EPA/600/8-85/013
June 1985

HEALTH RISK ASSESSMENT APPROACH FOR 2,3,7,8-TETRACHLORODIBENZO-p-DIOXIN

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TECHNICAL REPORT DATA
(Please read Instructions on the reverse before completing)

1. REPORT NO.	2.	3. RECIPIENT'S ACCESSION NO
EPA-600/8-85-013		P386-100674

4. TITLE AND SUBTITLE
Health Risk Assessment Approach for 2,3,7,8-Tetrachlorodibenzo-p-Dioxin

5. REPORT DATE
June 1985

6. PERFORMING ORGANIZATION CODE

7. AUTHOR(S)
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8. PERFORMING ORGANIZATION REPORT NO

9. PERFORMING ORGANIZATION NAME AND ADDRESS
[1]Environmental Criteria and Assessment Office
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10. PROGRAM ELEMENT NO

11. CONTRACT/GRANT NO

12. SPONSORING AGENCY NAME AND ADDRESS
Environmental Criteria and Assessment Office
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268

13. TYPE OF REPORT AND PERIOD COVERED

14. SPONSORING AGENCY CODE
EPA/600/22

15. SUPPLEMENTARY NOTES

16. ABSTRACT
2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) is one of the most toxic and environmentally stable pollutants. In addition to various toxic effects, TCDD has been found to cause teratogenic, fetocidal, reproductive and carcinogenic effects in animals. In humans it adversely affects various organ systems and is probably carcinogenic as well. This report documents the methodologies utilized by the United States Environmental Protection Agency in its development of health risk assessment from exposure to TCDD.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group

18. DISTRIBUTION STATEMENT	19. SECURITY CLASS (This Report)	21. NO. OF PAGES
Public	Unclassified	30
	20. SECURITY CLASS (This page)	
	Unclassified	

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

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

PREFACE

This document was compiled from the following documents prepared by the U.S. EPA, Office of Health and Environmental Assessment:

1) Ambient Water Quality Criteria for 2,3,7,8-Tetrachlorodibenzo-p-dioxin (EPA 440/5-84-007)

2) Health Assessment Document for Polychlorinated Dibenzo-p-dioxins (EPA 600/8-84-014A; External Review Draft)

3) Health and Environmental Effects Profile for Tetra-, Penta- and Hexachlorodibenzo-p-dioxins (ECAO-CIN-P004; Program Office Draft)

4) Drinking Water Criteria Document for 2,3,7,8-Tetrachlorodibenzo-p-dioxin (ECAO-CIN-405; Program Office Draft)

5) Guidelines for Developing Water Quality Criteria Documents (Federal Register, Volume 45, No. 231; November 2d, 1980)

6) Proposed Guidelines for Mutagenicity Risk Assessment (Federal Register, Volume 49, No. 227; November 23, 1984)

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While the material contained in this document was drawn from the six source documents listed in the previous page an acknowledgement is hereby given to those EPA employees whose scientific assessment work has been featured.

- Cancer Toxicology, Dr. Charles Hiremath, Carcinogen Assessment Group
- Cancer Epidemiology, Dr. David Bayliss, Carcinogen Assessment Group
- Risk Assessment, Dr. Steve Bayard, Carcinogen Assessment Group
- Mutagenicity, Dr. Sheila Rosenthal, Reproductive Effects Assessment Group
- Soil Exposure, John Schaum, P.E., Exposure Assessment Group
- Introduction, Acute, Subchronic and Chronic Toxicity, Mutagenicity and Risk Assessment, Dr. Debdas Mukerjee, Environmental Criteria and Assessment Office, Cincinnati
- Acute, Subchronic and Chronic Toxicity, and Risk Assessment, Dr. Michael Dourson, Environmental Criteria and Assessment Office, Cincinnati

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
AHH	Aryl hydroxycarbon hydroxylase
bw	Body weight
BCF	Bioconcentration factor
DMBA	Dimethylbenzanthracene
DNA	Deoxyribonucleic acid
FEL	Frank-effect level
GI	Gastrointestinal
HA	Health Advisory
LOAEL	Lowest-observed-adverse-effect level
LOEL	Lowest-observed-effect level
3-MC	3-Methylcholanthrene
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
ppb	Parts per billion
ppt	Parts per trillion
R	Bioconcentration factor
UF	Uncertainty factor
WC	Water consumption

1. INTRODUCTION

2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD), an isomer of a large series of chlorinated aromatic hydrocarbons classified as polychlorinated dibenzo-p-dioxins, is one of the most toxic and highly stable compounds found in the environment. It is a highly toxic compound with demonstrated acute, subchronic and chronic effects in animals and man. Acute and subchronic exposures of TCDD adversely affect the skin, liver, nerve and immune systems. It is teratogenic, fetotoxic and reduces fertility in laboratory animals. It is a proven animal carcinogen and is probably carcinogenic in humans.

This toxic substance is not produced commercially and has no industrial use. It is produced as an unwanted contaminant during the manufacture of chlorobenzenes, chlorophenols and their derivatives such as 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and 2-(2,4,5-trichlorophenoxy) propionic acid (silvex). The disposal of spent chemical manufacturing wastes in landfills or in uncontrolled disposal operations creates the opportunity for environmental hazards to develop. It has been detected in many species of commercial and noncommercial fish from several rivers and lakes in the United States. Fly ash from municipal waste incineration and soot from samples of a transformer fire in an office building have been found to have TCDD as a contaminant. Air filter samples collected during an industrial fire have also been found to contain TCDD. The release of TCDD into the atmosphere is due to uncontrolled endothermic reactions during the production of 2,4,5-T and other chlorophenol compounds. Another potential source of TCDD in the atmosphere is spraying of herbicides containing 2,4,5-T.

TCDD is resistant to biodegradation reactions in the soil. The half-life of TCDD in soil has been found to be more than a decade. It binds avidly to the organic content of soil.

The public health concern for human exposure to TCDD is due to the multiplicity of adverse health effects, which can result from very low levels of exposure and increasing knowledge about its widespread distribution in the environment. These considerations combined with its extreme stability in the environment make TCDD a potential major environmental concern.

U.S. EPA with its numerous regulatory activities has prepared several health assessment documents on dioxins that inventory the data from world scientific literature and provide interpretations for hazard and risk analysis estimations. Underpinning the health assessment activities are assessment methodologies for toxic effects consisting of carcinogenic and noncarcinogenic effects from chronic, subchronic and acute exposures.

This report documents the health assessment methodologies utilized by U.S. EPA in its development of TCDD health assessments and presents the key scientific information essential for risk analysis. The scientific data base as reported by reference in this report is current through May, 1984.

2. RISK ASSESSMENT APPROACH FOR CHRONIC EXPOSURE

2.1. HUMAN HEALTH RISK ASSESSMENT BASED ON CARCINOGENICITY DATA

2.1.1. Carcinogenicity Data Available for TCDD. In a preliminary study by Van Miller (1977a,b), 2,3,7,8-TCDD was tested for carcinogenicity following oral administration to rats. At the five highest dietary levels, 0.005, 0.05, 0.5, 1.0 and 5.0 ppb, which allowed long-term survival of the animals, an increase in the incidence of total tumors was observed. There were no tumors in animals at an exposure level of 0.001 ppm and in the control animals. This study, however, provides only suggestive evidence of a carcinogenic response since no increase in site specific tumors was detected and the group sizes, ~10 animals/group, were too small for an assessment of a treatment-related response. Kociba et al. (1978b), in a more extensive study, detected a positive carcinogenic response. In this study, the estimated intake of 2,3,7,8-TCDD from the diet was 0.0, 0.001, 0.01 and 0.1 µg/kg/day. In the high-dose group, both male and female animals had significant increases in site-specific tumors. The target organs and tumor types in male animals were squamous cell carcinomas of the tongue and of the hard palate, and adenomas of the adrenal cortex, while in female animals the target organs and tumor types were hepatocellular carcinomas, squamous cell carcinomas of the tongue and of the lung. The data demonstrate that dietary exposure to 2,3,7,8-TCDD at levels that produce a daily dose of 0.1 µg/kg produce increased tumor incidences in both male and female rats.

Under the National Toxicology Program, 2,3,7,8-TCDD was tested for carcinogenicity in rats following administration by gavage (NTP, 1980a). Both male and female animals were exposed to weekly doses of 0.0, 0.01, 0.05 and 5 µg/kg bw. The only tumors that appeared to be treatment-related were follicular cell adenomas or carcinomas of the thyroid in male animals,

and neoplastic nodules or hepatocellular carcinomas of the liver in female animals. The incidence of these tumors was significantly greater than control in the high-dose groups, and the incidences of both tumors showed a positive dose-related trend. Under the conditions of this assay, 2,3,7,8-TCDD was concluded to be carcinogenic in both male and female rats.

Further studies in mice exposed by gavage have provided support for the carcinogenicity of 2,3,7,8-TCDD. Toth et al. (1979) exposed male mice to 2,3,7,8-TCDD at doses of 0.0, 0.007, 0.07 and 7.0 µg/kg/week in a study to determine whether 2,4,5-TCPE, its contaminant 2,3,7,8-TCDD, or both were carcinogens. At the 0.7 µg/kg/week level there was a significantly increased incidence of liver tumors. Liver tumors were not significantly increased in the high-dose group; however, early mortality in this group may have precluded observing late developing tumors. Similar increased incidences of liver tumors were observed in the NTP (1980a) study in the high-dose male mice exposed to 0.5 µg/kg/week and in the high-dose female mice exposed to 2 µg/kg/week of 2,3,7,8-TCDD by gavage. Female mice also had an increased incidence of follicular cell adenomas of the thyroid. In both studies, 2,3,7,8-TCDD was carcinogenic to mice with effective doses ranging between 0.5 and 2 µg/kg/day depending on sex and the individual study.

The mouse skin two-stage tumorigenicity model has also been used to test the carcinogenic potential of 2,3,7,8-TCDD. Following long-term dermal application 3 times/week of 2,3,7,8-TCDD at levels of 0.01 and 0.005 µg/application to male and female mice, respectively, there was an increased incidence of skin tumors only in female mice (NTP, 1980b). Along with the indication that 2,3,7,8-TCDD was a complete carcinogen in this system, DiGiovanni et al. (1977) reported that 2,3,7,8-TCDD was also a tumor initiator in mouse skin. The ability of 2,3,7,8-TCDD to initiate tumors,

however, has yet to be confirmed since appropriate vehicle and promotion only control groups were not included. Attempts to demonstrate tumor promoting activity with 2,3,7,8-TCDD on mouse skin have produced negative results in some assays (NTP, 1980b; Berry et al., 1978, 1979); however, Poland et al. (1982) reported that 2,3,7,8-TCDD was a tumor promoter when tested on the skin of mice homozygous for the "hairless" trait but not in mice heterozygous for this recessive trait. Pitot et al. (1980) also reported that 2,3,7,8-TCDD was a promoter for DEN-initiated hepatocarcinogenesis in rats following parenteral administration of the compounds. On mouse skin, 2,3,7,8-TCDD was a complete carcinogen and possibly a tumor initiator, while no tumor promoting activity could be attributed to 2,3,7,8-TCDD in the assays. In rat liver initiated with DEN, 2,3,7,8-TCDD was a tumor promoter.

In studies of the interaction of 2,3,7,8-TCDD with other chemical carcinogens, Kouri et al. (1978) reported that 2,3,7,8-TCDD was a cocarcinogen with 3-MC when administered by subcutaneous injection. In the mouse skin bioassay, initiation with simultaneous administration of 2,3,7,8-TCDD and DMBA, however, did not affect tumor yield (DiGiovanni et al., 1977). Similarly, no effect was observed when 2,3,7,8-TCDD was administered either immediately before (5 minutes) or 1 day after DMBA initiation (Berry et al., 1979; DiGiovanni et al., 1977, 1979; Cohen et al., 1979). When treatment with 2,3,7,8-TCDD occurred 1-10 days before DMBA initiation, 2,3,7,8-TCDD demonstrated a potent anticarcinogenic action. Although 1-5 days prior exposure to 2,3,7,8-TCDD inhibited tumor initiation by BaP, 3-MC and BaP-diol-epoxide, the tumor initiating ability of the latter compound was also inhibited when 2,3,7,8-TCDD exposure occurred either 5 minutes before or 1 day after initiation (DiGiovanni et al., 1980). The increased AHH activity

resulting from 2,3,7,8-TCDD exposure may account for the anticarcinogenic activity by altering the metabolism of the initiating compound; however, DiGiovanni et al. (1980) suggested that the inhibition of the initiating activity of BaP-diol-epoxide 1 day after initiation indicates that more than one mechanism participates in the anticarcinogenic activity of 2,3,7,8-TCDD.

Two Swedish case-control studies report a highly significant association of soft-tissue sarcoma with exposure to phenoxy acid or chlorophenols (or both) (Hardell and Sandstrom, 1979; Eriksson et al., 1979, 1981). They do not, however, pinpoint the risk to the dioxin contaminants. In fact, in one study, the risk was found to extend to phenoxy acids free of dioxin impurities. In that study, the risk increased to 17 when phenoxy acids known to contain dioxin impurities were considered (polychlorinated dibenzodioxins and dibenzofurans). The extent of observer bias and recall bias introduced into these studies by the employment of an undesirable methodology (self-administered questionnaires) is probably not of sufficient magnitude to have produced the highly significant risks found in the studies. However, the possibility exists that these biases could have played a role in the determination of these risks, and consequently, the data must be considered limited for the carcinogenicity of phenoxy acid herbicides and chlorophenols in the absence of confirmatory studies.

Later studies that did not reveal a significant excess risk of soft-tissue sarcoma have severe problems with their methodologies (Eriksson et al., 1981; Cook et al., 1980). These problems make later studies inadequate to evaluate the risk of soft-tissue sarcomas from exposure to phenoxy acids and/or chlorophenols and, consequently, dioxin.

Therefore, the Swedish case-control studies provide limited evidence for the carcinogenicity of phenoxy acids and chlorophenols in humans. However, with respect to the dioxin impurities contained within, the evidence for human carcinogenicity based on the epidemiologic evidence is only suggestive, because it is difficult to evaluate the risk of dioxin exposure in the presence of the confounding effects of phenoxy acids and chlorophenol.

Substantially weaker evidence exists incriminating 2,4,5-T or 2,3,7,8-TCDD (or both) as the cause of malignant lymphoma (Hardell, 1979; Hardell et al., 1980; Hardell and Eriksson, 1981; Edling and Granstam, 1979) and stomach cancer (Axelson et al., 1980; Thiess and Frentzel-Beyme, 1977) in humans.

2.1.2. Qualitative Criteria for Determining Strength of Carcinogenic Evidence. The approach followed by the International Agency for Research on Cancer (IARC, 1982) has been utilized by EPA to determine the strength of carcinogenic evidence for a chemical. A chemical under study is classified in the following categories, according to the strength of scientific evidence for its carcinogenic properties in experimental animal test systems:

- "Sufficient Evidence" of Carcinogenicity. There is an increased incidence of malignant tumors 1) in multiple species or strains; 2) in multiple experiments (preferably with different routes of administration or using different dose levels); or 3) to an unusual degree with regard to incidence, site, or type of tumor, or age at onset. Additional evidence may be provided by data concerning dose-response effects as well as information on mutagenicity or chemical structure.

- "Limited Evidence" of Carcinogenicity. Data suggest a carcinogenic effect but are limited for the following reasons: 1) the studies refer to a single species, strain or experiment; 2) the experiments are restricted due to inadequate dosage levels, inadequate duration of exposure to the agent, inadequate period of follow-up, poor survival, too few animals, or inadequate reporting; or 3) the neoplasms produced often occur spontaneously or are difficult to classify as malignant by histological criteria alone (i.e., lung and liver tumors in mice).

- "Inadequate Evidence." Because of major qualitative or quantitative limitations, the studies cannot be interpreted as showing either the presence or the absence of a carcinogenic effect.

- "Negative Evidence." Within the limits of the tests used, the chemical is not carcinogenic. The number of negative studies is limited since, in general, studies showing no effect are less likely to be published than those suggesting carcinogenicity.

- "No Data." Data are not available.

When available human data are factored into the evaluation of carcinogenicity, it is found that there are three main sources of evidence for carcinogenic [illegible] humans:

1. Case [illegible]orts of individual cancer patien[illegible] who were exposed to the che[illegible].

2. Descriptive epidemiological studies in which individual exposures to the chemical or group of chemicals was found to be associated with an increased risk of cancer.

3. Analytical epidemiological (case-control in cohort) studies in which individual exposures to the chemical or group of chemicals was found to be associated with an increased risk of cancer.

In evaluating human evidence, three criteria must be met before a causal association may be inferred between exposure and human cancer:

1. There is no identified bias that could explain the association.

2. The possibility of confounding has been considered and ruled out as explaining the association.

3. The association is unlikely to be due to chance.

In general, although a single study may be indicative of a cause-effect relationship, confidence in inferring a causal association is increased when several independent studies are concordant in showing the association, when the association is strong, when there is a dose-response relationship, or

when a reduction in exposure is followed by a reduction in the evidence of cancer. Therefore, when evaluating human data, the IARC weight-of-evidence categories are as follows:

- "Sufficient Evidence" of Carcinogenicity. The data indicate a causal association between exposure and human cancer.
- "Limited Evidence" of Carcinogenicity. The data indicate a possible carcinogenic effect in humans, although the data are not sufficient to demonstrate a causal association.
- "Inadequate Evidence" of Carcinogenicity. The data are qualitatively or quantitatively insufficient to allow any conclusion regarding carcinogenicity for humans.

In the absence of sufficient evidence from human studies, evaluation of the carcinogenic risk to humans is based on consideration of the epidemiological and experimental animal evidence together.

As a final ranking step, the chemicals, groups of chemicals, or industrial processes are placed into one of three groups.

Group 1. The chemical, group of chemicals, or industrial process is carcinogenic for humans. This category is used only when there was sufficient evidence to support a causal association between the exposure and cancer.

Group 2. The chemical or group of chemicals is probably carcinogenic for humans. This category includes chemicals for which the evidence of human carcinogenicity is almost sufficient as well as chemicals for which it is only suggestive. To reflect this range, this category has been divided into higher (Subgroup A) and lower (Subgroup B) degrees of evidence. The data from experimental animal studies plays an important role in assigning chemicals to Group 2, particularly Subgroup B.

Group 3. The chemical or group of chemicals cannot be classified as to its carcinogenicity for humans.

Using the criteria developed by IARC (1982), a weight-of-evidence ranking for the carcinogenicity data of 2,3,7,8-TCDD can be made. Because of the induction of hepatocellular carcinoma in two strains of female rats and

both sexes of one mouse strain, along with the induction of thyroid tumors, subcutaneous fibrosarcomas, and lung and tongue tumors in both rats and mice, the evidence of carcinogenicity for 2,3,7,8-TCDD in animals would be regarded as "sufficient" if the classification system of the IARC were used. The demonstration of a promotion effect in rat liver after initiation with diethylnitrosamine and a cocarcinogenic response when 2,3,7,8-TCDD was injected simultaneously with 3-methyl chloranthrene further supports the "sufficient" classification in animals.

The human evidence for the carcinogenicity of 2,3,7,8-TCDD alone is regarded as "inadequate" using the IARC classification because of the difficulty of attributing the effects to 2,3,7,8-TCDD, which occurred as an impurity in the phenoxyacetic acids and chlorophenols to which the people were exposed. However, the human evidence for the carcinogenicity of chlorinated phenoxyacetic herbicides and chlorophenols with chlorinated dibenzodioxin and dibenzofuran impurities is "limited" according to the IARC criteria.

The overall evidence of carcinogenicity, considering both animal and human studies, would place 2,3,7,8-TCDD alone in IARC's Group 2B and 2,3,7,8-TCDD in association with the phenoxy herbicides and chlorophenols in Group 2A category (IARC, 1982). The IARC regards chemicals in both categories as probably carcinogenic in humans.

2.1.3. Approach for Quantitative Cancer Risk Assessment. The data used for a quantitative estimate is one or both of two types: 1) lifetime animal studies and 2) human studies where excess cancer risk has been associated with exposure to the agent. In animal studies it is assumed, unless evidence exists to the contrary, that if a carcinogenic response occurs at the dose levels used in the study, then responses will also occur at all lower doses with an incidence determined by an extrapolation model.

There is no solid scientific basis for any mathematical extrapolation model that relates carcinogen exposure to cancer risks at the extremely low concentrations that must be dealt with in evaluating environmental hazards. For practical reasons, such low levels of risk cannot be measured directly either by animal experiments or by epidemiologic studies. Therefore, scientific judgement depends on the current understanding of the mechanisms of carcinogenesis for guidance as to which risk model to use. At the present time, the dominant view of the carcinogenic process involves the concept that most cancer-causing agents also cause irreversible damage to DNA. There is reason to expect that the quantal type of biological response is associated with a linear nonthreshold dose-response relationship. This is particularly true at the lower end of the dose-response curve; at higher doses, there can be an upward curvature, probably reflecting the effects of multistage processes on the mutagenic response. The linear nonthreshold dose-response relationship is also consistent with the relatively few epidemiologic studies of cancer responses to specific agents that contain enough information to make the evaluation possible (e.g., radiation-induced leukemia, breast and thyroid cancer, skin cancer induced by arsenic in drinking water, liver cancer induced by aflatoxins in the diet). There is also some evidence from animal experiments that is consistent with the linear nonthreshold model (e.g., liver tumors induced in mice by 2-acetylaminofluorene in the large-scale ED_{01} study at the National Center for Toxicological Research, and the initiation stage of the two-stage carcinogenesis model in rat liver and mouse skin).

Because of its scientific basis, although limited, the linear nonthreshold model has been adopted by EPA as the primary basis for upper bound risk extrapolation in the low-dose region of the dose-response relationship.

The risk estimates made with this model should be regarded as conservative, representing the most plausible upper limit for the risk (i.e., the true risk is not likely to be higher than the estimate, but it could be lower).

The mathematical formulation chosen to describe the linear nonthreshold dose-response relationship at low doses is the linearized multistage model. This model employs enough arbitrary constants to be able to fit almost any monotonically increasing dose-response data, and it incorporates a procedure for estimating the largest possible linear slope (in the 95% confidence limit sense) at low extrapolated doses that is consistent with the data at all dose levels of the experiment. The following is a description of the Low-Dose Animal Extrapolation Model:

Let P(d) represent the lifetime risk (probability) of cancer at dose d. The multistage model has the form

$$P(d) = 1 - \exp\left[-(q_0 + q_1 d + q_2 d^2 + \ldots + q_k d^k)\right]$$

where

$$q_i \geq 0, \quad i = 0, 1, 2, \ldots, k.$$

Equivalently,

$$P_t(d) = 1 - \exp\left[-(q_1 d + q_2 d^2 + \ldots + q_k d^k)\right]$$

where

$$p_t(d) = \frac{P(d) - P(0)}{1 - P(0)}$$

is the extra risk over background rate at dose d.

The point estimate of the coefficients q_i, $i = 0, 1, 2 \ldots$, and consequently, the extra risk function, $P_t(d)$, at any given dose d, is calculated by maximizing the likelihood function of the data.

The point estimate and the 95% upper confidence limit of the extra risk, $P_t(d)$, are calculated by using the computer program GLOBAL 79 developed by Crump and Watson (1979). At low doses, upper 95% confidence limits on the extra risk and lower 95% confidence limits on the dose producing a given risk are determined from a 95% upper confidence limit, q_1^* on parameter q_1. Whenever q_1 is >0, at low doses the extra risk $P_t(d)$ has approximately the form $P_t(d) = q_1^* \times d$. Therefore, $q_1^* \times d$ is a 95% upper confidence limit on the extra risk and R/q_1^* is a 95% lower confidence limit on the dose producing an extra risk of R. Let L_0 be the maximum value of the log-likelihood function. The upper limit, q_1^*, is calculated by increasing q_1 to a value q_1^* such that when the log-likelihood is remaximized subject to this fixed value q_1^* for the linear coefficient, the resulting maximum value of the log-likelihood L_1 satisfies the equation

$$2 (L_0 - L_1) = 2.70554$$

where 2.70554 is the cumulative 90% point of the chi-square distribution with one degree of freedom, which corresponds to a 95% upper limit (one-sided). This approach of computing the upper confidence limit for the extra risk A(d), is an improvement on the Crump et al. (1977) model. The upper confidence limit for the extra risk calculated at low doses is always linear. This is conceptually consistent with the linear nonthreshold concept discussed earlier. The slope, q_1^*, is taken as an upper bound of the potency of the chemical in inducing cancer at low doses. [In the section calculating the risk estimates, $P_t(d)$ will be abbreviated as P.]

In fitting the dose-response model, the number of terms in the polynomial is chosen equal to (h-1), where h is the number of dose groups in the experiment, including the control group.

Whenever the multistage model does not fit the data sufficiently well, data at the highest dose are deleted and the model is refit to the rest of the data. This is continued until an acceptable fit to the data is obtained. To determine whether or not a fit is acceptable, the chi-square statistic

$$X^2 = \sum_{i=1}^{h} \frac{(X_i - N_i P_i)^2}{N_i P_i (1-P_i)}$$

is calculated where N_i is the number of animals in the i^{th} dose group, X_i is the number of animals in the i^{th} dose group with a tumor response, P_i is the probability of a response in the i^{th} dose group estimated by fitting the multistage model to the data, and h is the number of remaining groups. The fit is determined to be unacceptable whenever X^2 is larger than the cumulative 99% point of the chi-square distribution with f degrees of freedom, where f equals the number of dose groups minus the number of nonzero multistage coefficients.

2.1.3.1. SELECTION OF CARCINOGENICITY DATA -- for some chemicals, several studies in different animal species, strains and sexes are available, each run at several doses and different routes of exposure. A choice must be made as to which of the data sets from several studies to use in the model. The procedures used in evaluating these data are consistent with the approach of making a maximum-likelihood risk estimate. They are listed below as follows:

1. The tumor incidence data are separated according to organ sites or tumor types. The set of data (i.e., dose and tumor incidence) used in the model is the set where the incidence is statistically significantly higher than the control for at least one test dose level and/or where the tumor incidence rate shows a statistically significant trend with respect to dose level.

The data set that gives the highest estimate of the lifetime carcinogenic risk, q_1^*, is selected in most cases. However, efforts are made to exclude data sets that produce spuriously high risk estimates because of a small number of animals. That is, if two sets of data show a similar dose-response relationship, and one has a very small sample size, the set of data having the larger sample size is selected for calculating the carcinogenic potency.

2. If there are two or more data sets of comparable size that are identical with respect to species, strain, sex and tumor sites, the geometric mean of q_1^*, estimated from each of these data sets, is used for risk assessment.

3. If two or more significant tumor sites are observed in the same study, and if the data are available, the number of animals with at least one of the specific tumor sites under consideration is used as incidence data in the model.

2.1.3.2. **DERIVATION OF HUMAN EQUIVALENT DOSAGES** -- It is appropriate to correct for metabolism difference between species and any variation in adsorption factors by different routes of administration.

Following the suggestion of Mantel and Schneiderman (1977), it is assumed that mg/surface area/day is an equivalent dose between species. Since, to a close approximation, the surface area is proportional to the 2/3 power of the weight, as would be the case for a perfect sphere, the exposure in mg/day per 2/3 power of the weight is also considered to be equivalent exposure. In an animal experiment, this equivalent dose is computed in the following manner.

Let

L_e = duration of experiment

l_e = duration of exposure

m = average dose/day in mg during administration of the agent (i.e., during l_e) and

W = average weight of the experimental animal

Then, the lifetime average exposure is

$$d = \frac{l_e \times m}{L_e \times W^{2/3}}$$

2.1.3.3. ESTIMATION OF THE UNIT RISK FROM ANIMAL STUDIES -- The risk associated with d $mg/kg^{2/3}/day$ is obtained from GLOBAL 79, and for most cases of interest to risk assessment, can be adequately approximated by $P(d) = 1 - \exp(-q_1^* d)$. A "unit risk" in units X is simply the risk corresponding to an exposure of X = 1. To estimate this value, we simply find the number of $mg/kg^{2/3}/day$ corresponding to one unit of X and substitute this value into the above relationship. Thus, for example, if X is in units of $\mu g/m^3$ in the air, then for case (1), $d = 0.29 \times 70^{1/3} \times 10^{-3}$ $mg/kg^{2/3}/day$, and for case (2), d = 1, when $\mu g/m^3$ is the unit used to compute parameters in animal experiments.

If exposures are given in terms of ppm in air, we may simply use the fact that

$$1 \text{ ppm} = 1.2 \times \frac{\text{molecular weight (gas) } mg/m^3}{\text{molecular weight (air)}}.$$

Note that an equivalent method of calculating unit risk would be to use mg/kg/day for the animal exposures and then to increase the j^{th} polynomial coefficient by an amount

$$(W_h/W_a)^{j/3} \quad j = 1, 2, \ldots, k,$$

and use the mg/kg/day equivalents for the unit risk values. In the section calculating the unit risks from animal data, the final q_1^* will always be the upper-limit potency estimate for humans.

If the duration of the experiment, L_e, is less than the natural lifespan of the test animal, L, the slope, q_1^*, or more generally the exponent, g(d), is increased by multiplying a factor $(L/L_e)^z$. It is assumed that if the average dose, d, is continued, the age-specific rate of cancer will continue to increase as a constant function of the background rate.

The age-specific rates for humans increase at least by the second power of the age, and often by a considerably higher power, as demonstrated by Doll (1971). Thus, the cumulative tumor rate would be expected to increase by at least the third power of age. Using this fact, it can be assumed that the slope, q_1^*, or more generally the exponent, g(d), would also increase by at least the third power of age. As a result, if the slope q_1^* [or g(d)] is calculated at age L_e, it can be expected that if the experiment had been continued for the full lifespan, L, at the given average exposure, the slope q_1^* [or g(d)] would have been increased by at least $(L/L_e)^3$.

This adjustment is conceptually consistent with the proportional hazard model proposed by Cox (1972) and the time-to-tumor model considered by Crump and Watson (1979), where the probability of cancer by age t and at dose d is given by

$$P(d,t) = 1 - \exp [-f(t) \times g(d)].$$

2.1.3.4. *INTERPRETATION OF QUANTITATIVE ESTIMATES* -- For several reasons, the unit-risk estimate based on animal bioassays is only an approximate indication of the absolute risk in populations exposed to known carcinogen concentrations. First, there are important species differences in uptake, metabolism and organ distribution of carcinogens, as well as species differences in target site susceptibility, immunologic responses, hormone function, dietary factors and disease. Second, the concept of equivalent doses for humans compared with animals on a mg/surface area basis is virtually without experimental verification regarding carcinogenic response. Finally, human populations are variable with respect to genetic constitution and diet, living environment, activity patterns and other cultural factors.

The unit-risk estimate can give a rough indication of the relative potency of a given agent compared with other carcinogens. The comparative

potency of different agents is more reliable when the comparison is based on studies in the same test species, strain and sex and by the same route of exposure, preferably by inhalation.

The quantitative aspect of the carcinogen risk assessment is included here because it may be of use in the regulatory decision-making process (setting regulatory priorities, evaluating the adequacy of technology-based controls, etc.). However, it should be recognized that the estimation of cancer risks to humans at low levels of exposure is uncertain. At best the linear extrapolation model used here provides a rough but plausible estimate of the upper limit of risk (i.e., it is not likely that the true risk would be much more than the estimated risk, but it could very well be considerably lower). The risk estimates presented in subsequent sections should not be regarded as an accurate representation of the true cancer risks even when the exposures are accurately defined. The estimates presented may be factored into regulatory decisions to the extent that the concept of upper risk limits is found to be useful.

2.1.4. **Cancer Risk Assessment for TCDD via Oral Route and Derivation of the Ambient Water Quality Criteria for TCDD.** Often exposures are not given in units of mg/day, and it becomes necessary to convert the given exposures into mg/day. Similarly, in drinking water studies, exposure is in ppm in the water. For example, in most feeding studies exposure is in terms of ppm in the diet. In these cases the exposure in mg/day is

$$m = ppm \times F \times r$$

where ppm is parts per million of the carcinogenic agent in the diet or water. F is the weight of the food or water consumed/day in kg, and r is the absorption fraction. In the absence of any data to the contrary, r is

assumed to be equal to one. For a uniform diet, the weight of the food consumed is proportional to the calories required, which in turn is proportional to the surface area, or 2/3 power of the weight. Water demands are also assumed to be proportional to the surface area, so that

$$m \propto ppm \times W^{2/3} \times r$$

or

$$\frac{m}{rW^{2/3}} \propto ppm$$

As a result, ppm in the diet or water is often assumed to be an equivalent exposure between species. However, this is not felt to be justified since the calories/kg of food is very different in the diet of man in comparison with that of laboratory animals, primarily because of moisture content differences. Consequently, the amount of drinking water required by each species also differs because of the amount of moisture in the food. Therefore, we use an empirically derived factor, $f = F/W$, which is the fraction of a species' body weight that is consumed/day as food. The following rates are used:

		Fraction of Body Weight Consumed as	
Species	W	f_{Food}	f_{Water}
Man	70	0.028	0.029
Rats	0.35	0.05	0.078
Mice	0.03	0.13	0.17

Thus, when exposure is given as a certain dietary or water concentration in ppm, the exposure in $mg/W^{2/3}$ is

$$\frac{m}{rW^{2/3}} \quad \frac{ppm \times f}{W^{2/3}} \quad \frac{ppm \times f \times W}{W^{2/3}} = ppm \times f \times W^{1/3}$$

When exposure is given in terms of mg/kg/day = m/Wr = s, the conversion is simply

$$\frac{m}{rw^{2/3}} = s \times W^{1/3}$$

The positive animal cancer data available for calculating a unit-risk estimate for 2,3,7,8-TCDD include the following:

1. The Kociba et al. (1978a) diet study on Sprague-Dawley rats, Spartan substrain. Significant cancers in the males included stratified squamous cell carcinomas of the tongue and squamous cell carcinomas of the nasal turbinates and hard palate. Significant cancers in the females included lung, nasal turbinate and hard palate cancers, and liver tumors. As with the males, the total number of animals with at least one of these significant tumors was recorded.

2. The NCI gavage study (NTP, 1980a) in Osborne-Mendel rats and B6C3F1 mice.

   a. 2,3,7,8-TCDD in male rats caused an increase in follicular cell adenomas and carcinomas combined of the thyroid. However, these tumors were not considered biologically significant for risk assessment purposes. In females, the combined neoplastic nodules and hepatocellular carcinomas were considered significant, and these data were used. The adrenal cortical adenomas or carcinomas were not considered biologically significant.

   b. 2,3,7,8-TCDD in male mice caused an increase in hepatocellular carcinomas and in combined hepatocellular adenomas and carcinomas. In female mice, 2,3,7,8-TCDD caused an increase in subcutaneous tissue fibrosarcomas, lymphomas or leukemias of the hematopoietic system, liver hepatocellular carcinomas and adenomas, and thyroid follicular cell adenomas.

The above data have been fitted to the linearized multistage model described in the methodology section. The data from which the steepest slope factor (q_1^*) (i.e., greatest potency) was calculated were from an independent pathologist's (Dr. R. Squire) review of the Dow Chemical Company lifetime rat feeding study. This factor is

$$q_1^* = 4.25 \times 10^5 \text{ (mg/kg/day)}^{-1}$$

based on the tumors in female Sprague-Dawley rats. For the purpose of these calculations, the largest dose group in the study was eliminated because inclusion of all of the dose groups resulted in a poor fit of the model ($p<0.01$). Early increased mortality in the high-dose group was also adjusted for by eliminating animals that died during the first year, so that the first tumors considered were those detected during the 13th month of the study. The results yield acceptable fits of the data without dropping the responses at the highest dose levels. The slope estimates for the Kociba and Squire analyses, 1.51×10^{5} and 1.61×10^{5} $(mg/kg/day)^{-1}$, were averaged by taking the geometric mean, and the final estimate thus becomes

$$q_1^* = [(1.51 \times 10^5) \times (1.61 \times 10^5)]^{1/2} = 1.56 \times 10^5 \ (mg/kg/day)^{-1}.$$

This upper-limit estimate represents a range of uncertainty that is related as much to the fitting procedure as to the model itself. The dropping of the highest dose-response data and the resulting increased 95% upper-limit slope estimate based on the Squire analysis, can be defended on the basis that the highest dose data in this bioassay is 100 times that of the lowest and would, therefore, contain very little information about the shape of the dose-response curve at low dose levels. It could also be argued on the basis of a saturation effect of either dose or response; the data can partially support either hypothesis. An adjustment of the multistage model needed to incorporate such an effect or effects, however, is felt to be unwarranted by the sparsity of the supporting evidence. As an alternative, to incorporate this uncertainty, a range of 95% upper-limit estimates of $q_1^* = 9.0 \times 10^4$ to 4.25×10^5 $(mg/kg/day)^{-1}$ has been chosen to accommodate this unusual data set.

In order to estimate a unit risk for a 1 µg/ℓ concentration in drinking water, the following conversion is used:

$$1\ \mu g/kg/day \times 70\ kg \times 10^3\ ng/\mu g \times 1\ day/2\ \ell = 3.5 \times 10^4\ ng/\ell$$

based on human consumption of 2 ℓ water/day for a lifetime. Therefore, unit risk corresponding to 1 ng 2,3,7,8-TCDD/ℓ water is

$$q_1^* = 1.56\times10^2\ (\mu g/kg/day)^{-1} \times \frac{1\ \mu g/kg/day}{3.5\times10^4\ ng/\ell} = 4.5\times10^{-3}\ (ng/\ell)^{-1}$$

Similarly, the lower and upper limits of the range vary from $q_1^* = 2.6\times10^{-3}$ to $1.2\times10^{-2}\ (ng/\ell)^{-1}$.

After the value of q_1^* in $(mg/kg/day)^{-1}$ has been determined, the lifetime risk, P, from an average daily exposure of x mg/kg/day is found from the equation $P = q_1^* x$. Therefore, if the lifetime risk is set at $P = 10^{-5}$ for calculation purposes, the intake, I, in mg/day for a 70 kg person can be found by the equation $I = 70\times10^{-5}/q_1^*$. The intake of the agent from ambient water is assumed to come from two sources: 1) drinking an average of 2 ℓ of water/day and 2) ingesting an average of 6.5 g of fish/day. Because of accumulation of residues in fish, the amount of the pollutant in fish (mg/kg of edible fish) is equal to a factor B times the water concentration.

Information on exposure can be valuable in developing and assessing a water quality criterion. Exposure from consumption of contaminated water and contaminated fish and shellfish products is used as a source of information in criterion formulation. Data for all modes of exposure are useful in relating total intake to the expected contribution from contaminated water, fish and shellfish. In addition, information for all routes of exposure, not limited to drinking water and fish and shellfish ingestion, can be used to justify or assess the feasibility of the formulation of criteria for ambient water.

The use of fish consumption as an exposure factor requires the quantitation of pollutant residues in the edible portions of the ingested species. Accordingly, BCFs are used to relate pollutant residues in aquatic organisms to the pollutant concentration in the ambient waters in which they reside.

To estimate the average per capita intake of a pollutant from consumption of contaminated fish and shellfish, the results of a diet survey were analyzed to calculate the average consumption of freshwater and estuarine fish and shellfish. A species is considered to be a consumed freshwater or estuarine fish and shellfish species if at some stage in its life cycle, it is harvested from fresh or estuarine water for human consumption in significant quantities.

Three different procedures are used to estimate the weighted average BCF depending upon the lipid solubility of the chemical and the availability of bioconcentration data.

For lipid-soluble compounds, the average BCF is calculated from the weighted average percent lipids in the edible portions of consumed freshwater and estuarine fish and shellfish, which was calculated from data on consumption of each species and its corresponding percent lipids to be 3.0%. Because the steady-state BCFs for lipid-soluble compounds are proportional to percent lipids, BCFs for fish and shellfish can be adjusted to the average percent lipids for aquatic organisms consumed by Americans. For many lipid-soluble pollutants, there exists at least one BCF for which the percent lipid value was measured for the tissues for which the BCF is determined.

With 3.0% as the weighted average percent lipids for freshwater and estuarine fish and shellfish in the average diet, a BCF, and a corresponding percent lipid value, the weighted average BCF can be calculated.

In those cases where an appropriate BCF is not available, the equation "Log BCF = (0.85 Log P) - 0.70" can be used to estimate the BCF for aquatic organisms containing about 7.6% lipids from the octanol/water partition coefficient P. An adjustment for percent lipids in the average diet versus 7.6% is made in order to derive the weighted average BCF.

For nonlipid-soluble compounds, the available BCFs for the edible portion of consumed freshwater and estuarine fish and shellfish are weighted according to consumption factors to determine a weighted BCF representative of the average diet.

Therefore, the total intake I can be written as the sum of two terms:

$$I(\text{mg/day}) = C(\text{mg/l}) \times R(\text{l/kg fish}) \times 0.0065 \text{ kg fish/day} + C(\text{mg/l} \times 2 \text{ l/day})$$

$$= C(2 + 0.0065R)$$

where C represents the water concentration in mg/l and R is the bioconcentration factor. Therefore, the water concentration in mg/l corresponding to a lifetime risk of 10^{-5} for a 70 kg person is calculated by the formula:

$$\text{Water concentration} = \frac{70 \times 10^{-5}}{q_1^*(2 + 0.0065\ R)}$$

For 2,3,7,8-TCDD, the calculated or estimated values for q_1^* and R are:

$$q_1^* = \frac{1.56 \times 10^5}{\text{mg/kg/day}}$$

$$R = 5000 \text{ (U.S. EPA, 1984a)}$$

and therefore

$$\text{water concentration} = \frac{70 \times 10^{-5}}{1.56 \times 10^5\ [2 + 0.0065(5000)]}$$

$$= 1.3 \times 10^{-10} \text{ mg/l @ } 10^{-5} \text{ risk level}$$

2.1.5. Cancer Unit Risk Estimates for 2,3,7,8-TCDD via the Inhalation Route. The positive animal cancer data available for calculating a unit-risk estimate for 2,3,7,8-TCDD are as follows:

1. The Koc'ba et al. (1978a) diet study on Sprague-Dawley rats, Spartan substrain. Significant cancers in the males included stratified squamous cell carcinomas of the tongue and squamous cell carcinomas of the nasal turbinates and hard palate. Significant cancers in the females included lung, nasal turbinate and hard palate cancers, and liver tumors have been observed. As with the males, the total number of animals with at least one of these significant tumors was recorded.

2. The NCI gavage study (NTP, 1980a) in Osborne-Mendel rats and B6C3F1 mice.

   a. 2,3,7,8-TCDD in male rats caused an increase in follicular cell adenomas and carcinomas combined of the thyroid. However, these tumors were not considered biologically significant for risk assessment purposes. In females, the combined neoplastic nodules and hepatocellular carcinomas were considered significant, and these data were used. The adrenal cortical adenomas or carcinomas were not considered biologically significant.

   b. 2,3,7,8-TCDD in male mice caused an increase in hepatocellular carcinomas and in combined hepatocellular adenomas and carcinomas. In female mice, 2,3,7,8-TCDD caused an increase in subcutaneous tissue fibrosarcomas, lymphomas or leukemias of the hematopoietic system, and liver hepatocellular carcinomas.

The above data have been fit with the linearized multistage model described in the methodology section.

The data from which the largest slope factor (q_1^*) was calculated were from an independent pathologist's (Dr. R. Squire's) review of the Dow Chemical Company (Kociba et al., 1978a) lifetime rat feeding study. This factor is

$$q_1^* = 4.25 \times 10^5 \text{ (mg/kg/day)}^{-1}.$$

This unit-risk estimate from an oral study must be transformed before an estimate can be made of the effect from exposure in the ambient air.

Exposure will be assumed to occur only through respiration of dioxin-contaminated particulates. The amount of exposure depends on the particulate size distribution. Based on the report of the Task Group on Lung Dynamics (1966), it can be assumed that 100% of particulates of <0.1 micron in size pass the nasopharyngeal (upper respiratory tract) barrier and are deposited on the tracheobronchial and alveolar passages. For the larger-size particles, the percentage deposition of 5-micron particles in the lower respiratory tract is not >30%. Even those larger particles retained by the upper respiratory tract, however, may be swallowed and eventually absorbed by ingestion. In the absence of any specific data on the size distribution and eventual fate of the particulates, the information developed by the International Commission on Radiological Protection, Committee 2, will be used. The Committee developed the following estimates for retention of particulate matter in the lungs. For non-readily soluble compounds, 25% will be exhaled, 50% will be deposited in the upper respiratory passages and subsequently swallowed, and the final 25% will be deposited in the lungs (lower respiratory passages). Of this final 25%, half is eliminated from the lungs and swallowed in the first 24 hours, making a total of 62.5% swallowed; the remaining 12.5% remains in the lung alveoli for long periods of time, with some eventually being transferred to pulmonary lymph nodes.

If we take a worst-case estimate and assume that all of the swallowed material is eventually absorbed into the body, then we can assume total uptake of 75% of the inhaled material. We further assume a breathing rate of 20 m^3/day for a 70 kg man. Based on the above assumptions and the fact that 1 pg is equal to 10^{-9} mg, the lifetime cancer risk for an ambient concentration of 1 pg/m^3 of 2,3,7,8-TCDD is 3.3×10^{-5} as calculated below:

q_1^* (resp) = 1.56×10^5 (mg/kg/day)$^{-1}$ x 1×10^{-9} mg/pg x 0.75 x 20 m^3/70 kg

or q_1^* (resp) = 3.3×10^{-5} (pg/m^3)$^{-1}$

2.1.6. Determination of Relative Potency. One of the uses of unit risk is to compare the potency of carcinogens. To estimate the relative potency on a per-mole basis, the unit risk slope factor is multiplied by the molecular weight, and the resulting number is expressed in terms of $(mMol/kg/day)^{-1}$. This is called the relative potency index.

When human data are available for a compound, they have been used to calculate the index. When no human data are available, animal oral studies are selected over animal inhalation studies because most of the chemicals have animal oral studies; this allows potency comparisons by route

The potency index for 2,3,7,8-TCDD based on tongue, lung, and nasal turbinate and hard palate tumors in the female rat in the Dow 2,3,7,8-TCDD feeding study (Kociba et al., 1978a) is $5x10^7$ $(mMol/kg/day)^{-1}$. This is derived as follows: the 95% upper-limit slope estimate from the Dow study using the Squire review data is $q_1^* = 1.56x10^3$ $(mg/kg/day)^{-1}$, multiplying by the molecular weight of 322 yields a potency index of $5x10^7$. Rounding off to the nearest order of magnitude gives a value of 10^8.

Ranking of the relative potency indices is subject to the uncertainty of comparing estimates of potency of different chemicals based on different routes of exposure to different species, using studies of different quality. Furthermore, all the indices are based on estimates of low-dose risk using linear extrapolation from the observational range. Thus, these indices are not valid for the comparison of potencies in the experimental or observational range if linearity does not exist there.

2.2. COMPARISON OF EPA'S RISK ASSESSMENT APPROACH WITH OTHER METHODS

2.2.1. Alternative Methodological Approaches Utilized by EPA for Cancer Risk Assessment for TCDD. The methods used for quantitative assessment are consistently conservative (i.e., tending toward high estimates of risk).

The most important part of the methodology contributing to this conservatism in this respect is the linear nonthreshold extrapolation model. There are a variety of other extrapolation models that could be used, all of which would give lower risk estimates. These alternative models have not been used in the following analysis but can be found in EPA report 600/8-84-014A. The models presented are the one-hit, probit and Weibull models. It is felt that with the limited data available from these animal bioassays, especially at the high dosage levels required for testing, almost nothing is known about the true shape of the dose-response curve at low environmental levels. The risk estimates obtained by use of the linear nonthreshold model are upper limits, and the true risk could be lower.

Another alternative method involves the choice of animal bioassay as the basis for extrapolation. The present approach is to use the most sensitive respon -. Alternatively, the average responses of all of the adequately test- ..oassay animals could be used.

Extrapolations from animals to humans could also be done on the basis of relative weights rather than surface areas. The latter approach, used here, has more basis in human pharmacological responses; it is not clear which of the two approaches is more appropriate for carcinogens. In the face of uncertainty on this point, it seems appropriate to use the most conservative method. In the case of 2,3,7,8-TCDD gavage studies, the use of extrapolation based on surface area rather than weights increases the unit risk estimates by a factor of 5.8 based on rats and ~13 based on mice.

2.2.2. Comparison of EPA's Carcinogenic Potency and Criteria with Approaches Followed by FDA and CDC. The U.S. Food and Drug Administration concluded that an advisory level of 25 ppt for Great Lakes fish contaminated

with 2,4,7,8-TCDD does not pose an unacceptable risk to public health (FDA, 1981). EPA has reviewed the recent testimony before Congress of Dr. S.A. Miller (FDA, 1983), discussing cancer risk associated with ingestion of these fish. The FDA estimate of the 95% upper-limit carcinogenic potency factor for 2,3,7,8-TCDD is $q_1^* = 1.75 \times 10^4$ $(mg/kg/day)^{-1}$, which is less potent than EPA's estimate of $q_1^* = 1.56 \times 10^5$ $(mg/kg/day)^{-1}$ by a factor of 9. Even though both Agencies used the same data base (Kociba et al., 1978a) and risk extrapolation model, some subtle differences in methodology exist that account for this factor of 9. The major part of this difference is a factor of 5.38 that EPA uses for rat-to-man extrapolation on the assumption that dose per unit body surface area, rather than dose per unit body weight, is an equivalent dose between species (45 FR 79351). Most of the remaining factor of ~1.7 is due to the FDA's use of the Kociba's histopathological diagnosis alone, without including that of Squire, and EPA's adjustment of its calculations to compensate for the high early mortality observed in the Kociba et al. (1978a) study.

FDA and EPA also differ in their assessment of human exposure to 2,3,7,8-TCDD in fish, in keeping with their respective regulatory approaches. EPA calculates water quality criteria to protect a body of water as though it were the direct source of 100% of a human population's average daily intake of water and/or freshwater and estuarine fish or shellfish. The concentration of a pollutant in the tissues of all such fish or shellfish is further assumed to be determined by the water concentration and the BCF of the pollutant. FDA, on the other hand, premised its exposure assessment on the assumption that only limited amounts of fish having 2,3,7,8-TCDD levels at or near the advisory level will actually be consumed.

For example, FDA assumed that for this substance, significant contamination problems were limited to bottom feeders such as catfish and carp. However, available data indicate that other species, especially trout and salmon, taken from some areas of the Great Lakes may also have tissue residues of 2,3,7,8-TCDD that exceed 25 ppt. It also assumed that actual average residue levels in the flesh of bottom-feeding species reaching the market would not exceed one-third of the advisory level (i.e., ~8 ppt) and further, that for most individuals, 90% of the fish consumed would consist of other species showing no measurable contamination, or would be taken from uncontaminated areas. Under these assumptions, and using an upper 90 percentile value for freshwater fish consumption of 15.7 g/day, the FDA potency estimate yields an upper-limit risk estimate of 2.86×10^{-4} for consumers of these fish. If the same exposure assumptions were used with EPA's potency estimate a somewhat higher upper limit risk of 2.92×10^{-3} would result.

The Center for Disease Control (CDC) has also calculated an upper-limit potency value for 2,3,7,8-TCDD (Kimbrough et al., 1984). The CDC estimate is based on the Squire histopathological results, and, like that of FDA, extrapolates from rat to man on a basis of dose equivalence per unit body weight. The CDC difference from both the EPA and FDA approaches is that the curve fit was done, not on administered dose, but on liver concentration at terminal sacrifice. Also, like FDA, CDC did not adjust for high early mortality. The final result is that the CDC 95% upper-limit potency value estimate when converted back to administered dose is $q_1^* = 3.6 \times 10^{4}$ $(mg/kg/day)^{-1}$, which is more potent by a factor of 2 than that of FDA and less potent by a factor of 4 than that of the EPA. The difference between the EPA and FDA risk estimates results from the difference in potency estimates and the use by FDA of an average human body weight of 80 kg vs. 70 kg used by EPA.

In January 1984 the three Agencies met to review the differences in carcinogenic potency estimation. The three Agencies agreed that they were using virtually the same methodologies for potency estimation although there were differences in some assumptions used. Further, there was agreement that correction for mortality is appropriate, making the differences less between the EPA estimate and the other estimates. Lastly, the Agencies agreed that the remaining differences are within the range of uncertainty inherent in the risk assessment process.

2.2.3. Comparison of Approaches by EPA and CDC for Estimating Soil Ingestion Exposure. This section explains the differences between the approaches used by CDC and EPA in estimating soil ingestion exposure to TCDD. Both Agencies have also analyzed other exposure pathways such as dust inhalation, dermal absorption, fish ingestion, and beef/dairy products ingestion. This explanation addresses only soil ingestion, however, because it appears to be most important in normal residential situations and was the most influential pathway affecting CDC's selection of 1 ppb as the level of concern for TCDD in residential soils. In actuality, inhalation contributed another 0.5% and dermal another 4.0%, based upon the ingestion value, to the total CDC exposure estimate.

2.2.3.1. CDC APPROACH (SOIL INGESTION ONLY) -- This discussion is based on a paper by Kimbrough et al. (1984).

The CDC approach is based on the following equation:

$$\text{Total Lifetime Dose} = \sum_{t=1}^{25,550} (TCDDt)\,(INGt)\,(GI)\,(SEASt)$$

where

TCDDt = Concentration of TCDD in soil as a function of time
INGt = Ingestion rate of soil as a function of time
GI = GI tract absorption fraction
SEASt = Seasonal multiplier as a function of time
t = time

The values for each of the above parameters are explained below.

TCDDt = CDC assumes that TCDD in soil will degrade with a half-life of 12 years

Assuming first-order kinetics:

$$TCDDt = Co \exp(-kt)$$

where

Co = initial concentration of TCDD in soil
k = degradation rate constant
= 0.00016 $days^{-1}$
t = time (days)

CDC assumes soil ingestion rate varies with age as shown below:

Age Group	Ingestion Rate (g/day)
0-9 months	0
9-18 months	1
1.5-3.5 years	10
3.5-5 years	1
>5 years	0.1

CDC assumes that 30% of the TCDD in soil will be absorbed into the body.

The seasonal multiplier is assumed to equal one in the warm months (i.e., April-September) and zero in the colder months (October-March). Because of the lack of data in this area, CDC supported the ingestion and seasonal multiplier assumptions on the basis of best scientific judgment rather than specific references.

Substituting the above factors into the original equation yields a total lifetime dose of 1100 Co (ng of TCDD) where Co is in units of ng TCDD/g soil or ppb. This is converted to exposure by dividing by 70 kg body weight and 70 years or 25,550-day lifetime, yielding an average daily exposure of 6.15×10^{-4} Co (ng/kg/day).

2.2.3.2. EPA APPROACH (SOIL INGESTION ONLY) -- This discussion is based on a paper by John Schaum, U.S. EPA (1984b).

The EPA approach is based on an equation conceptually similar to the one used by CDC:

$$\text{Total Lifetime Dose} = (\text{ING})\ (\text{GI})\ (\text{ED})\ (\text{Co})\ (\text{DEF})$$

where

ING = Ingestion rate
GI = GI tract absorption fraction
ED = Exposure duration
Co = Initial concentration of TCDD in soil
DEF = Degradation effects ratio

The parameter value assumptions are discussed below:

The amount of TCDD-contaminated soil that children may ingest as a result of normal playing around their home is very difficult to estimate. The ingestion rates will depend on the mouthing and pica tendencies of the children.

Based on measurements of the amount of soil found on children's hands and observations of mouthing frequencies, Lepow et al. (1975) estimated that children could ingest at least 100 mg of soil per day. This estimate does not account for direct ingestion of soil, which could increase daily ingestion rates to 5 g/day (Chisolm, 1982). EPA has adopted this range as a first approximation unless site-specific data are available suggesting more appropriate values.

Poiger and Schlatter (1980) found that 13.8-18.2% of the TCDD adsorbed to soil for 8 days reached the liver in 24 hours. Assuming that this represents 70% of the body burden (Fries and Marrow, 1975), the total GI tract absorption is 20-26%. McConnell et al. (1984) also found that the absorption of TCDD from soil in the GI tract was "highly efficient" in test animals.

For this pathway, the exposure duration represents the number of days that a child consumes contaminated soil. Obviously this number can vary tremendously depending on individual behavior patterns, access to contaminated areas, soil conditions, etc.

The children studied by Lepow et al. (1975) ranged from 2-6 years old. Lacking other data, it was assumed that this represents the ages for which mouthing tendencies and the related lack of understanding of personal hygiene will cause the most significant soil ingestion.

In a residential setting, behavior patterns and seasonal conditions will most influence this parameter. Children who enjoy playing outdoors could contact soil very frequently. In warm climates such people could contact soil every day. In the coldest parts of the United States, such as Minneapolis, the soil is frozen an average of 118 days/year (Baker, 1984). Although other types of inclement weather, illness, travel and other factors could reduce the duration period, no data could be found clearly connecting these phenomena to the potential for soil contact. Accordingly, the exposure duration was assumed to last 247-365 days/year from ages 2-6 for a total of 1240-1830 days.

The degradation of TCDD in soil is difficult to measure. Most investigators have found that it is generally resistant to biological and chemical degradation, but susceptible to photolytic degradation (U.S. EPA, 1984a).

Young (1983) measured the half-life of TCDD in soil as 10-12 years and attributes most of the degradation to photodecomposition. EPA has adopted this value as a lower limit since it assumes that the TCDD is located at or near the surface and consequently at least partially exposed to sunlight.

However, Young (1983) states that physical mechanisms such as wind or water erosion could also account for the observed losses. Given this uncertainty and fact that much of the TCDD in soil may not be exposed to sunlight, it appears that under some conditions essentially no degradation would occur over the time frame of interest, i.e., 70 years. Thus, the half-life is assumed to range from 10 years to infinity.

Assuming first-order kinetics, the effects of degradation on exposure can be determined as shown below:

$$DEF = \frac{\text{Degradation Exposure}}{\text{Nondegradation Exposure}} = \frac{\int_0^t Cdt}{Cot} = \frac{(1-e^{-kt})}{kt}$$

This degradation effects ratio (DEF) will always have an upper limit of 1 when it is assumed that degradation will not occur (i.e., half-life equals infinity). The lower limit is calculated using a 10-year half-life and the time period over which the exposure occurs or 6 years. This provides the maximum degradation. Using $k = 0.00016$ days^{-1} and $t = 6$ years or 2190 days, DEF = 0.84. Thus, DEF is assumed to range from 0.84 to 1.0.

Substituting the above factors into the original equation yields a total lifetime dose ranging from 21 Co to 2400 Co (ng of TCDD) where Co is in units of ng TCDD/g soil or ppb. This is converted to exposure by dividing by 14 kg bw [representative of a 2- to 6-year-old child (Snyder et al., 1975)] and 70 years or 25,550-day lifetime, yielding an average daily exposure of 5.9×10^{-9} Co to 6.7×10^{-3} Co (ng/kg/day).

2.2.3.3. SUMMARY OF DIFFERENCES -- Table 1 summarizes the differences between the parameter values chosen by EPA and CDC. The cumulative effects of these differences cause EPA's exposure estimate to range from approximately one-tenth of CDC's estimate to 10 times CDC's estimate. Thus, it should be noted that the EPA range bounds the CDC estimate by ± 1 order of magnitude. Also, it should be noted that the mathematical relationships used to manipulate these parameters are conceptually the same in the EPA and CDC approach.

2.3. HUMAN HEALTH RISK ASSESSMENT BASED ON CHRONIC NONCARCINOGENIC TOXICITY DATA (INCLUDING REPRODUCTIVE EFFECTS DATA)

Human health risk assessment from chronic exposure to a chemical involves extrapolation of data on adverse responses observed in human epidemiologic studies or in experimental animals to project acceptable risk in humans. Since the level of acceptable risk in humans should be very low, the degree of extrapolation from high-dosed animal data to projected low-dose human exposure tends to be great.

For estimating human health risk from chronic exposure to a noncarcinogenic toxicant, the following grades of threshold toxic responses from animal experimentations are generally considered:

- No-Observed-Effect Level (NOEL)
- No-Observed-Adverse-Effect Level (NOAEL)
- Lowest-Observed-Effect Level (LOEL)
- Lowest-Observed-Adverse-Effect Level (LOAEL)

With a knowledge of projected risk in humans, the ADI of the noncarcinogenic chemical can be estimated from data reflecting one of the above toxic responses. ADI for a chemical under study is calculated from total exposure data that include contributions from the diet and air.

TABLE 1

Summary of Parameter Value Differences

Factor	EPA	CDC	EPA/CDC Ratio
Total ingested dose (ng)*	100 Co to 9200 Co	3700 Co	0.027-2.5
Fraction absorbed	0.2-0.26	0.3	0.67-0.87
Body weight (kg)	14	70	0.2
Lifetime (years)	70	70	1
Exposure (ng/kg/day)*	5.9×10^{-5} Co to 6.7×10^{-3} Co	6.1×10^{-4} Co	0.10-11.0

*Assumes Co is in ppb units

In deriving ADI from experimental data considerable scientific judgment is utilized in selecting the appropriate uncertainty factor. Uncertainty factor (or safety factor) is an indication of degree of uncertainty that is considered during extrapolation of experimental data, primarily from animal bioassays, to human system. Factors considered in selecting the appropriate uncertainty factor include whether the data have been derived from human or animal experimentations; the number, species and various aspects tested in case of animal experimentations; quality and utilization of controls both vehicle and positive; dose levels; route; and exposure schedules. An in-depth critical analysis of data is performed to distinguish between results that constitute a toxicologically sufficient data base and data that may be spurious in nature.

- An uncertainty factor of 10 is used when valid experimental data from chronic exposure are available.
- An uncertainty factor of 100 is used when sufficient chronic animal data are available but human data are either fragmentary or not available.
- An uncertainty factor of 1000 is used when chronic animal data are not available but satisfactory subchronic animal data are available. No chronic or acute human data are available.

2.3.1. Noncarcinogenic Toxicity Data Available for Chronic Exposure to TCDD. Chronic toxicity data for 2,3,7,8-TCDD are available from long-term studies of experimental animals. There are also some limited data from human populations exposed to chemicals contaminated with 2,3,7,8 TCDD. In addition, studies on teratogenicity and fetotoxicity will also be examined when evaluating the data for assessing the effects of chronic exposure to 2,3,7,8-TCDD.

In chronic toxicity studies of rats and mice, it was, again, the liver that appeared to be the most sensitive organ. Changes in the liver of rats included initially fatty infiltration, and necrosis at higher doses. According to the rat studies, 0.001 μg/kg/day was a NOEL, while 0.05 and 0.1 μg/kg/day were the NOAEL and LEL, respectively, for liver damage (Kociba et al., 1978b, 1979; NTP, 1980a). In mice, a NOEL was not determined, and the lowest doses tested, 0.0015 and 0.006 μg/kg/day, produced liver damage in male and female B6C3F1 mice (NTP, 1980a), while the lowest dose tested in Swiss mice, 0.001 μg/kg/day, produced amyloidosis of the kidney, spleen and liver (Toth et al., 1978, 1979). In nonhuman primates, chronic exposure to 2,3,7,8-TCDD in the diet at 50 or 500 ppt resulted in hair loss, edema and pancytopenia (Allen et al., 1977; Schantz et al., 1979). Data were not available to determine a NOEL for monkeys. The guinea pig, the most sensitive species to the acute toxic effects of 2,3,7,8-TCDD, has not been used in a chronic bioassay.

2,3,7,8-TCDD has been demonstrated to be teratogenic in all strains of mice tested (Courtney et al., 1970; Courtney and Moore, 1971; Courtney, 1976; Neubert and Dillman, 1972; Smith et al., 1976). Poland and Glover (1980) demonstrated interstrain differences in the induction of terata. Responsive mice, containing high levels of the Ah receptor, are highly susceptible to the effects of 2,3,7,8-TCDD in producing cleft palate, whereas the nonresponsive mice, which contain low (or 0) levels of the Ah receptor protein, are resistant to this teratogenic effect of 2,3,7,8-TCDD. The most common malformations observed were cleft palate and kidney anomalies; however, occasionally, other malformations have been reported. Smith et al. (1976) reported that no terata were observed at 0.01 μg/kg while cleft palates were increased at 0.1 μg/kg and suggested that 0.1 μg/kg was the minimum effective dose for mice. In rats, 2,3,7,8-TCDD has produced

fetotoxic effects and kidney malformations (Courtney and Moore, 1971; Sparschu et al., 1971; Khera and Ruddick, 1973; Giavini et al., 1982a; Murray et al., 1979). Fetotoxicity has also been observed in rabbits (Giavini et al., 1982b; Norman et al., 1978), ferrets (Muscarella et al., 1982) and monkeys (Schantz et al., 1979; Allen et al., 1979; Barsotti et al., 1979; McNulty, 1978). The three-generation study of Murray et al. (1979) reported a NOAEL for rats of 0.001 µg/kg/day with the next higher dose of 0.01 µg/kg/day demonstrating increases in anomalies. Nisbet and Paxton (1982) used different statistical methods to evaluate this three-generation study and concluded that the lowest dose produced effects was actually a LOAEL. This LOAEL for reproductive effects is similar to the LOAEL for liver damage and amyloidosis observed in chronic toxicity studies in mice (NTP, 1980a; Toth et al., 1978, 1979).

There seems to be general agreement that human exposure to 2,3,7,8-TCDD, whether acute or chronic, leads to chloracne, altered liver function, hematological abnormalities, porphyria cutanea tarda, altered pigmentation, hirsutism and some peripheral neuropathy (Poland et al., 1971; Ott et al., 1980; Pazderova-Vejlupkova et al., 1981; Singer et al., 1982). A number of studies, mostly correlation studies, have been conducted on groups of persons exposed to 2,3,7,8-TCDD to assess reproductive hazard. Although some studies have shown a positive association between exposure to 2,4,5-T and birth defects or abortions (Hanify et al., 1981), other studies have failed to demonstrate any association. In investigations concerning potential exposure to 2,3,7,8- TCDD through the manufacture of TCP, there has been no positive substantiated association between exposure and reproductive difficulties. In these studies, exposure was always to a mixture of compounds, with 2,3,7,8-TCDD being a contaminant. Hence, it is not possible

to attribute with certainty any positive finding to 2,3,7,8-TCDD. It is also possible, since levels of 2,3,7,8-TCDD contamination of 2,4,5-T and TCP were only estimated, that the negative results reflect exposure levels too low or study designs too insensitive to elicit a detectable response.

2.3.2. Estimation of Acceptable Daily Intake for TCDD (for Comparative Purposes Only). 2,3,7,8-TCDD is an unusually toxic compound with demonstrated acute, subacute and chronic effects in animals and man. Acute or subchronic exposures to 2,3,7,8-TCDD can adversely affect the skin, the liver, the nervous system and the immune system.

2,3,7,8-TCDD displays an unusually high degree of reproductive toxicity. It is teratogenic, fetotoxic and reduces fertility. In a three-generation reproductive study, Murray et al. (1979) reported a reduction in fertility after daily dosing at 0.1 or 0.01 µg 2,3,7,8-TCDD/kg in the F_1 and F_2 generations of Sprague-Dawley rats. In addition, equivocal adverse effects were seen at the lowest dose (0.001 µg/kg/day); this dose, therefore, represents a LOAEL. Schantz et al. (1979) found reductions in fertility and various other toxic effects in rhesus monkeys fed a 50 ppt 2,3,7,8-TCDD diet for 20 months. This corresponds to a calculated daily dose of 0.0015 µg 2,3,7,8-TCDD/kg/day. These results suggest that monkeys may be somewhat more sensitive than rats, since the effects in monkeys were more severe and not equivocal.

A toxicity-based criterion for 2,3,7,8-TCDD has been calculated for comparison with the cancer-based criterion (U.S. EPA, 1984a). Since the study by Schantz et al. (1979) supports the findings of Murray et al. (1979), it seems reasonable to determine an ADI based on the LOAEL. If one selects an uncertainty factor of 100 based on the existence of lifetime animal studies and the knowledge that there is suggestive evidence of reproductive effects

in man (Hanify et al., 1981), as per U.S. EPA (1980) guidelines, and then an additional 10 because of a LOAEL is used as the basis of this calculation. The ADI thus calculated would be:

$$ADI = \frac{10^{-3}\ \mu g/kg/day\ (LOAEL)}{100 \times 10} = 1 \times 10^{-6}\ \mu g/kg/day.$$

According to the methods published by U.S. EPA (1980), an additional uncertainty factor between 1 and 10 must be used because the calculation is based on a LOAEL. An uncertainty factor of 10 was chosen because of the adverse effects seen in rhesus monkeys at 0.0015 µg/kg/day, despite the equivocal nature of the effects in rats seen at the 0.001 µg/kg/day dose level. The ADI for a 70 kg man would be 7.0×10^{-5} µg TCDD/day.

2.4. HUMAN HEALTH RISK ASSESSMENT BASED ON MUTAGENICITY DATA

2.4.1. Mutagenicity Data Available on TCDD. A limited number of initial studies on the mutagenicity of 2,3,7,8-TCDD in bacteria reported positive results in S. typhimurium strain TA1532 in the absence of a mammalian metabolic activation system (Hussain et al., 1972; Seiler, 1973). More recent attempts to repeat these results with strain TA1532 or related strains have failed (Geiger and Neal, 1981; Nebert et al., 1976; Gilbert et al., 1980; McCann, 1978). These authors also reported no increase in mutation rate when 2,3,7,8-TCDD was tested in the presence of a mammalian metabolic activation system. In other in vitro assays, 2,3,7,8-TCDD has produced a positive response in reversion to streptomycin independence in E. coli Sd-4 cells and questionable positive response with prophage induction in E. coli K-39 cells (Hussain et al., 1972). Also, 2,3,7,8-TCDD has been reported to be mutagenic in the yeast S. cerevisiae in both the in vitro assay with S-9 and the host-mediated assay (Bronzetti et al., 1983). Rogers et al. (1982) also reported positive mutagenicity results in the mouse lymphoma assay system. In the E. coli studies, the poor survival of the cells or the

interference of the vehicle solvent, DMSO, with the assay makes the evaluation of the studies difficult. With the data available, it is not possible to resolve the conflicting reports on the mutagenic potential of 2,3,7,8-TCDD.

Overall, the data indicate little potential for the interaction of 2,3,7,8-TCDD with nucleic acids or the ability of 2,3,7,8-TCDD to produce chromosomal aberrations. Kondorosi et al. (1973) demonstrated that 2,3,7,8-TCDD did not react with RNA *in vitro* in the absence of a metabolic activation system. *In vivo* studies using radiolabeled 2,3,7,8-TCDD indicated some association of nonextractable label with RNA and DNA (Poland and Glover, 1979); however, the level of bound label was very low. Similar marginal data were available on the clastogenic effect of 2,3,7,8-TCDD. Although two *in vivo* studies in rats (Green and Moreland, 1975; Loprieno et al., 1982) failed to demonstrate any treatment-related chromosomal aberration, a second study by the same authors (Green et al., 1977) using a longer exposure period reported a small increase in the number of aberrations. A similar small increase was observed by Loprieno et al. (1982) following a single intraperitoneal injection of 2,3,7,8-TCDD in mice. In humans exposed to 2,3,7,8-TCDD during the manufacture of 2,4,5-TCPE and Buminol, Czeizel and Kiraly (1976) reported an increase in the number of chromosomal aberrations, while no increase was detected in individuals exposed to 2,3,7,8-TCDD following an industrial accident in Seveso, Italy (Reggiani, 1980; Mottura et al., 1981). The studies of the clastogenic effect of 2,3,7,8-TCDD were presented with little or no experimental detail to assist in evaluating the merits of the reports. The data available are too limited to indicate whether 2,3,7,8-TCDD can interact with nucleic acids or produce chromosomal aberrations.

The differences among the results reported could be due to several factors, such as treatment protocols, solubility problems, purity of the samples tested and the high toxicity of 2,3,7,8-TCDD. This chemical may be a weak mutagen, but because it is very toxic, the dose range for detecting a positive genetic effect may be very narrow. Therefore, additional experimentation is necessary before any conclusive determination can be made. Suggested further testing includes additional studies of the ability of 2,3,7,8-TCDD to induce forward mutations in mammalian cells in culture, additional yeast and bacterial studies and the sex-linked recessive lethal test in Drosophila.

EPA follows the procedures outlined in the Proposed Guidelines for Mutagenicity Risk Assessment (1984) for conducting qualitative and quantitative mutagenicity risk assessments. In the case of 2,3,7,8-TCDD, the information available is too limited and conflicting for applying quantitative risk assessment methodologies. Qualitatively, the presently available data provide limited evidence that TCDD poses heritable risk for humans. The following is a description of the methodology EPA uses in qualitatively assessing mutagenic risk.

Pertinent information regarding the mutagenicity of PeCDDs and HxCDDs were not located in the available literature.

2.4.2. Qualitative Mutagenic Risk Assessment Methodology. The evidence for a chemical's ability to produce mutations and to interact with the germinal target are integrated into a weight-of-evidence judgment that the agent may pose a hazard as a potential human germ-cell mutagen. All information bearing on the subject, whether indicative of potential concern or not, are evaluated. Whatever evidence may exist from humans is also factored into the assessment.

Bacteria and eukaryotes, including fungi, plants, insects and various mammalian systems, are commonly utilized for assaying potential mutagenic and cytogenetic aberrations that are due to exposure to a test chemical. Table 5-1 in the NAS Committee on Chemical Environmental Mutagens report (1982) lists these assays.

Information available will vary greatly from chemical to chemical because there are many mutagenicity test systems, and there has been no systematic attempt to develop information on all chemicals of concern. The responses noted for different tests may also vary from chemical to chemical since often one does not find consistent positive or negative results across all tests. Chemicals may show positive effects for some endpoints in some test systems, but negative responses in others. Each review takes into account the limitations in the testing and in the types of responses that may exist.

Certain responses in tests that do not measure well-defined mutagenic endpoints (i.e., SCE induction in mammalian germ cells) or germ-cell tests in higher eukaryotes (i.e., Drosophila tests) may provide a basis for raising the weight of evidence from one category to another.

Sufficient evidence for potential human germ-cell mutagenicity includes cases in which positive responses are demonstrated in a mammalian germ-cell test. Also, in general, sufficient evidence exists when there is confirmed mutagenic activity in other test systems (positive responses in at least two different test systems, at least one of which is in mammalian cells), and there is sufficient evidence for germ-cell interaction.

Suggestive evidence encompasses a weight-of-evidence category between sufficient and limited that includes cases in which there is some evidence for mutagenic activity and for interaction with germ cells.

Limited evidence for potential human germ-cell mutagenicity exists when evidence is available only for mutagenicity tests (other than mammalian germ cells) or only for chemical interactions in the gonad.

3. RISK ASSESSMENT STRATEGY FOR ACUTE EXPOSURE TO 2,3,7,8-TCDD

Methodology for the assessment of health hazards associated with exposure of human populations to chemical contaminants in the environment has been developed recently by organizations such as the U.S. EPA and the National Academy of Sciences (NAS). Since the purpose of these assessments was to derive health-based criteria for pollutants in ambient and drinking waters, which would designate levels of the pollutant that would be safe for humans even with lifetime exposure, the emphasis of these methodologies has been placed on prediction and assessment of effects from chronic exposure. When less than chronic exposure is addressed, it is usually in reference to extrapolating health effects data obtained from short duration exposures to anticipated effects and associated doses following chronic exposure.

With today's new awareness of chemical hazards in the environment, it has become apparent that situations exist where lifetime exposure to a pollutant would not be anticipated. Examples of such situations include contamination of a drinking water system, which is followed by remedial action to eliminate the contaminant, or exposure to toxicants from dump sites during clean-up operations. As a result of this need, initial steps are being taken to develop hazard assessment methodology concerned with less than lifetime exposures. As indicated by the Office of Drinking Water, the development of criteria (HAs) allowing greater levels of contamination of water if exposure is assumed to be of short duration does not mean that the presence of these higher levels of contaminants is condoned. Rather, the HAs are prepared in order to provide useful information on the potability of a drinking water supply in cases where contamination occurs.

An approach similar to that described for derivation of an ADI for chronic exposure is used for determination of a 1-day HA. The 1-day HA is intended to represent the concentration in water that will not cause adverse health effects after exposure for a single day in a 10 kg child consuming 1 L of water/day or a 70 kg adult consuming 2 L of water/day. The 10 kg child is used because a child consumes a greater amount of water/body weight than an adult and represents a more sensitive member of the population. If sufficient data are available to differentiate between the sensitivity of children and adults, separate assessments will be conducted. Since HAs are developed only for transient periods of exposure rather than for lifetime, the carcinogenic potential of a compound and the estimated risks associated with exposure to that compound are not taken into consideration. If the qualitative evaluation of carcinogenicity data indicates that a chemical might be a potent carcinogen, an HA for this chemical would be provided only with great caution.

An HA is based upon the identification of an adverse health effect associated with the most sensitive noncarcinogenic endpoint of toxicity. The induction of this health effect is related to a particular dose of the substance given over a specified period of time in a human or animal study. To estimate a level at which no adverse effects would be expected to occur in members of the human population, an appropriate UF is applied to the LOEL or NOAEL identified in these studies. For a 1-day HA, studies of durations from 1-14 days are used.

The 1-day HA is calculated by dividing the dose (d, in mg/kg bw) obtained from a study that most closely defines a NOAEL for the most sensitive

endpoint in the most sensitive species by a UF using the following guidelines:

10 - for a human no-observed-adverse-effect level
100 - for a human adverse-effect level
100 - for an animal no-observed-adverse-effect level
1000 - for an animal adverse-effect level (lowest)

The HAs are then calculated as follows:

$$HA = (d \times bw) \div (UF \times wc)$$

where

bw = body weight, 10 kg for child
70 kg for adult

wc = water consumption, 1 ℓ for child
2 ℓ for adult

Acute lethal data will not be used to derive an HA.

Pharmacokinetic data will be considered in a manner similar to that described for derivation of an ADI from chronic exposure. The data available may actually be more relevant in assessing the appropriateness of acute studies, since most pharmacokinetic studies are of short duration. As discussed previously, when pharmacokinetic data are similar between species, species-to-species extrapolation can be performed with greater confidence. Likewise, pharmacokinetic data can provide confidence that a route-to-route extrapolation is appropriate or suggest that caution is required in performing such manipulations.

3.1. TOXICITY DATA AVAILABLE FOR SHORT-TERM ACUTE EXPOSURE TO 2,3,7,8-TCDD

The characteristic effects of exposure to 2,3,7,8-TCDD are thymic atrophy and weight loss. In rats and rabbits, and to a lesser extent in guinea pigs and monkeys, liver damage is a major pathological symptom.

Death is preceded by a prolonged period of weight loss, during which severe deterioration of the animals is observed; however, no specific lesion has been identified as the cause of death. Death occurs only after 2-3 weeks following an acute exposure. This unusual characteristic of 2,3,7,8-TCDD toxicity has resulted in many short-term studies that report only minor effects at doses near, or sometimes many-fold greater than, the LD_{50}. 2,3,7,8-TCDD is also an immune suppressant in mice, rats and guinea pigs.

The acute toxicity of 2,3,7,8-TCDD is extremely species-dependent. Acute oral LD_{50}s ranging from 0.6 µg/kg bw for male guinea pigs (Schwetz et al., 1973) to 5051 µg/kg bw for hamsters (Henck et al., 1981) have been reported. The relative sensitivity of man, compared with other species, to 2,3,7,8-TCDD toxicity cannot be determined from the existing data.

Four studies were found that identified NOAELs or LOAELs that could be useful in the derivation of an HA (Harris et al., 1973; Madge, 1977; Smith et al., 1981; Turner and Collins, 1983).

Harris et al. (1973) administered a single oral dose of 2,3,7,8-TCDD in acetone:corn oil to groups of CD rats of mixed sex. Weights were determined at least once each week. Rats given 50 or 100 µg/kg bw demonstrated a decreased weight gain and increased mortality. In the high-dose group, mortality approached 50% with a mean time interval until death of 18.3 days. A dose of 25 µg/kg bw, the LOAEL in this study, resulted in a decreased body weight in females at 1 week postdosing and a decreased rate of weight gain in males for 2 weeks postdosing. After 2 weeks, both male and female rats gained weight at the same rate as the controls. Doses of 1 or 5 µg/kg bw had no effect on body weight.

Madge (1977) investigated the effect of 2,3,7,8-TCDD on intestinal absorption in CD-1 mice. Mice were given single oral doses of 10, 25, 75,

150, 200 or 300 µg 2,3,7,8-TCDD/kg bw. Absorption of D-glucose, D-galactose, L-argenine and L-histidine was measured 7 days later, using the everted intestinal sac technique. Absorption of D-glucose was decreased at all dose levels; however, absorption of the other compounds was not affected by any of the treatment. The decrease in D-glucose absorption was dose-related over the range of 0-75 µg/kg bw. In this study, 10 µg/kg bw constituted a LOAEL.

Smith et al. (1981) investigated the effect of 2,3,7,8-TCDD on hepatic porphyrin levels in C57Bl/10 and DBA/2 mice. A single oral dose was administered in arachis oil (0, 5, 15, 50, 75, 150, 300, 600 or 1200 µg/kg bw) and hepatic porphyrin levels were determined at intervals for up to 12 weeks. There were large strain differences in susceptibility to porphyria induction, with the C57Bl/10 strain being ~20 times as sensitive as the DBA/2 strain. In this study, the lowest dose that induced porphyria was 50 µg/kg bw. Thus, 50 µg/kg bw was a LOAEL and 15 µg/kg bw represented a NOAEL.

Turner and Collins (1983) administered single oral doses of 0.1, 0.5, 2.5, 12.5 or 20 µg/kg bw of 2,3,7,8-TCDD to groups of 4-6 female guinea pigs. Survivors were killed 42 days after dosing and examined for histopathologic changes in the liver. Four of the 6 animals in the highest dose group and 1 of 5 in the 12.5 µg/kg group died before the end of the observation period. Mild histopathologic changes including steatosis (fatty change), focal necrosis, and cytoplasmic degeneration were noted in animals from all treated groups, but not in controls, and were not dose-related.

All of the LOAELs and NOAELs determined for rats and mice are above the LD_{50} for guinea pigs (0.6-2.1 µg/kg). Although no NOEL or NOAEL is available for guinea pigs, a LOAEL of 0.1 µg/kg can be derived from the study of Turner and Collins (1983).

3.2. ESTIMATION OF 1-DAY HEALTH ADVISORY

The data on very short-term exposures, 1-14 days, are sufficient for the derivation of an HA. As discussed in Section 3.1., the available studies established LOAELs for rats and mice that are greater than the LD_{50} for guinea pigs. A NOAEL is not available for guinea pigs, but a LOAEL of 0.1 µg/kg can be derived from the study of Turner and Collins (1983). This LOAEL can be used to calculate a 1-day Health Advisory, using a UF of 1000 for an animal LOAEL:

$$HA = dose \times bw \div (UF \times wc)$$

where

bw = body weight, 70 kg for adult
10 kg for child

wc = water consumption, 2 ℓ for adult
1 ℓ for child

Thus, for an adult:

1-day HA (adult) = 0.1 µg/kg bw x 70 kg bw) ÷ (1000 x 2 ℓ)
= 0.0035 µg/ℓ (0.007 µg/day or 0.0001 µg/kg bw/day)

For a child:

1-day HA (child) = (0.1 µg/kg bw x 10 kg bw) ÷ (1000 x 1 ℓ)
= 0.001 µg/ℓ (0.001 µg/day or 0.0001 µg/kg bw/day)

4. RISK ASSESSMENT APPROACH FOR SHORT-TERM (SUBCHRONIC) EXPOSURE TO 2,3,7,8-TCDD

In situations where exposure to a toxicant will continue for a few days, a 10-day HA is used as the basis for decision-making on the safety of drinking water. To provide a margin of safety for cumulative effects of the toxicant, studies of 30-90 days duration in humans or experimental animals are used to derive the 10-day HA rather than a study of ~10 days' duration. Using studies of appropriate duration, the 10-day HA is calculated by the same method as the 1-day HA. It would be anticipated that the advisory would become progressively more conservative as the study used approached 90 days. This short-term advisory is also calculated for both the 10 kg child and the 70 kg man.

In the absence of appropriate studies, the 10-day HA can also be calculated by dividing the 1-day HA by 10. This method should provide protection from toxicants that have cumulative effects. It should be noted that a 1-day HA cannot be calculated by multiplying the 10-day HA by 10. This form of extrapolation has no scientific basis, and nonlinear associations between effect and total dose may result in highly toxic doses at the level of the projected 1-day HA.

As is apparent from the discussion on the 1- and 10-day HAs, the methodology for determining safe levels of xenobiotics for less than lifetime exposures has not been fully developed. One of the greatest areas of concern is how to address data for a chemical that is known to be an animal carcinogen. The development and validation of this hazard assessment methodology will be of concern to regulatory agencies in the future.

4.1. TOXICITY DATA AVAILABLE FOR SUBCHRONIC EXPOSURE TO TCDD

There is less information on species variability in response to subchronic dosing than was available for acute exposures. In a subchronic gavage study (NTP, 1980a), B6C3F1 mice were 10 times more susceptible to the induction of toxic hepatitis than were Osborne-Mendel rats. In other studies, the lowest reported LOAEL in rats (0.001 µg/kg bw/day) (Murray et al., 1979) is similar to a LOAEL that has been reported for guinea pigs (0.0057 µg/kg bw/day) (Vos et al., 1973). Murray et al. (1979) investigated the teratogenic and reproductive effects of 2,3,7,8-TCDD in Sprague-Dawley rats in a three-generation study. The animals were maintained on diets that resulted in doses of 0, 0.001, 0.01 or 0.1 µg 2,3,7,8-TCDD/kg bw/day. The f_0 rats were maintained on the treatment diets for 90 days before the initial mating. This group was mated twice, resulting in the f_{1A} and f_{1B} generations. The f_{1A} and f_{1B} rats were mated at ~130 days of age, producing the f_2 and f_3 litters, respectively. Under these conditions, doses of 0.1 and 0.01 µg/kg bw/day produced reduced fertility and fetal survival. The authors reported a NOAEL of 0.001 µg/kg bw/day. Nisbet and Paxton (1982) reevaluated this study, using different statistical methods. They concluded that the 0.001 µg/kg bw/day dose level resulted in a significantly reduced gestational index, decreased fetal weight, increased liver-to-body weight ratios and an increased incidence of dilated renal pelvis. Thus, they classified 0.001 µg/kg bw/day as a LOAEL rather than a NOAEL. Since at least some of these effects may be the result of exposure during gestation, it is appropriate to consider this study in the calculation of short-term as well as long-term HAs; however, the difficulty in separating the effects from short-term exposure during gestation from effects that are due to longer-term exposure makes this study inappropriate for the derivation of a 10-day HA.

Vos et al. (1973) administered 8 weekly doses of 0.008, 0.04, 0.2 or 1.0 µg 2,3,7,8-TCDD/kg bw (0.0011, 0.0057, 0.029 or 0.14 µg/kg bw/day) in acetone:corn oil to groups of 10 female Hartley guinea pigs by gavage. Body weights were determined weekly. The effects of 2,3,7,8-TCDD on the immune system were determined by measuring the response to a subcutaneous injection of tetanus toxoid (humoral immunity) and the delayed-type hypersensitivity to tuberculin (cell-mediated immunity). The lowest dose at which an effect on the immune response was observed was 0.0057 µg/kg bw/day; the NOAEL was 0.0011 µg/kg bw/day.

4.2. ESTIMATION OF 10-DAY HEALTH ADVISORY

Two studies have reported adverse effects from subchronic exposures to very low levels (<0.01 µg/kg bw/day) of 2,3,7,8-TCDD (Murray et al., 1979; Vos et al., 1973). The usefulness of the Murray et al. (1979) study for the development of a 10-day HA is limited by the design, which makes it difficult to distinguish between effects produced by short-term exposure during gestation and effects from longer-term exposures.

The study by Vos et al. (1973) defines a NOAEL of 0.0011 µg/kg bw/day and a LOAEL of 0.0057 µg/kg bw/day in guinea pigs, the most susceptible species to the acute effects of 2,3,7,8-TCDD. These values agree well with the NOAEL/LOAEL derived from the Murray et al. (1979) study. Using an UF of 100 for an animal NOAEL, a 10-day HA can be calculated from the reported NOAEL for guinea pigs (0.0011 µg/kg bw/day):

$$HA = (dose \times bw) \div (UF \times wc)$$

where

bw = body weight, 70 kg for adult
10 kg for child

wc = water consumption, 2 ℓ for adult
1 ℓ for child

Thus, for an adult:

10-day HA (adult) = (0.0011 µg/kg bw x 70 kg bw) ÷ (100 x 2 ℓ)
= 0.00039 µg/ℓ (0.00078 µg/day or 0.000011 µg/kg bw/day)

For a child:

10-day HA (child) = (0.0011 µg/kg bw x 10 kg bw) ÷ (100 x 1 ℓ)
= 0.00011 µg/ℓ (0.00011 µg/day or 0.000011 µg/kg bw/day)

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