cysts, and ulceration at 150 mg/kg. Toxic nephrosis, which was observed beginning at 75 mg/kg, occurred only in the female mice.

Chronic irritation, manifested by forestomach lesions, was chosen as the critical effect because it occurred at lower doses than the toxic nephrosis. The irritant effects on the forestomach are consistent with the observation of dermal irritation (Treon et al., 1955; Industrial Bio-test Laboratories, 1975a; HEW, 1978) and other portal-of-entry effects from HCCPD exposure (NTP, 1994; Clark et al., 1982). Female rats were more susceptible to the forestomach irritation than male rats or either sex of mice. The incidence of forestomach histopathology in female rats was 0/10, 0/10, 2/10, 5/10, 9/10, and 9/10 for the 0, 10, 19, 38, 75, or 150 mg/kg doses, respectively. Benchmark dose modeling was applied to these data because there was a

clear increase in response with dose and there were at least two doses that produced more than minimal but less than maximal effects.

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

UF = 1,000

Chronic studies are preferred for RfD development. To account for the uncertainty in using a subchronic study for RfD derivation, a UF of $10^{1/2}$ is applied. Rather than using the default of 10, this UF was derived by comparing the data from the subchronic and chronic inhalation studies (NTP, 1994). This approach is justified by the fact that HCCPD produces local effects by both oral and inhalation routes of exposure. The subchronic NOAEL to chronic NOAEL ratio from NTP (1994) was 0.8 for respiratory effects in rats while the ratio for mice was 3 (see Section I.B.2 for a more thorough discussion of NTP, 1994). Because it is more typical for the subchronic NOAEL to be larger than the chronic NOAEL, 3, or $10^{1/2}$, was chosen as the subchronic-to-chronic UF for the RfD. In the absence of data on which to base a pharmacokinetic or pharmacodynamic comparison of rodents to humans, the default UF of 10 is used for interspecies extrapolation. There are no data documenting the nature and extent of variability in human susceptibilities to HCCPD, so the default UF of 10 is used to protect sensitive human subpopulations. The database for HCCPD includes studies of genotoxicity, developmental toxicity, systemic toxicity, and cancer, but no reproductive studies are available. An additional UF of $10^{1/2}$ is added for this database deficiency. Thus, the total UF is 1,000.

MF = 1

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

The irritant effect on the forestomach observed in the critical study is consistent with portal-of-entry effects from HCCPD exposure. Respiratory tract damage (NTP, 1994; Clark et al., 1982) and skin lesions (Treon et al., 1955; Industrial Bio-test Laboratories, 1975a; HEW, 1978) are observed during inhalation and dermal exposures, respectively. The kidney also has been a target organ in oral studies (Abdo et al., 1984) as well as in an inhalation study (Clark et al., 1982) that noted mild degenerative kidney and liver lesions in rats at doses that also produce respiratory tract necrosis. One report of accidental human exposure suggests that the liver may also be a target organ (Kominsky et al., 1980). HCCPD was not a developmental toxin by oral gavage in rats, mice, or rabbits (Chernoff and Kavlock, 1983; Murray et al., 1980; Goldenthal et al., 1978).

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.7 (PDF).

I.A.5. Confidence in the Oral RfD

Study — Medium
Database — Low
RfD — Low

The confidence in the principal study is medium. Although the study was well conducted, an adequate number of doses were examined, and corroborative results in two species were obtained, the design was lacking because no data on hematology, clinical chemistry, or urine analyses were collected. Confidence in the database is low. There are no good-quality supporting subchronic oral studies with which to compare the effects noted. Oral developmental studies in three species (Chernoff and Kavlock, 1983; Goldenthal et al., 1978; Murray et al., 1980), however, indicate that HCCPD is not a developmental toxin at doses (i.e., 75 mg/kg, Murray et al., 1980) higher than those that cause portal-of-entry irritation (i.e., 19 mg/kg in Abdo et al., 1984); however, the database lacks functional information on reproductive toxicity. In the absence of data on the relative sensitivity of adults and juveniles, HCCPD's effects in children cannot be predicted (see Section 4.7.1 of U.S. EPA, 2001). Thus, confidence in the RfD can also be considered low. Additional data of increasing scientific and regulatory interest include immunotoxicity, acute and subchronic neurotoxicity, and developmental neurotoxicity.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

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

Source Document — U.S. EPA, 2001.

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in the finalization of this IRIS Summary. A record of these comments is included as an appendix to the Toxicological Review for Hexachlorocyclopentadiene. ***To review this appendix, exit to the toxicological review, Appendix A, Summary of and Response to External Peer Review Comments (PDF)***.

Agency Consensus Date - 06/19/2001

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

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

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

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

Hexachlorocyclopentadiene (HCCPD)
CASRN — 77-47-4
Last Revised — 07/05/2001

The inhalation Reference Concentration (RfC) is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). It is generally expressed in units of mg/m^3. In general, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Inhalation RfCs were derived according to the Interim Methods for Development of Inhalation Reference Doses (EPA/600/8-88/066F, August 1989) and subsequently, according to Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA/600/8-90/066F, October 1994). RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.B.1. Inhalation RfC Summary

The RfC is new to the IRIS file for HCCPD. The assessment placed on IRIS 01/31/1987 did not include an RfC.

Critical Effect	Exposures*	UF	MF	RfC
Suppurative inflammation of the nose **Chronic inhalation study in B6C3F1 mice** **NTP, 1994**	NOAEL: 0.56 mg/m^3 $NOAEL_{ADJ}$: 0.1 mg/m^3 $NOAEL_{HEC}$: 0.024 mg/m^3 LOAEL: 2.23 mg/m^3 $LOAEL_{ADJ}$: 0.4 mg/m^3 $LOAEL_{HEC}$: 0.095 mg/m^3	100	1	2E-4 mg/m^3

*Conversion Factors and Assumptions — Conversion from intermittent exposure to continuous exposure: 0.56 mg/m^3 × 6/24 hrs × 5/7 days = 0.1 mg/m^3. Conversion to human equivalent concentration (HEC) for interspecies dosimetric adjustment: $NOAEL_{HEC}$ was calculated for an effect in the extrathoracic (ET) region. MV_A = 0.049 L/min, MV_H = 13.8 L/min, $[SA_{ET}]_A$ = 3 cm^2, $SA(_{ET})_H$ = 200 cm^2. $RGDR_{ET} = (MV_A/[SA_{ET}]_A) / (MV_H/SA[_{ET}]_H) =$ 0.237. $NOAEL_{HEC} = NOAEL_{ADJ} \times RGDR_{ET}$ = 0.1 mg/m^3 × 0.237 = 0.024 mg/m^3.

I.B.2. Principal and Supporting Studies (Inhalation RfC)

There are no chronic human inhalation studies suitable for dose-response assessment. The only available chronic human studies found no exposure-related diseases. Thus, the one available chronic animal study was chosen as the principal study. NTP (1994) reports well-designed inhalation bioassays with two species that are suitable to evaluate dose-response.

NTP. (1994) Toxicology and carcinogenesis studies of hexachlorocyclopentadiene in F344/N rats and B6C3F1 mice (inhalation studies). National Toxicology Program Technical Report Series 437:318.

Sixty rats or mice per sex were exposed to atmospheres containing 0, 0.11, 0.56, or 2.23 mg/m^3 HCCPD for 5 days/week for 2 years. Ten male and 10 female rats and mice from each exposure group were evaluated at 15 months. The stability of the compound was monitored

throughout the study, and it was found that no degradation took place for up to 2 years. Standard bioassay data including body weights, organ weights, urinalysis, and histopathology were collected.

Exposure to HCCPD did not significantly affect survival of rats or mice, but the decrease in survival of female mice approached statistical significance in the 2.23 mg/m^3 group owing to suppurative inflammation of the ovary. Body weights of rats were unchanged by HCCPD exposure, but body weights of male and female mice were reduced in the 2.23 mg/m^3 group. Exposure was associated with a yellow-brown granular pigmentation within the cytoplasm of epithelial cells lining the respiratory tract in both rats and mice. The pigmentation, possibly produced by lipid peroxidation (NTP, 1994), was not associated with any discernible pathology and, therefore, not considered to be an adverse effect. Although the designation of this pigmentation as nonadverse conflicts with ATSDR's treatment (ATSDR, 1999), it is consistent with the guidance in the RfC methodology (U.S. EPA, 1994), which indicates that "enzyme induction and subcellular proliferation or other changes in organelles, consistent with possible mechanism of action, but no other apparent effects" should be ranked low in severity. Furthermore, the guidance states that "effects that may be considered marginal are designated as adverse only to the extent that they are consistent with other structural and functional data suggesting the same toxicity," indicating pigmentation does not qualify as an adverse effect in this situation.

In female rats, significant increases in the incidence of squamous metaplasia of the larynx were seen in the 0.11 and 2.23 mg/m^3 groups. The lesion, described as stratified squamous epithelium several cell layers thick in areas usually lined by columnar epithelium, was considered to be of minimal severity in all groups. Because there is individual variation in the location of the transition between squamous and columnar epithelia and in obtaining consistent tissue sections in the treated rats, NTP indicated that the significance of this metaplasia is unknown. In addition, a dose-response relationship was not evident. Thus, the NOAEL for rats was 2.23 mg/m^3 HCCPD and there was no LOAEL.

Increases in suppurative inflammation of the nose were noted at 2.23 mg/m^3 HCCPD in both male and female mice during the interim evaluation at 15 months and at study termination. Suppurative inflammation of the nose in mice was chosen as the critical effect since it was the only respiratory tract effect that occurred in both rats and mice. Neither sex of mice was clearly more sensitive to the effect than the other, so both sexes were used for the dose-response analysis. The incidence of this effect was 4/99, 0/100, 4/100, and 76/98 in the 0, 0.11, 0.56, and 2.23 mg/m^3 groups, respectively. Thus, the NOAEL in mice for suppurative inflammation of the nose was 0.56 mg/m^3 HCCPD and the LOAEL was 2.23 mg/m^3. The available data did not meet the suggested criteria for applying a benchmark concentration analysis (U.S. EPA, 1995) of at least three dose levels with two doses eliciting a greater than

minimum and less than maximum response. Thus, the duration-adjusted NOAEL of 0.10 mg/m^3 is used to derive the RfC.

Female mice also exhibited a dose-related increase in the incidence of suppurative ovarian inflammation that was significantly different from controls at 0.56 and 2.23 mg/m^3 HCCPD. However, these lesions were common in NTP studies at the time of the HCCPD study (1984), and have since been reduced through better laboratory practice (Rao et al. 1987). The NTP Pathology Working Group on the HCCPD study did not consider these lesions to be a direct effect of the chemical, but felt they were most likely secondary to stress resulting from exposure. Ovarian abscesses in B6C3F1 mice resulted from bacterial infection, with the bacterium *Klebsiella oxytoca* being isolated most commonly. Dose related increases in ovarian abscesses have been seen in other NTP chronic studies and the reason for this apparent treatment-related effect has been unclear. It has been suggested that stress related to exposure may depress the immune system allowing infection by opportunistic bacteria. The ovarian inflammation is unlikely to have been mouse grouping related, as the mice were housed separately in this inhalation study. In addition, selection of ovarian inflammation as the critical endpoint would have led to a higher RfC, even though the point of departure would have been lower, because of the changed regional deposition dose-ratio (RGDR) calculation resulting from use of a nasal effect (portal of entry) to a systemic effect (ovarian suppuration). Based on these considerations, the Agency has chosen not to base its RfC on this end point.

A 13-week study (NTP, 1994) provides supporting evidence that the respiratory tract is the major target of inhalation exposure to HCCPD. In a range-finding experiment to determine doses for the 2-year bioassays, the same strains of animals (10 per sex per species) were exposed to atmospheres containing 0, 0.45, 1.7, 4.5, 11, or 22 mg/m^3 HCCPD for 5 days per week, 6 hours per day. No chemical-related differences in hematology, clinical chemistry, or urinalysis parameters were reported in exposed rats.

All rats in the 11 and 22 mg/m^3 groups died. Necropsy of rats in the 11 and 22 mg/m^3 groups revealed extensive coagulation necrosis in the respiratory epithelium of the nose, larynx, trachea, bronchi, and bronchioles. Necrosis was accompanied by inflammatory signs such as vascular congestion, edema, fibrin accumulation, and neutrophil and mononuclear cell infiltration. Male rats in the 4.5 mg/m^3 group exhibited significantly increased absolute and relative lung weights, as well as necrotizing and suppurative inflammation of the nose, bronchus, and bronchioles and squamous metaplasia of the nose. The squamous metaplasia was focal in nature, generally observed on the tips of the turbinates, and characterized by stratification of the epithelium to form three to four poorly defined layers of flattened, nonkeratinized polygonal cells. Female rats seemed to be less sensitive. At the 4.5 mg/m^3 exposure, the only nasal effect was suppurative inflammation, and fewer females than males exhibited necrotizing and suppurative inflammation of the bronchus and bronchioles. Because

no respiratory lesions were seen at exposures lower than 4.5 mg/m^3 HCCPD, the NOAEL was 1.7 mg/m^3. This is similar to the NOAEL of 2.3 mg/m^3 observed for rats in the chronic study.

All mice in the 11 and 22 mg/m^3 groups died within five weeks. Before the end of the study, seven deaths occurred in the 4.5 mg/m^3 group, one death occurred in the 1.7 mg/m^3 group, and three deaths occurred in the 0.45 mg/m^3 group. Six deaths in the female control group were attributed to a defective feeder. No chemical-related differences in hematology, clinical chemistry, or urinalysis parameters were reported in exposed mice. Males in the 0.45 mg/m^3 group exhibited a statistically significant decrease in weight that was not toxicologically significant (i.e., <10%). Body weights of exposed animals were similar to controls in all other groups.

In both rats and mice some statistically significant hematological changes in red blood cell parameters occurred. Although these changes were not dose-related, they are consistent with an adaptive response to impairment of pulmonary gas exchange and add to the weight-of-evidence that the respiratory system is the major target. Clark et al. (1982) also noted hematological effects in subchronic studies.

As evidenced by a somewhat lower frequency of effects, mice were not as sensitive to the respiratory toxicity of HCCPD as were rats. Male mice exhibited significant increases in suppurative inflammation of the nose and squamous metaplasia of the trachea at 4.5 and 11 mg/m^3; and acute necrosis and suppurative inflammation of the nose; acute necrosis of the larynx, trachea, and lung; and congestion of the lung at 22 mg/m^3; Female mice had serous inflammation of the nose; at 4.5 mg/m^3; and suppurative inflammation of the nose, squamous metaplasia of the larynx and trachea, and necrotizing inflammation of the lung; at 11 mg/m^3. At the highest dose, female mice presented the same spectrum of effects as male mice. No respiratory effects were observed in mice at 1.7 mg/m^3. The chronic study observed a NOAEL of 0.56 mg/m^3 HCCPD in mice. The 1.7 mg/m^3 NOAEL in the 13-week study (NTP, 1994) supports the use of the chronic study (NTP, 1994) as the principal study because a lower NOAEL was observed.

Clark, DG; Pilcher, A; Blair, D; et al. (1982) Thirty week chronic inhalation study of hexachlorocyclopentadiene (HEX) in rats. Group Research Report SBGR.82.051. NTIS/OTIS43022.

This study also showed that the respiratory tract is the major target organ of inhaled HCCPD. Wistar rats inhaled, via whole-body exposure, 0, 0.05, 0.1, or 0.5 ppm (conversion of 1 ppm = 11.3 mg/m^3 yields 0, 0.56, 1.1, or 5.6 mg/m^3, respectively) HCCPD for 6 hours/day, 5 days/week, for 30 weeks and recovered from exposure for 14 weeks. Chemical purity of the compound decreased from 96% to 90% during the course of the study because of oxidation.

Bronchopneumonia was noted in four males and two females, which died during exposure to 5.6 mg/m^3. Two of the deceased rats had enlarged adrenals and the thorax contained watery or bloodstained fluid.

Males in the 1.1 mg/m^3 and 5.6 mg/m^3 groups had significantly higher mean erythrocyte counts, hemoglobin concentrations, hematocrit, and absolute numbers of neutrophils, and significantly lower lymphocyte counts than the controls. Mean absolute numbers of lymphocytes were lower in females at the 5.6 mg/m^3 dose.

Body weights of males from the 5.6 mg/m^3 dose group were significantly lower than those of controls. Several increases in body weights in females exposed to HCCPD compared with controls were noted, but by the end of the recovery period, body weights of females exposed to 1.1 and 5.6 mg/m^3 HCCPD were significantly lower than controls. Kidney weights were significantly increased in females in the 5.6 mg/m^3 group after exposure for 30 weeks. Male heart weights were decreased at 30 weeks in the 5.6 mg/m^3 group. The organ weight effects were not considered to be biologically significant by the study authors. Clark et al. (1982) also observed mild degenerative changes in the livers and kidneys of rats in the 5.6 mg/m^3 group.

Rats at the 5.6 mg/m^3 dose showed pulmonary degenerative changes including epithelial hyperplasia, edema, and sloughing of the bronchiolar epithelium in both sexes and epithelial ulceration and necrosis in the males. No degenerative changes in the lungs were observed in the 0.56 or 1.1 mg/m^3 dose groups. The authors suggested that the toxic action of HCCPD involved an extreme local irritation of the respiratory tract and that the mild degenerative changes in the livers and kidneys of a few animals were unlikely to contribute significantly to toxicity in the rat. The 1.1 mg/m^3 NOAEL for respiratory effects in rats in this study supports the use of NTP (1994) as the principal study because a lower NOAEL was observed in mice.

I.B.3. Uncertainty and Modifying Factors (Inhalation RfC)

UF = 100

The default uncertainty factor for interspecies extrapolation is 10. Half of that factor, $10^{1/2}$, reflects the pharmacokinetic component of interspecies uncertainty and half represents the pharmacodynamic component of interspecies uncertainty. The pharmacokinetic component of interspecies uncertainty is accounted for by the dosimetric adjustment, which converts animal exposure concentrations of HCCPD to HEC. Thus, an uncertainty factor of $10^{1/2}$ is employed for interspecies extrapolation to reflect the pharmacodynamic component of interspecies uncertainty. There are no data documenting the nature and extent of variability in human susceptibilities to HCCPD, so the default UF of 10 is used to protect sensitive human

subpopulations. A factor of $10^{1/2}$ is applied for an incomplete database because the inhalation database lacks developmental and reproductive toxicity. The total UF is 100.

MF = 1

I.B.4. Additional Studies/Comments (Inhalation RfC)

Portal-of-entry irritation effects due to HCCPD have also been observed for oral (Abdo et al, 1984) and dermal (Treon et al., 1955; Industrial Bio-test Laboratories, 1975; HEW, 1978) routes of exposure. Necrosis of bronchial epithelium and pulmonary hyperemia and edema were observed in rats, mice, rabbits, and guinea pigs exposed to high concentrations of HCCPD in acute and subacute experiments (Treon et al., 1955). Tracheobronchial irritation was reported in humans after accidental exposure to high levels of HCCPD vapor (Kominsky et al., 1980).

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.7 (PDF).

I.B.5. Confidence in the Inhalation RfC

Study — High
Database — Medium
RfC — Medium

The overall confidence in the RfC assessment is medium. The confidence in the principal study is high because it was well designed and followed standard guidelines for toxicity studies of chronic duration. The overall confidence in the database is medium. There are two chronic inhalation studies in two species accompanied by three (two with rats, one with mice) subchronic studies that verify that the respiratory tract is the major target organ. However, the inhalation database lacks reproductive and developmental studies. Oral developmental studies in three species (Chernoff and Kavlock, 1983; Goldenthal et al., 1978; Murray et al., 1980), however, indicate that HCCPD is not a developmental toxin at doses (i.e., 75 mg/kg in Murray et al., 1980) higher than those that cause portal-of-entry irritation (i.e., 19 mg/kg in Abdo et al., 1984). This suggests that the possible developmental effects of inhaled HCCPD may be less sensitive than the portal-of-entry respiratory tract effects. As there are no studies on the effects of HCCPD in juvenile animals, its effects in children cannot be predicted (see Section 4.7.1 of U.S. EPA, 2001). Additional data that would increase confidence in the assessment include immunotoxicity, acute and subchronic neurotoxicity, and developmental neurotoxicity.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

I.B.6. EPA Documentation and Review of the Inhalation RfC

Source Document — U.S. EPA, 2001.

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS Summary. A record of these comments is included as an appendix to the Toxicological Review for Hexachlorocyclopentadiene. ***To review this appendix, exit to the toxicological review, Appendix A, Summary of and Response to External Peer Review Comments (PDF)***.

Agency Consensus Date — 06/19/2001

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

I.B.7. EPA Contacts (Inhalation RfC)

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

II. Carcinogenicity Assessment for Lifetime Exposure

Hexachlorocyclopentadiene (HCCPD)
CASRN — 77-47-4
Last Revised — 07/05/2001

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per

(mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per µg/L drinking water or risk per µg/m^3 air breathed. The third form in which risk is presented is a concentration of the chemical in drinking water or air associated with cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

II.A. Evidence for Human Carcinogenicity

The current carcinogenicity assessment for HCCPD is a revision of the assessment placed in IRIS in 1990.

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

The apparent inability of HCCPD to cause genotoxic effects, and the lack of evidence for both human and animal carcinogenicity by the inhalation route, justify the conclusion that HCCPD is not likely to present a human cancer risk via inhalation exposure. According to the existing Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1986a), evaluation of the weight-of-evidence for carcinogenicity to humans indicates that HCCPD is most appropriately categorized as Group E, Evidence of Noncarcinogenicity to Humans, via inhalation exposure. In accordance with U.S. EPA's Proposed Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1996), HCCPD is not likely to be a human carcinogen by the inhalation route based on current data indicating no evidence of cancer in well-conducted bioassays in two species of rodents; the absence of increased deaths from cancer in the limited human occupational studies available; and lack of mutagenicity in a variety of test systems. In a well conducted 2-year inhalation bioassay, no increased incidence of tumors was reported in male or female rats and mice up to 2.2 mg/m^3 (NTP, 1994). Several occupational epidemiological studies reported no increase in cancer mortality associated with HCCPD exposure, in the presence of other chlorinated production compounds. Mutagenicity studies were negative in five strains of *S. typhimurium*; negative in mouse micronucleus assays; showed no evidence of transformation of BALB/3T3 cells or forward mutations in mouse lymphoma cells; did not induce DNA repair when incubated with rat hepatocytes; and failed to induce lethal mutations in the offspring of male *Drosophila*. The only positive result for mutagenicity was an isolated statistically significant increase in sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells, but chromosome damage did not occur in metaphase stage rat liver cells. Because the existing chronic health effect data in both humans and animals do not

include the oral route of exposure, the potential for carcinogenicity by the oral route is unknown. Additionally, there are no data on the carcinogenic potential of HCCPD in developing organisms.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.7 (PDF).

II.A.2. Human Carcinogenicity Data

Inadequate. Several retrospective mortality studies have been conducted on employees in plants that either produced HCCPD or used it in the manufacture of chlorinated pesticides. These studies, however, are inadequate to assess carcinogenicity of hexachlorocyclopentadiene alone because they do not estimate exposure levels to the chemical or correlate excess deaths with exposure. The studies are also limited by exposure of cohorts to other chemicals, relatively short follow-up periods, small number of person-years, and lack of data on cigarette smoking.

Shindell and Associates (1980) conducted a mortality study of 783 workers employed at least 3 months between January 1, 1946, and December 31, 1979, at the Velsicol Chemical Corporation plant in Marshall, IL. This plant manufactured synthetic chlorinated hydrocarbon insecticides using HCCPD as an intermediate. The vital status of 97.4% of the cohort was known. The causes of death examined included malignant neoplasms, diseases of the heart and circulatory system, cerebrovascular disease, trauma, and others. The number of observed deaths in each category was compared to the number of expected deaths calculated from race- and sex-specific U.S. mortality rates for appropriate 5-year periods. No excess deaths related to any specific job class or product were seen. Except for "other deaths" in females, the number of deaths observed appear lower than the number expected. The 22 deaths from cancer included brain, kidney, liver, lung, and digestive system cancers; 8 of the 22 cancer deaths were from lung cancer. The number of expected deaths for each specific cancer was not calculated.

Shindell and Associates (1981) conducted a mortality study with 1,115 workers employed for at least 3 months between January 1, 1952, and December 31, 1979, at the Velsicol Chemical Corporation plant in Memphis, TN. This plant manufactured synthetic chlorinated hydrocarbon insecticides using HCCPD as an intermediate. The vital status of 92.8% of the cohort was known. The study design was the same as that of the Shindell and Associates (1980) study described above. Deaths from strokes and from trauma showed an increase over

the number of expected deaths, but the increases were not statistically significant. The distribution of the standard mortality ratio of cancer deaths by cancer site and job showed a nonsignificant excess of lung cancer in maintenance workers. The study authors concluded that there was no pattern of neoplasia suggestive of job-related risk.

Wang and MacMahon (1979) also conducted a retrospective mortality study of the workers at the Velsicol Chemical Corporation plants in Marshall, IL, and Memphis, TN. The study group included 1,403 males who worked at either plant longer than 3 months before the spring of 1976. Person-years were calculated for January 1, 1946, to June 30, 1976, for Marshall employees and for January 1, 1952, to December 31, 1976, for Memphis employees. Approximately 34% of the subjects had fewer than 10 years follow-up and 36% had 20 or more years of follow-up study. Expected deaths for these person-years were calculated from white male national mortality rates through 1975. Observed deaths due to all causes were significantly fewer than expected. Deaths due to cerebrovascular disease, however, were statistically elevated over those expected. Deaths due to all cancers were fewer than expected, but deaths due to lung cancer were greater than expected, although not significantly. There was no relationship between lung cancer deaths and duration of exposure to HCCPD or duration of follow-up. No data on cigarette smoking are available for this study group. There was one death each from cancer of the liver, bladder, prostate, and central nervous system.

A mortality study was performed involving cohorts that overlapped the one used in the Wang and MacMahon study (1979) but extended the follow-up period (Brown et al. 1980). Different cohorts from four chemical plants that manufactured organochlorine pesticides were used in this study. These cohorts comprised all workers at each plant who had worked at least 6 months prior to December 31, 1964. Causes of deaths among the cohorts occurring prior to December 31, 1976, were recorded. Observed deaths in the cohorts were far fewer than expected, reflecting the healthy-worker effect. The expected value was calculated using U.S. white-male cause-specific mortality rates, but the report did not specify the ethnicity or sex of the employees studied. The increase in cerebrovascular disease observed in the Wang and MacMahon study (1979) was not reported in this study. A deficit in deaths from all malignant neoplasms in each plant was observed, but the numbers of workers dying from cancer were too few to provide statistically significant values. There were slight, but not statistically significant, increases in stomach cancer deaths in one plant, and slight excesses of cancer of the esophagus, cancer of the rectum, liver cancer, and cancer of the lymphatic and hematopoietic system in another plant. However, exposure to multiple organochlorine compounds in each of the plants precludes linking these cancer cases with exposure to HCCPD or any other individual compound.

Buncher et al. (1980) conducted an occupational mortality study with 341 workers at the Hooker Chemical Corporation plant in Montague, MI. The plant produced HCCPD and other

chlorinated hydrocarbons. Employees who had worked at least 90 days between October 1, 1953, and December 31, 1974, were included in the cohort. Follow-up was through December 31, 1978. Expected deaths were calculated using sex-, age- and year-specific U.S. mortality rates. Deaths due to all causes, all cancers, diseases of the circulatory system, diseases of the digestive system, and external causes were all fewer than expected. The six observed cancer deaths included one of the kidney and two of the respiratory system. The ratio of observed-to-expected deaths for the respiratory cancers (0.87) and colon cancer (1.75) are near 1.0 and are not statistically significant. The remaining cancers have ratios greater than or equal to 5; however, the small number of deaths prevents drawing a firm conclusion. The short follow-up period is also a limitation.

II.A.3. Animal Carcinogenicity Data

No evidence of carcinogenicity. NTP (1994) conducted a 2-year inhalation study with rats and mice and concluded that HCCPD exhibited no evidence of carcinogenic activity (NTP, 1994). Groups of 60 animals per sex per species were exposed, via whole-body inhalation, for 5 days per week, 6 hours per day, to 0, 0.11, 0.56, or 2.23 mg/m^3 HCCPD. The study was well designed and involved two rodent species and an appropriate number of subjects at each dose. No exposure-related increases in neoplasms were seen in male or female rats or mice. In male rats, a significant increase in the incidence of pars distalis adenoma of the pituitary (33/50, or 66%) was seen in the 2.3 mg/m^3 group. As the historical control incidence of pars distalis adenoma in male F344/N rats from other NTP inhalation studies is 60%, with a range of 45%-68%, this effect was not considered to be related to HCCPD exposure.

II.A.4. Supporting Data for Carcinogenicity

The weight-of-evidence for mutagenicity indicates that HCCPD is not mutagenic. A battery of genotoxicity studies performed by the NTP yielded generally negative results for HCCPD (NTP, 1994). NTP (1994) confirmed previous negative results for HCCPD in the Ames test (Brooks et al., 1984; Industrial Bio-test Laboratories, 1977). Negative results were also seen for changes in micronucleated erythrocyte frequency in B6C3F1 mice exposed to HCCPD for 13 weeks by inhalation, and for induction of sex-linked recessive lethal mutations in male *Drosophila melanogaster*. The negative results in *Drosophila melanogaster* confirmed those of other investigators (Mason et al., 1992; Zimmering et al., 1985). HCCPD did not induce a significant increase in morphological transformation in BALB/3T3 cells and did not induce forward mutations in mouse lymphoma cells at noncytotoxic concentrations (Litton Bionetics, Inc., 1978). Cytogenetic effects manifested as sister chromatid exchanges and chromosomal aberrations were observed in Chinese hamster ovary cells exposed to HCCPD with and without S9 (NTP, 1994), but chromosome damage did not occur in metaphase-stage rat liver

(RL4) cells (Brooks et al., 1984). HCCPD at subtoxic concentrations also did not induce DNA repair when incubated with rat hepatocytes in vitro (Brat, 1983).

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)

II.D.1. EPA Documentation

Source Document — U.S. EPA, 2001.

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS Summary. A record of these comments is included as an appendix to the Toxicological Review for Hexachlorocyclopentadiene. ***To review this appendix, exit to the toxicological review, Appendix A, Summary of and Response to External Peer Review Comments (PDF)***.

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

Consensus date - 06/19/2001

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

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

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

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Hexachlorocyclopentadiene (HCCPD)
CASRN — 77-47-4

VI.A. Oral RfD References

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VI.B. Inhalation RfC References

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VII. Revision History

Hexachlorocyclopentadiene (HCCPD)
CASRN — 77-47-4

Date	Section	Description
09/01/1990	II.	Carcinogen assessment on-line
07/05/2001	I.A	Revised RfD
07/05/2001	I.B.	Added RfC
07/05/2001	II.	Revised carcinogen summary
10/28/2003	I.A.6., I.B.6., II.D.2.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Hexachlorocyclopentadiene (HCCPD)
CASRN — 77-47-4
Last Revised — 07/05/2001

- 77-47-4
- C-56
- GRAPHLOX
- HCCP
- HCCPD
- HEX
- HEXACHLORO-1,3-CYCLOPENTADIENE
- HEXACHLOROPENTADIENE
- PCL
- PERCHLOROCYCLOPENTADIENE