

Research and Development



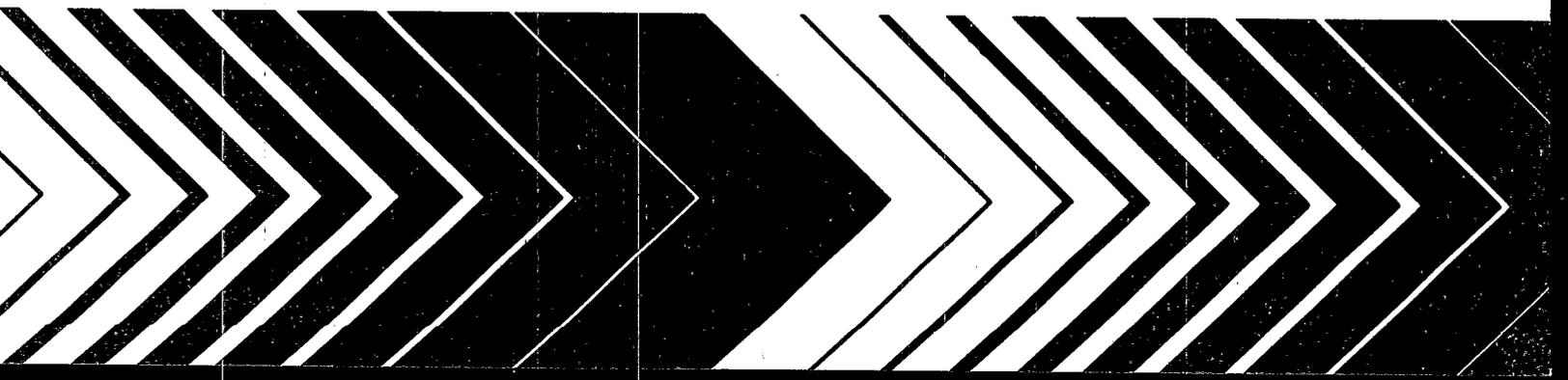
A Cancer Risk-Specific Dose Estimate for 2,3,7,8-TCDD

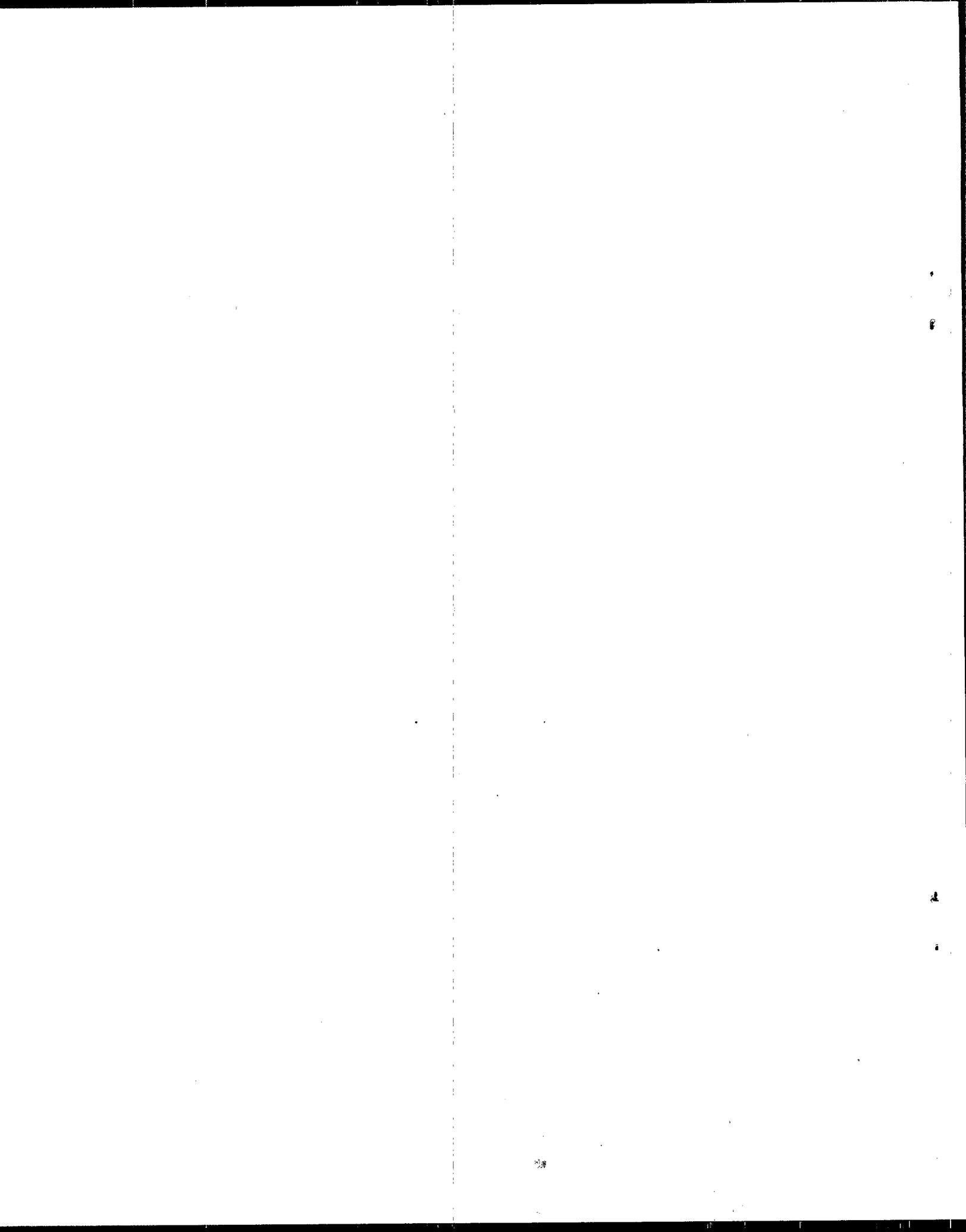
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EPA-600/6-88/007Aa
June 1988
Review Draft

A CANCER
RISK-SPECIFIC DOSE ESTIMATE
FOR 2,3,7,8-TCDD

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U.S. Environmental Protection Agency
Washington, D.C.

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PREFACE

Responding to both internal and external questions about the U.S. Environmental Protection Agency's (EPA's) 1985 Health Assessment Document for Polychlorinated Dibenzo-p-Dioxins, the EPA Administrator asked the Assistant Administrator of the Office of Research and Development (ORD) to re-examine the data and methodology upon which the assessment for 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD) was based in light of new data or alternative interpretations of the older literature that have become available since 1985 and, if appropriate, to modify EPA's approach. This report, entitled "A Cancer Risk-Specific Dose Estimate for 2,3,7,8-TCDD,"* and its appendices present the results of that effort.

Although there are many components to any risk assessment for 2,3,7,8-TCDD, two factors have been particularly important in recent Agency decisions, i.e., estimates of cancer potency and estimates of human exposure. Consequently, while other issues were reviewed and are briefly discussed in the appendices to this report, the report itself focuses on cancer potency and

*In EPA terminology, the risk specific dose (RsD) is an estimate of dose, or exposure, that would equal the dose estimated to result in an upper-bound estimate of incremental lifetime cancer risk, e.g., one in a million.

The reference dose (RfD), which is referred to later in this document, is an estimate (uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime (U.S. EPA, 1987b).

exposure issues. This analysis is thus not a complete risk characterization for 2,3,7,8-TCDD, but rather a re-examination of the hazard identification and dose-response assessment for the potential human carcinogenicity of this chemical.

An ad hoc inter-office workgroup (hereafter, the "Workgroup") prepared the report and recommendations. While scientists outside of this group have provided useful analyses, review, and comment, the conclusions and recommendations are those of the Workgroup alone. Similarly, although the appendices to the report contain important background information on a broad range of 2,3,7,8-TCDD issues discussed in the report, the special focus of the report precluded use of many of these analyses in the final document. Other major related sources include:

- the report of an EPA Workshop on the Development of Risk Assessment Methodologies for Tumor Promoters,
- the report on Estimating Exposure to 2,3,7,8-TCDD
- the report of the "Dioxin" Update Committee

This report, its appendices, and the reports listed above represent an effort by many people within EPA to grapple with the difficult scientific issues presented by the very large but incomplete data base on 2,3,7,8-TCDD. Credit for each report or appendix in this overall effort belongs to the individual authors.

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I. OVERVIEW

This report re-examines the scientific basis and methods used by the U.S. Environmental Protection Agency (EPA) for estimating the cancer potency for 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD) (U.S. EPA, 1985). The object is to determine if the 1985 assessment should be modified in light of recent data and other plausible risk assessment methods or alternative data interpretations.

The analysis uses two different approaches. One examines EPA's earlier analysis in terms of new data and recent reviews that offer scientific information and views for re-assessing 2,3,7,8-TCDD cancer risks. The other involves comparing EPA's 1985 assessment with that of other regulatory agencies in this country and elsewhere. The Agency Workgroup could not reach consensus on all issues. However, for the reasons developed below, the Workgroup convened for this task agreed that (1) the 1985 assessment that associates a 0.006 pg/kg/day dose with a plausible upper-bound increased cancer risk of one in a million (10^{-6}) should be reconsidered, and (2) a majority of the group agreed that a change to a 0.1 pg/kg/day dose as a plausible upper-bound associated with an increased lifetime risk of one in a million is consistent with the available data and theories, and represents a reasonable science policy position for the Agency.

A. NEW DATA AND METHODS

Although the scientific literature is replete with studies on 2,3,7,8-TCDD, which might be brought into a comprehensive characterization of cancer risk, most discussions and debate about quantitative risk focus on the

interpretation and use of a small subset of animal and human studies. Laboratory studies conclusively establish a relationship between exposure to 2,3,7,8-TCDD and cancer in test animals. There is, however, considerable uncertainty and controversy about the mechanism by which 2,3,7,8-TCDD causes cancer, an uncertainty that can strongly influence both qualitative assessments and the mathematical methods used to assess cancer risk to humans. Also, variabilities in conduct and response among studies in human populations that may have been exposed to 2,3,7,8-TCDD--an assumption that is itself uncertain--raise additional questions and obscure the overall assessment.

A question often asked is whether 2,3,7,8-TCDD is a "complete carcinogen," a "promoter," or whether it produces cancer by some unknown mechanism that may functionally have elements of initiation, promotion, and progression.¹ The previous EPA assessment (U.S. EPA, 1985) analyzed 2,3,7,8-TCDD as a complete carcinogen. Recent studies support the assertion put forth a number of years ago that one of the major mechanisms of action for 2,3,7,8-TCDD involves the "promotion" of carcinogenesis in cells. However, despite changes and additions to the data base, the analysis for risk assessment is neither obvious nor simple, and important uncertainties remain.

These considerations give rise to the issues upon which this analysis is founded.

¹According to generally accepted theory (OSTP, 1985; U.S. EPA, 1986a), both complete carcinogens and promoters are capable of increasing cancer incidence in humans. Thus, the question of complete carcinogenicity versus promotion has little effect on identifying potential human cancer hazard associated with exposure to 2,3,7,8-TCDD. Differences, however, in mechanisms of carcinogenesis may lead to differences in approaches to quantitative risk assessment, with resulting differences in numerical risk estimates.

- Is the carcinogenic mechanism of action better understood today than it was for the previous assessment?
- Is the linearized multistage (LMS) model as employed by the EPA to estimate the risk associated with exposure to carcinogens appropriate for estimating risk from exposure to 2,3,7,8-TCDD?
- Are there other appropriate ways to characterize the risk associated with exposure to 2,3,7,8-TCDD that more fully incorporate the biological data? Are these approaches more appropriate than the LMS model (as used by EPA) for 2,3,7,8-TCDD assessments?
- Does the choice of approach (and related assumptions) have any bearing on a discrepancy perceived by some between the observed human cancer experience and human risk estimates based on animal studies?
- What is currently understood about the mechanism(s) of action of 2,3,7,8-TCDD?
- How significant are the remaining uncertainties?

This analysis identifies several reasonable approaches to estimating 2,3,7,8-TCDD cancer risk, but concludes that there do not appear to be compelling scientific reasons for regarding any one of them as a "most appropriate" approach. Indeed, among the several contributors to this report, there was a diversity of viewpoints. Preferring somewhat different assumptions and interpretive criteria, the individual contributors brought different perspectives to the review process. Therefore, based on rationales grounded in science and/or science policy, several different risk assessment approaches have been considered.

The Workgroup recognizes that there is a range of cancer risk estimates for 2,3,7,8-TCDD (see Figure 1). Estimates at one end of the range are based on several different linearized models and those at the other end are based on

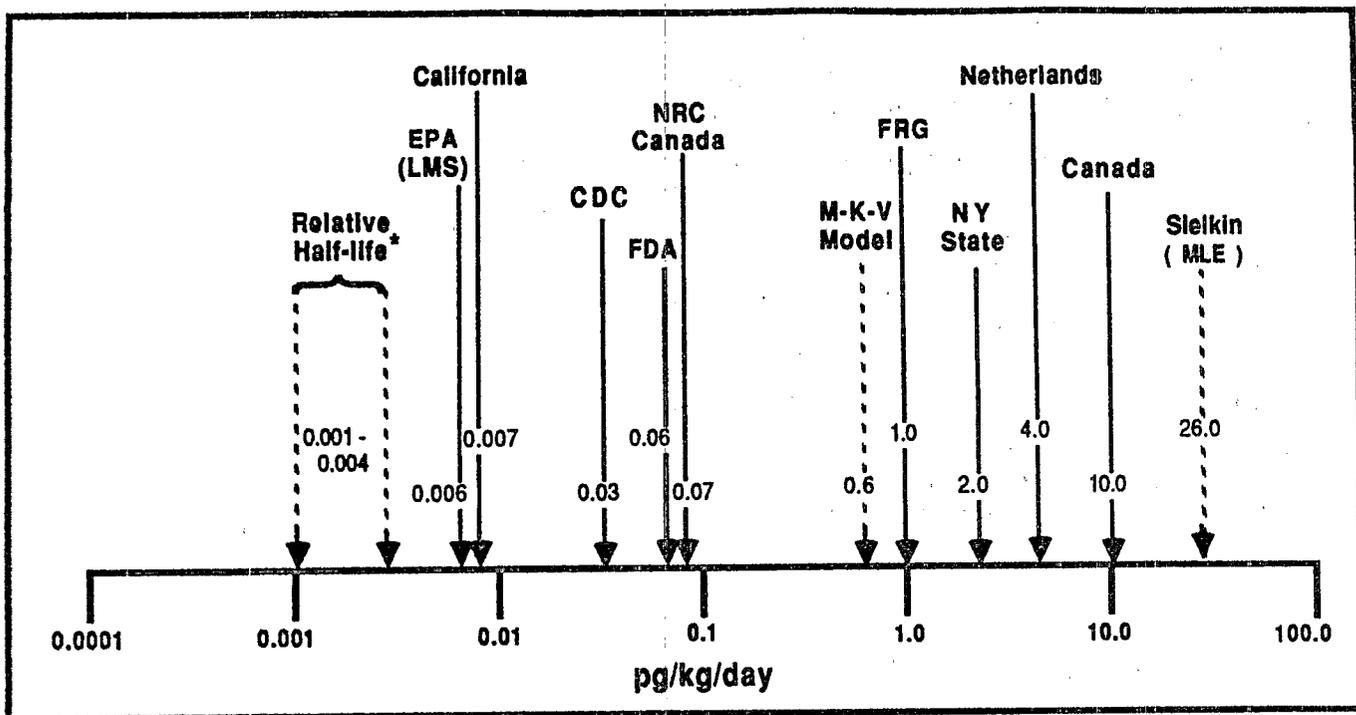


Figure 1. Some examples of risk specific doses (10^{-6}) and reference doses calculated by individual scientists, scientific organizations, and regulatory agencies for 2,3,7,8-TCDD. Solid lines represent conclusions reached by regulatory agencies or scientific organizations; hatched lines represent research efforts. Some values represented as lines with a single point could be represented as a range. The point shown is generally the lowest RsD or RfD of the range.

* Very preliminary analysis, taking into account the longer half-life of 2,3,7,8-TCDD in humans relative to rats.

Abbreviations used in the chart are as follows:

- CDC Centers for Disease Control, U.S. Public Health Service
- EPA U.S. Environmental Protection Agency
- FDA U.S. Food and Drug Administration
- FRG Federal Republic of Germany
- LMS Linear multistage model
- M-K-V Moolgavkar, Knudson, Venzon
- MLE Maximum likelihood estimate
- NRC National Research Council, Canada

The line indicated as "Canada" represents both Health and Welfare Canada and the Province of Ontario, Canada

Source: Taken from Appendix A.

a traditional toxicological approach.² Based on science policy considerations developed in section III.B.2.b.6., the Workgroup proposes that the Agency adopt a dose of 0.1 pg/kg/day as a plausible upper-bound increased lifetime risk of one in a million. The estimate is consistent with the available data and theories and represents a reasonable science policy position.

B. COMPARISON OF POTENCY ESTIMATES

Plausible upper-bound cancer potency estimates for 2,3,7,8-TCDD published by EPA, other U.S. agencies, some state agencies, foreign governments, and individual investigators fall within a range that spans more than three orders of magnitude. This range represents the lack of current consensus regarding approaches to estimating levels associated with potential cancer risk. Comparison of the various assessments has two purposes: (1) to demonstrate how scientists, using the same data but different assumptions and/or science policies, arrive at different risk estimates, and (2) to discuss alternative methods to EPA's customary approach, which is based on the upper-confidence limit (UCL) of the LMS model, for estimating human cancer risk from exposure to 2,3,7,8-TCDD. This explicit discussion of assumptions and policy choices highlights some of the uncertainties inherent in the risk assessment process generally, and in analyses and assessments specific to the carcinogenicity of 2,3,7,8-TCDD.

²It should be recognized that neither of these methods attempts to estimate the "true risk" posed by exposure to a chemical. In the case of the linearized models, because our understanding of the mechanism of carcinogenesis is so limited, an upper limit to the risk is calculated. In its risk assessment, using the LMS model, EPA stresses that the true risk is likely to be lower than the "plausible upper bound," and may be zero. Likewise, the traditional toxicological approach does not attempt to estimate risk; rather, it estimates a lifetime daily dose likely to be without significant risk.

Alternative approaches to estimating cancer risk are discussed in terms of existing 2,3,7,8-TCDD risk assessments to give EPA risk assessors and risk managers established points of reference and to distinguish science, science policy, and assumptions. The analysis shows that differences among the risk assessments for 2,3,7,8-TCDD developed by various regulatory agencies are not due to disagreements about the scientific data base per se, but rather are due to the judgments, science policy positions, and methods used in estimating human risk. Indeed, a major factor accounting for the differences in the various assessments is the judgment reached on whether or not a threshold exists for the carcinogenic activity of 2,3,7,8-TCDD. U.S. agencies, including EPA, have selected the LMS model, a mathematical model based on a dose-response function that does not have a threshold (that is, some non-zero risk can be calculated for all dose levels) and has a low-dose response characteristic that is essentially linear. Some Canadian and European environmental agencies, as well as some state agencies in this country, have selected a traditional toxicological approach based on an experimentally established no-observed-effect-level (NOEL)³ to estimate a presumed "safe dose." While choice of model often reflects, in part, the historical or philosophical tradition of a particular agency, in the case of 2,3,7,8-TCDD it also reflects important differences in the way different scientists interpret and weigh the scientific evidence and related uncertainties.

³Dose in the chronic animal bioassay at which no increase in tumor incidence was observed.

C. ORGANIZATION

The background information in Chapter II refers to a report on sources and routes of human exposure to 2,3,7,8-TCDD, summarizes animal and human data on the potential for human cancer, and surveys existing quantitative cancer risk assessments for 2,3,7,8-TCDD. The section on mechanisms of carcinogenesis evaluates 2,3,7,8-TCDD in light of several different mechanistic hypotheses, while the remainder of the chapter focuses on mathematical approaches for risk extrapolation. Chapter III synthesizes the range of qualitative and quantitative considerations bearing on the human cancer risk potential of 2,3,7,8-TCDD, and explains the basis for selecting 0.1 pg/kg/day as a cancer risk-specific dose (10^{-6}) for this chemical.

While this report draws on EPA's 1985 Health Assessment Document (HAD) for Polychlorinated Dibenzo-p-Dioxins (U.S. EPA, 1985) for certain data, it incorporates new information and alternative interpretations of the scientific evidence.⁴ The analysis follows EPA's Guidelines for Carcinogen Risk Assessment which call for articulation of "major assumptions, scientific judgments and to the extent possible, estimates of the uncertainties embodied in the assessment. . .distinguishing clearly between fact, assumption, and science policy" (U.S. EPA, 1986a).

⁴Other sources include a "Dioxin" Update Committee Report of a meeting held July 1-2, 1986 (submitted to the Office of Pesticides and Toxic Substances August 28, 1986; hereafter called the "Pitot Report") (U.S. EPA, 1986c), the "Report of the EPA Workshop on the Development of Risk Assessment Methodologies for Tumor Promoters" (hereafter called the U.S. EPA "Promoter Workshop") (U.S. EPA, 1987c), and six issue papers developed as background information for this reanalysis (Appendices A through F).

II. ANALYSIS

In this chapter data from laboratory and human studies are evaluated in terms of the factors that influence risk assessment methodology generally and that raise specific questions about existing cancer risk assessments for 2,3,7,8-TCDD. In place of models that appear to be based upon a dichotomous view of carcinogens as either complete carcinogens or pure promoters, researchers are exploring more sophisticated models which span a variety of direct and indirect mechanisms, including a combination of several modes of action. Qualitative answers to the questions regarding mechanism(s) by which 2,3,7,8-TCDD exerts its carcinogenicity could have a significant effect on the quantitative estimates of risk.

This chapter addresses these questions. Section A identifies relevant data from laboratory and human studies. Section B briefly reviews current theories on mechanisms of carcinogenesis as they apply to this chemical. In section C, several risk assessment models are reviewed in light of current data on 2,3,7,8-TCDD and mechanistic considerations. The special question of body burden data, particularly its meaning for the epidemiologic studies, is reviewed in section D. The implications of these several factors for human cancer risk from exposure to 2,3,7,8-TCDD is discussed in section E.

A. BACKGROUND

This section summarizes basic data on the effects of 2,3,7,8-TCDD in animal, human, microbial, and in vitro studies. Section 1 outlines data on sources and routes of exposure; section 2 summarizes the animal and human studies that provide the foundation for most risk assessments for 2,3,7,8-TCDD;

and section 3 presents relevant ancillary information. These summaries abstract data reviewed and analyzed in the issue papers prepared for this report (Appendices A through F) and other sources cited.

1. Exposure Considerations

A comprehensive review and analysis of human exposure to 2,3,7,8-TCDD appears in a draft document entitled "Estimating Exposures to 2,3,7,8-TCDD" (U.S. EPA, 1987a). This report should be consulted for information on sources of 2,3,7,8-TCDD, its movement through the environment, routes of human exposure, and possible human doses resulting from those exposures.

The report was prepared by scientists and engineers from the Exposure Assessment Group, Office of Health and Environmental Assessment. The primary purpose of the report is to provide a review and update of information related to exposure to 2,3,7,8-TCDD that has come to light since 1984. In addition, this report provides an illustration of the application of this information in performing exposure assessments for 2,3,7,8-TCDD. This is accomplished by using the information to construct several scenarios where contaminated material may result in exposure to 2,3,7,8-TCDD, and estimating what the exposure would be for various pathways from source to humans exposed. Sources used as examples in this report include contaminated soil, various land disposal situations, and municipal waste incinerators. It must be emphasized that these scenarios are not to be interpreted as an exposure/risk assessment for all sources of these types. This report should, however, provide a sound starting point for many exposure assessments of 2,3,7,8-TCDD contamination.

2. Carcinogenicity of 2,3,7,8-TCDD

The carcinogenic potential of 2,3,7,8-TCDD for humans has been the focus of intensive study and debate for almost a decade, and the issue is still not

resolved. While chronic exposure studies in laboratory animals demonstrate that 2,3,7,8-TCDD is a potent carcinogen in rodents, epidemiologic data have been much more difficult to interpret and more controversial. These issues are addressed in this section and described more fully in the issue papers prepared by Bayard (Appendix A) and Bayliss (Appendix B).

a. Chronic Animal Studies

There is general agreement that 2,3,7,8-TCDD is carcinogenic in laboratory animals. The critical studies are from two independent laboratories and show effects in both rats and mice. These and other experimental animal studies are fully discussed in EPA's HAD (U.S. EPA, 1985).

In a chronic toxicity and oncogenicity study by Kociba et al. (1978), dietary doses of approximately 0, 1,000, 10,000, and 100,000 pg/kg/day 2,3,7,8-TCDD were fed to rats for up to 2 years (1 pg = 10^{-12} gram, so that 100,000 pg/kg/day is equal to 0.1 ug/kg/day). In the high-dose group, both male and female animals had significant site-specific increases in tumors. The target organs and tumor types in male animals were squamous cell carcinomas of the tongue, hard palate, and nasal turbinates, and adenomas of the adrenal cortex; in female animals, the target organs and tumor types were hepatocellular carcinomas and squamous cell carcinomas of the tongue, nasal turbinates, and lung. Most investigators interpret this study as demonstrating that dietary exposure to 2,3,7,8-TCDD at 100,000 pg/kg/day or greater results in increased tumor incidences in both male and female rats. If neoplastic

nodules are combined with hepatocellular carcinomas, a statistically significant response is also seen at 10,000 pg/kg/day in female rats.⁵

The National Toxicology Program (NTP) has also tested 2,3,7,8-TCDD for carcinogenicity in rats and mice following administration by gavage (NTP, 1982). Rats were exposed to weekly doses of 0.0, 10,000, 50,000, and 500,000 pg/kg. 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 in the high-dose groups than in controls, and the incidence of tumors at both sites showed a positive dose-related trend. Under the conditions of this bioassay, the NTP concluded that 2,3,7,8-TCDD was carcinogenic in both male and female rats.

In the NTP mouse study, male mice were exposed to weekly doses of 0.0, 10,000, 50,000, and 500,000 pg/kg, while female mice were exposed to weekly doses of 0.0, 40,000, 200,000, and 2,000,000 pg/kg. An increased incidence of liver tumors was also observed in the NTP study in the high-dose male mice and in the high-dose female mice. Female mice also had an increased incidence of follicular-cell adenomas of the thyroid. In this study, 2,3,7,8-TCDD was carcinogenic to mice, with effective doses ranging between 500,000 and 2,000,000 pg/kg/week (0.5 and 2.0 ug/kg/week) depending on sex.

⁵The EPA Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1986a) address the question of combining benign and malignant lesions of identical histogenic origin. In addition, the Agency's Risk Assessment Forum has published guidance on the use of various proliferative hepatocellular lesions of the rat in risk assessment (U.S. EPA, 1986b). In the case of 2,3,7,8-TCDD, both would recommend combining benign and malignant lesions; however, both suggest that when such lesions are combined, the impact of the benign lesions on the quantitative response should be presented explicitly.

On the basis of information contained in these two studies, and other animal data described in the HAD (U.S. EPA, 1985), the Agency concluded that the evidence from animal studies for a carcinogenic response induced by exposure to 2,3,7,8-TCDD is "sufficient" under the weight-of-evidence system in EPA's then Proposed Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1984).

b. Epidemiologic Studies

Several epidemiologic studies designed to evaluate cancer in humans potentially exposed to 2,3,7,8-TCDD or substances presumed to contain 2,3,7,8-TCDD are subjects of sharp debate. Results of these studies, including both cohort and case-control designs, are arguably conflicting, with some studies reporting high risks and others reporting low or no detectable risks.

Although most of the studies have followed standard epidemiologic procedures, the conclusions of all are subject to specific limitations. Of particular concern are uncertainties about the nature and extent of actual exposure to 2,3,7,8-TCDD.⁶ In every instance, because of a lack of empirical exposure data, some surrogate basis for estimating exposure has been used. Studies in which human populations have been examined for carcinogenic responses to exposure to substances containing 2,3,7,8-TCDD are reviewed in the issue paper by Bayliss (Appendix B).

Two epidemiologic studies from Sweden (Hardell and Sandstrom, 1979; Eriksson et al., 1981) are considered by many to be critical studies in assessing potential human cancer risk. They suggest a high cancer risk associated with exposure to chemicals contaminated with 2,3,7,8-TCDD. These

⁶Recent analyses of tissue from subjects in some of these studies suggest that "control" and "exposed" have roughly the same levels of 2,3,7,8-TCDD in their tissues (Hardell, 1987). The impact of this finding on the interpretation of the studies has not been fully assessed.

studies have reported statistically significant, five- to sevenfold elevated risks of soft tissue sarcoma (STS)⁷ related to occupational exposure to phenoxy herbicides and/or chlorophenols, some of which were assumed to contain 2,3,7,8-TCDD. While some methodological questions have been raised about these studies, it appears that the elevated risks (at some level of exposure) are real and should be considered in hazard evaluation.

In addition to the two Swedish studies and certain case reports, other studies (including studies in certain U.S. populations) may give some support to the association between exposure to 2,3,7,8-TCDD and STS (see Appendix B); however, such an assessment is widely debated. These and other studies have also reported associations between other forms of cancer and exposure to 2,3,7,8-TCDD or chemicals likely to be contaminated with chlorinated dibenzo-p-dioxins (CDDs). For example, Hardell et al. (1981) reported a statistically significant risk of non-Hodgkin's lymphoma (NHL) in agricultural, forestry, and woodworking employees exposed to phenoxy herbicides, chlorophenols, or both. The relative risk ratio ranged from 4.3 to 6.0 for both classes of compounds together as well as separately. In addition to NHL, results from these studies have raised questions about increased risks of stomach cancer, prostate cancer, Hodgkin's disease, and kidney cancer. Since reports of increased risks for cancers other than STS and NHL occur sporadically throughout these studies, they are generally considered inconclusive.

⁷"Soft tissue sarcomas constitute a category of rare cancers with a total mortality rate of 1 STS per 100,000 persons per year in the United States. The soft tissue sarcomas are malignant neoplasms of diverse histologic subtypes, which occur throughout the body in mesenchymal connective tissue other than bone. These malignancies are often not reported accurately on death certificates and may not be recognized accurately by general pathologists" (Fingerhut, 1986). The effect of such misdiagnoses could either under- or overreport the number of STS cases in a study.

In contrast, several studies involving populations believed to have been exposed to 2,3,7,8-TCDD or 2,3,7,8-TCDD-containing chemicals have not shown any significant increased incidence of cancer (Appendix B).

Studies of Vietnam veterans have been the subject of particular interest because it is thought that some of these veterans were exposed to 2,3,7,8-TCDD as a result of exposure to Agent Orange in Vietnam.⁸ Based on Agent Orange use and potential for exposure under the conditions in Vietnam, it has been assumed some subsets of the population may have been exposed to relatively high levels of 2,3,7,8-TCDD. To date, most of these studies have shown no statistically significant correlation between Vietnam service (and, therefore, possible exposure to 2,3,7,8-TCDD) and an increased risk of cancer. For example, the Ranch Hand study has so far reported only a limited number of deaths (six) from cancer among the exposed group, none of which was from STS or lymphoma (Fingerhut et al., 1984). Studies of the mortality patterns among New York service men with and without Vietnam experience found no significant association between cancer and service in Vietnam (Greenwald et al., 1984), although it should be noted that a study of Massachusetts Vietnam veterans reports a significant excess of connective tissue sarcomas compared to non-Vietnam veterans (Kogan and Clapp, 1985).

Although the epidemiologic data are not persuasive regarding one interpretation over another, the high relative risks seen in the Swedish studies are noteworthy. While an association may exist between exposure to

⁸Agent Orange, an herbicide widely used in Vietnam, was composed of equal parts of butylesters of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and 2,4-dichlorophenoxyacetic acid (2,4-D). 2,3,7,8-TCDD, a contaminant in Agent Orange, has been shown to originate from the 2,4,5-T component with levels ranging from 0.1 to 47 ug/g (U.S. EPA, 1985).

chemicals contaminated with 2,3,7,8-TCDD (e.g., phenoxy herbicides) and increased incidences of cancer, the data are still too uncertain to attribute the effects seen to 2,3,7,8-TCDD.⁹

In light of the above considerations, and in accordance with the Agency's Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1986a), the human evidence supporting an association between exposure to 2,3,7,8-TCDD and cancer is considered inadequate.

3. Altered Cell Function

Animals given 2,3,7,8-TCDD as a single dose of 300,000 to 3,000,000 pg/kg exhibited a significant increase in a variety of enzymes responsible for the toxification/detoxification of foreign chemicals in the liver (increased enzymatic activity has also been found in other organs) (Poland and Glover, 1975). Sloop and Lucier (1987) have shown a statistically significant increase in arylhydrocarbon hydroxylase (AHH) in animals exposed to 15,000 pg/kg of 2,3,7,8-TCDD in corn oil.¹⁰ In other systems it has been shown that the toxification/detoxification process can, in some cases, yield genotoxic intermediates when metabolizing ingested chemicals to harmless substances

⁹One current investigation involves a National Institute for Occupational Safety and Health (NIOSH) registry of U.S. workers who have been employed in industries that manufactured chemicals thought to be contaminated with 2,3,7,8-TCDD, as well as other chlorinated dibenzo-p-dioxins (CDDs) and chlorinated dibenzofurans (CDFs). A study of this group of 7,000 workers, scheduled for completion in 1989, could provide substantial, valuable, and additional information on the question of the carcinogenic potential of 2,3,7,8-TCDD in humans.

¹⁰AHH is a cytochrome P450-mediated microsomal mono-oxygenase that metabolizes numerous chemicals. AHH is induced by a sequence of events starting with the binding of 2,3,7,8-TCDD to the Ah receptor located at the cellular membrane. It is the translocation of the Ah receptor/2,3,7,8-TCDD complex to the nucleus and binding to the DNA that leads to the transcription/induction of AHH.

suitable for excretion. 2,3,7,8-TCDD is poorly metabolized, and therefore the increased activity of these enzymes is likely to have little effect on the genotoxic potential of 2,3,7,8-TCDD itself. Available data suggest that 2,3,7,8-TCDD has little or no ability to act as a direct genotoxin. However, the increase in toxification/detoxification enzymes does increase the possibility that other exogenous chemicals will be activated to genotoxic substances. Thus, it is possible to postulate a process whereby 2,3,7,8-TCDD, through a secondary route, causes cancer through a mechanism involving genotoxicity.

The available information on enzyme induction indicates that 2,3,7,8-TCDD is one of the most potent inducers studied. Poland and Glover (1984) found that 0.85 nmoles/kg of 2,3,7,8-TCDD elicited the ED₅₀ level of AHH hydrocarbon hydroxylase in rat liver compared to 25,500 nmoles/kg of 3-methylcholanthrene.¹¹

In addition, the increased enzymatic activity elicited by 2,3,7,8-TCDD remains elevated, near peak level, for over 30 days while the enzymatic activity elicited by 3-methylcholanthrene returned to normal in 8 days, reflecting the influence of 2,3,7,8-TCDD's long half-life (see Appendix A). Limited data using human cells in culture indicate that enzyme induction is likely to take place in humans exposed to 2,3,7,8-TCDD (Jaiswal et al., 1985). Additional cellular data suggest an impact of 2,3,7,8-TCDD on such diverse responses as increased proliferation, antagonism of hormone-mediated responses, cytotoxicity, and in vitro transformation (see section B).

¹¹3-Methylcholanthrene is used routinely by investigators as an inducer of AHH.

While this information is of interest and does signal qualitative concern for carcinogenicity in humans exposed to 2,3,7,8-TCDD, it is not possible at present to factor these observations into a quantitative risk assessment.

4. Weight-of-Evidence Conclusion

Based on sufficient evidence in animal studies, inadequate human evidence, and consideration of ancillary or supportive information, 2,3,7,8-TCDD is classified as a B2--probable human carcinogen in EPA's weight-of-evidence scheme. The Agency reached the same conclusion in the 1985 HAD without invoking the contribution of the ancillary data.

This classification represents a qualitative judgment as to the likelihood that 2,3,7,8-TCDD may be a human carcinogen at some dose. It does not reflect a calculation of potency nor does it resolve the issue of threshold versus nonthreshold approaches to describe the carcinogenic dose-response. In its simplest terms, this classification represents the consensus of scientific opinion that ". . .in the absence of adequate data on humans, it is biologically plausible and prudent to regard agents for which there is sufficient evidence. . .of carcinogenicity in experimental animals as if they presented a carcinogenic risk to humans." (IARC, 1987).

B. MECHANISMS OF CARCINOGENESIS

Qualitative evidence for designating a chemical as a potential human carcinogen comes from a variety of observations--human epidemiologic studies, chronic animal bioassays, in vitro studies, metabolic studies, and mechanism studies. Thus, conclusions depend not on a single piece of information, but rather, a weight-of-evidence assessment of all data bearing on whether the chemical is or is not carcinogenic.

At present, carcinogenesis, as a process, is hypothesized to be a continuum of events characterized by a number of steps--some irreversible and others reversible--that result in the transformation of a normal cell to a malignant one. While some of these steps have been defined by responses observed in laboratory experiments, the actual sequence of cellular events leading to (1) initiation of a cell, (2) clonal expansion of the population of initiated cells, and (3) progression leading to malignant transformation is still unknown for even a single chemical.¹² Thus, chemicals are often categorized by responses seen in vivo and in vitro studies and/or where in the carcinogenic process they act. For example, simply stated, a "complete carcinogen" is one that can lead to tumor formation in the absence of any other known exogenous factor and a "promoter" is a substance that can affect the growth and clonal expansion of a population of initiated cells, and can alter gene expression (U.S. EPA, 1987c).

While such categories are theoretically easy to describe, in practice it is often difficult (if not impossible) to separate carcinogens into discrete categories based on mechanism of action. This process is further complicated by the possibility of multiple carcinogenic mechanisms, direct and indirect, occurring as a result of exposure to a single compound. In fact, especially at low doses it is not clear that any carcinogen affects all stages; the hypothesis of "linearity-at-low-doses" does not require this.

¹²It should be noted, that initiation, promotion, and transformation may also be made up of a series of steps.

1. Hypothesis 1: 2,3,7,8-TCDD as a Direct-Acting, Complete Carcinogen

a. Qualitative Consideration

At present, carcinogens are defined operationally because of a lack of understanding of the mechanisms by which chemicals cause cancer. Thus, observations of an increased number of rare tumors, a decrease in the time-to-tumor, or a statistically significant increase of site-specific tumor incidence in multiple species and strains in animal bioassays have generally been taken to support the conclusion that the test chemical is a complete carcinogen. Unfortunately, the bioassay gives us no information about the process leading to the tumorigenic response. To give further support to the characterization of a chemical as a direct-acting, complete carcinogen, i.e., one that acts through a mechanism that involves DNA damage, the weight-of-evidence analysis includes information from a variety of other observations. These include short-term mutagenicity studies, irreversible binding to DNA, clastogenicity, and other indications of genotoxicity. Positive results in some or all of these types of tests are considered by some as necessary before a chemical can be considered to be a complete carcinogen. Conversely, negative results in these types of tests are considered by some as an indication that a chemical may not be a complete carcinogen. Although some mechanisms, such as oncogene activation, may also be considered as "direct" negative results in more traditional genotoxicity tests, they have been used to argue against interpretation of positive bioassays results as the consequence of direct, complete carcinogenesis.¹³

¹³The use of the term "direct" in this context is meant to convey the notion of a direct impact of a chemical or its metabolites on the carcinogenic process and should not be confused with the use of the term direct (parent compound) versus indirect (metabolite) carcinogenicity as described by some in the scientific literature.

2,3,7,8-TCDD produces tumors in animals in lifetime studies (Kociba et al., 1978; NTP, 1982). Tumors were seen at multiple sites in rats and mice of both sexes. However, attempts to demonstrate that 2,3,7,8-TCDD is either mutagenic or genotoxic have been mostly negative. Recent reviews by Fishbein (1987), Giri (1987), and Shu et al. (1987) of over 20 studies have concluded that 2,3,7,8-TCDD is probably not genotoxic. In addition, Randerath et al. (1987) demonstrated that 2,3,7,8-TCDD exposure does not result in measurable DNA adducts, and, therefore, probably does not bind irreversibly to DNA. Furthermore, Lim et al. (1987) published data that show a lack of clastogenicity in animals exposed to 2,3,7,8-TCDD. Thus, the kind of mechanistic data that would support classification of 2,3,7,8-TCDD as a direct-acting, complete carcinogen on the basis of genotoxicity are lacking.

A recent review comparing the results from short-term tests and long-term chronic bioassays for 76 chemicals (Tennant et al., 1987) showed that the concordance between short-term tests and a response in a chronic bioassay was only 60%. While highly predictive for certain classes of compounds and for those substances that are routinely positive, this review indicates that the lack of positive results in short-term tests is often not a predictor of the outcome of a chronic bioassay, and, therefore, may not be a reliable predictor of direct, complete carcinogenicity. Also, Reynolds et al. (1987) have shown that at least two chemicals that test negative in mutagenicity tests conducted by the NTP can activate oncogenes which may result in a specific irreversible cellular change. This is considered by many scientists to affect control of cell proliferation and, perhaps, to be an important step in the carcinogenic process. These kinds of observations suggest that as new approaches to investigating molecular events potentially involved in the carcinogenic process

become available, our understanding of how particular chemicals exert their carcinogenic effect may change.

It is important to note that while the promoting capability of 2,3,7,8-TCDD has been clearly demonstrated in the liver, the tumors observed in one animal bioassay in the lung, soft palate, and nasal turbinates can be taken as evidence supporting complete carcinogenicity; although, even in these tissues, promotion of pre-existing initiation (or complete carcinogenesis by unknown mechanisms that are not representative of response at the administered dose), based on locally high levels of 2,3,7,8-TCDD found in food particles, cannot be ruled out (Kociba, 1984). In addition, studies that use a liver system to show promoting effects of 2,3,7,8-TCDD yield data suggesting that some initiating potential cannot be totally ruled out. In sum, it is not possible, at this time, to conclude definitively whether or not 2,3,7,8-TCDD is acting as a complete carcinogen in some tissues.

b. Quantitative Considerations

For complete carcinogens that act by directly causing an irreversible initiating event and then by fostering promotion and progression of the cells to a frank tumor, no threshold would be expected on the basis of current theory. In addition, if a carcinogen caused its effect by adding irreversibly to a background process already underway, linearity at low doses would be expected. The EPA has integrated the two concepts of irreversibility and additivity in deriving the use of a plausible upper bound from the LMS model for carcinogens as a matter of science policy. While a number of models, in addition to the LMS model, incorporate the concept of low-dose linearity, there is currently no biological basis for the choice of one of these alternatives over the LMS model.

Consequently, if the Agency considers 2,3,7,8-TCDD to be a direct-acting, complete carcinogen, then, the use by EPA of a plausible upper bound derived from the LMS model is appropriate and consistent with Agency science policy. To the extent that the mechanism of action of 2,3,7,8-TCDD is not in accord with the derivation of the model, the use of the LMS model may be less appropriate.

2. Hypothesis 2: 2,3,7,8-TCDD as a "Pure" Promoter

a. Qualitative Considerations

Like complete carcinogens, promoters are defined operationally. Promoters are defined as providing a certain pattern of results in initiation/promotion tests. In theory, therefore, because "pure" promoters do not cause initiation, one might expect a promoter to give negative results in an animal carcinogenicity bioassay. In practice, however, a promoter could yield positive results in such a test because of initiated cells present as a result of "background" events that can be promoted to yield a tumorigenic response. For most promoters, the sensitivity of the bioassay would be expected to be too low to yield a statistically significant response based only on background events. Thus, under these terms, bioassay studies would allow certain promoters to be distinguished from complete carcinogens.

In order to characterize a chemical as having promoting potential only, additional information from other tests is generally considered to be necessary, such as: a lack of initiating potential as measured by a lack of genotoxicity, reversibility of the promotion response, inhibition of cell-to-cell communication¹⁴ and/or demonstration of a dose-response having

¹⁴Several investigators (e.g., Trosko, 1983) have suggested that many promoters may act by inhibiting cell-to-cell communication as measured in metabolic cooperation or dye-transfer studies.

threshold characteristics. It should be noted, however, that promoters do not necessarily have to exhibit all of these characteristics, but that positive results in these kinds of tests can help to support the categorization of a chemical as having only promotion potential.

Currently, two in vivo systems are commonly used to study the promotional phase of the carcinogenic process--rat liver and mouse skin. In both systems the animal is given a very small amount of a known potent initiator followed by a promoter; in the case of one of the controls, the order is reversed. Assuming the test compound is a promoter only, the results of such experiments can be expected to yield results as follows:

<u>Test Protocol</u>	<u>Result</u>
initiator only	no tumors
initiator followed by a promoter	tumors
promoter followed by an initiator	no tumors
promoter only	no tumors

In both rat liver and in some mouse skin studies, 2,3,7,8-TCDD is a potent promoter when tested with a known initiator (U.S. EPA 1986c; 1987c). In both systems, however, a low incidence of tumors in animals given only 2,3,7,8-TCDD suggests that 2,3,7,8-TCDD may have some initiating potential or that the observed tumors are the result of potent promotion of background events or unidentified initiators found in the animals' environment (e.g., substances in food). The results of such a study involving diethylnitrosamine (DEN) and 2,3,7,8-TCDD in partially hepatectomized rats are illustrated in Table 1.

In addition to the in vivo studies for promotional activity, a number of laboratories have investigated the promotion potential of 2,3,7,8-TCDD in

TABLE 1. PROMOTING EFFECT OF 2,3,7,8-TCDD (TCDD) ON HEPATOCARCINOGENESIS IN PARTIALLY HEPATECTOMIZED FEMALE RATS BY A SINGLE DOSE OF DIETHYLNITROSAMINE (DEN)

Group	Treatment	No. of animals	No. of enzyme-altered foci per cubic centimeter of liver	Mean volume of enzyme-altered foci (cubic millimeter)	% liver volume occupied by foci	No. of rats with carcinoma
1	DEN ^a	4	309 ± 98 ^b	0.02	0.7	0
2	TCDD (low dose) ^c	4	34 ± 17	0.05	0.2	0
3	TCDD (high dose) ^d	5	25 ± 7	0.04	0.1	0
4	Phenobarbital (control)	4	56 ± 13	0.01	0.1	0
5	DEN + TCDD (low dose)	5	1068 ± 166	0.08	9.0	0 ^e
6	DEN + TCDD (high dose)	7	871 ± 66	0.49	43.0	5 ^f
7	DEN + phenobarbital	10	533 ± 103	0.15	6.0	8

^a DEN given at dose of 10 mg/kg.

^b Mean ± SD.

^c 0.14 ug/kg/2 weeks.

^d 1.40 ug/kg/2 weeks.

^e Three rats exhibited neoplastic nodules in the liver.

^f One rat exhibited neoplastic nodules in the liver.

Source: Pitot et al., 1980.

isolated cell systems (see, for example, Abernethy et al., 1985). The results of these studies clearly demonstrate that 2,3,7,8-TCDD affects isolated cells as a promoter but does not alter the cells in a manner which would suggest that an initiating event has occurred. Hence, under the most stringent conditions (in vitro), 2,3,7,8-TCDD may act as a "pure" promoter, but under in vivo conditions the results are not as clear cut.

The reversibility of clonal expansion after the removal of a promoting substance has been considered a key effect in characterizing promotional activity. For example, Pitot et al. (1987) showed that the size of liver foci in rats increased in the presence of phenobarbital (a chemical generally regarded as a "pure" promoter) and then returned to normal when phenobarbital was removed from the diet.¹⁵ Investigation of 2,3,7,8-TCDD for reversibility of foci formation in similar experiments has not been attempted because of its long half-life in tissues, making results less easily interpretable.

It can also be argued that 2,3,7,8-TCDD does not meet the above criteria for a "pure" promoter. Some tumors observed in the lung, nasal turbinate, and hard palate may be the result of "complete carcinogenicity," although, as discussed previously, this is not uniformly accepted. Similarly, the reversibility of the promoter step has not been demonstrated for 2,3,7,8-TCDD. Finally, some evidence of clastogenicity exists although the results have not been duplicated (Green et al., 1977).

¹⁵It should be noted that re-administration of phenobarbital in this experiment resulted in a greater than anticipated clonal expansion which could be interpreted to mean that in addition to reversible effects, some irreversible step(s) had occurred.

b. Quantitative Considerations

A "pure" promoter that acts by facilitating clonal expansion of a population of initiated cells without any capacity to induce irreversible changes in DNA may be expected to demonstrate a threshold, theoretically, although no quantitative framework exists which demonstrates that thresholds must exist under all circumstances. For example, the Moolgavkar, Knudson, and Venson (M-V-K) model, now being investigated by a number of scientists for modeling the carcinogenicity of promoters, does not require an assumption of a threshold. The theoretical basis for the threshold response would be the likelihood of a dose at which the net response of clonal expansion and normal cell death (or control of cell proliferation) would be zero. Consequently, for such a situation an appropriate method to estimate a level of exposure that would be unlikely to pose a significant risk may be the traditional toxicological approach for organ-specific toxicity via the derivation of a reference dose (RfD). This RfD is calculated from the no-observed-adverse-effect-level (NOAEL) based on carcinogenicity noted in the bioassay, divided by several uncertainty factors.

To the extent that the data demonstrate that 2,3,7,8-TCDD is a "pure" promoter, the traditional toxicological approach is arguably appropriate. Conversely, data that indicate that 2,3,7,8-TCDD has the ability to initiate the carcinogenic process or that 2,3,7,8-TCDD may be a complete carcinogen would make the application of the above method less appropriate.

3. Hypothesis 3: Secondary or Indirect Mechanisms of Carcinogenesis

a. General Considerations

As stated earlier in this chapter, a carcinogenic response in animals may be the result of direct interaction of the chemical (or its metabolites) under

test with sensitive cellular targets. On the other hand, this response may be the result of indirect effects or even a combination of the two.

While it is not possible to distinguish between direct and indirect responses in animal bioassays, a variety of test data may be used to draw a conclusion that indirect carcinogenicity may be responsible for an observed effect. The nature of such indirect effects may be such that the chemical affects the pool of "initiated cells" either qualitatively by making cells more sensitive to initiating agents or quantitatively by causing increased numbers of initiated cells. On the other hand, chemicals may indirectly affect the establishment or progression of preneoplastic lesions by making the cellular environment more conducive to such events or by inhibiting the cellular processes which keep tumor growth in check. It is quite plausible that induction or inhibition of enzymes, competitive inhibition of normal feedback mechanisms regulating cell proliferation, cytotoxicity, or effects on the immune system could be responsible for an indirect increase in carcinogenic response.

A wide variety of experimental data may be used to evaluate the inference of indirect carcinogenicity. These may be studies focused on molecular mechanisms or they may be at the level of altered organ function. The following section discusses such experimental data on 2,3,7,8-TCDD. It should be understood that this discussion is included to establish the plausibility of this approach, and does not represent an indepth review of potential mechanistic data. A number of lines of evidence require further development before their impact on carcinogenicity can be assessed. A more detailed discussion of several aspects of this approach can be found in Appendix F.

b. Qualitative Evaluation of 2,3,7,8-TCDD as an Indirect
or Secondary Carcinogen

(1) Enhancement of Initiation

One way in which 2,3,7,8-TCDD could affect the pool of initiated cells is by inducing enzymes that activate other endogenous and exogenous chemicals to proximate carcinogens. The effects of 2,3,7,8-TCDD on the induction of AHH activity is well established in a number of in vitro and in vivo systems (Poland and Knutson, 1982). This enzyme induction could result in increased levels of reactive intermediates from other xenobiotic chemicals, and ultimately increased numbers of initiated cells and increased potential carcinogenicity. Further enhancement of carcinogenicity could result from the potent promotional activity of 2,3,7,8-TCDD acting on indirectly initiated cells. Studies have shown increased genotoxicity of chemicals such as benzo(a)pyrene that require metabolic activation when they are administered or incubated with 2,3,7,8-TCDD in systems capable of responding to enzyme inducers (Pahlman and Pelkonen, 1987).

The integrity of the DNA molecule is generally thought to be important for normal cellular function. Specific types of DNA damage alter DNA molecular weight and may increase the probability of initiation. One measure of both normal metabolic processing and increases in DNA damage is quantification of single strand breaks in DNA. Such strand breaks may be caused by increased levels of free radicals in actively metabolizing tissues. Direct measurements of strand breaks have indicated increased breakage with exposure to 2,3,7,8-TCDD (Randerath et al., 1987). Studies that examined changes in DNA molecular weight after 2,3,7,8-TCDD treatment have provided conflicting results. Molecular weight increases were observed in treated animals

indicating fewer rather than increased numbers of single strand breaks. Strand breaks may also be associated with increases in DNA adducts either directly or indirectly to chemical exposures. Randerath et al. (1987) found no DNA adducts within the limits of detection of his assay in the livers of rats chronically exposed to low doses of 2,3,7,8-TCDD, and Romkes and Safe (1987) did not find 2,3,7,8-TCDD enhancement of DNA adduct formation from endogenous steroids.

Changes in DNA repair capacity could also have an impact on the pool of initiated cells. While few studies have measured repair parameters after 2,3,7,8-TCDD treatment, several observations can be noted. Treatment with 2,3,7,8-TCDD causes increases in O-6-methylguanine content in DNA. This observation may be consistent with an indirect effect on methylating capacity or on a failure to rapidly repair these lesions. Studies to date have not demonstrated that 2,3,7,8-TCDD causes increases in unscheduled DNA synthesis (UDS). This observation suggests that, under the conditions of the study, DNA damage has not increased to a level that can be measured with this type of DNA repair. Based on recent studies by Busser and Lutz (1987) and Den Engelse et al. (1986), effects on the repair system itself cannot be ruled out.

Another way that 2,3,7,8-TCDD could impact the pool of initiated cells indirectly is through its ability to cause organ-specific cell proliferation, thereby increasing the number of pre-existing initiated cells, which may represent an increase of potential tumors. The ability of 2,3,7,8-TCDD to cause hypertrophy and hyperplasia in several tissues where tumors arise has been noted in chronic-toxicity studies (Kociba et al., 1978). The question of stimulation of DNA synthesis caused by exposure to 2,3,7,8-TCDD is still an open one (Busser and Lutz, 1987).

(2) Enhancement of Carcinogenic Progression

Currently accepted theory suggests that an aspect of the carcinogenic process is the ability of chemical carcinogens to affect the progression of preneoplastic cells or foci towards the malignant state. It is generally held that this part of the process shows an irreversible dedifferentiation based on permanent genetic change. In the case of 2,3,7,8-TCDD, the long half-life of the molecule in human and animal systems allows for a constant impact over a prolonged period of time, somewhat akin to the constitutive presence of a regulator of cellular differentiation. While there is no evidence of permanent genetic changes associated with 2,3,7,8-TCDD exposure, there are data to suggest that the chemical can affect terminal differentiation and carcinogenic transformation in vitro. Increases in "flat cell"/"XB cell" (Gierthy and Crane, 1985) transformation support the notion of the potential to cause dedifferentiation, and studies in "10T1/2 cells" (Abernethy et al., 1985) show increased cellular transformation.

These activities represent a release from growth control which is characteristic of the carcinogenic process and might allow for the appearance of increased carcinogenic response in an indirect manner. Further support for this role of 2,3,7,8-TCDD comes from its apparent ability to act as a hormone agonist or antagonist (Umbreit and Gallo, 1988), without competing for sites on certain hormone receptors. The suggestion that 2,3,7-8 TCDD may be acting through cellular receptors as opposed to acting through the disruption of membranes, as many "classical promoters" do, is further supported by evidence that 2,3,7,8-TCDD does not disrupt cell-to-cell communication in vitro (Lincoln et al., 1987). Disruption of cell-to-cell communication has been suggested by some investigators (e.g., Trosko, 1983) to be an attribute of many promoting

compounds. This activity, or perhaps lack of activity, is found in cells with and without an inducible AHH system, so the characteristic is independent of that event, again suggesting the necessary but not sufficient role that enzyme induction might have in the carcinogenic process. This issue is described more fully in the issue paper prepared by Gallo (Appendix F).

c. Quantitative Considerations

The suggestion, in qualitative terms, that 2,3,7,8-TCDD may be acting as an indirect or secondary complete carcinogen through multiple mechanisms affects the way that this chemical is viewed in quantitative terms. This hypothesis is also consistent with the observed potency of 2,3,7,8-TCDD in producing a carcinogenic response in vivo, in that the observed tumors could be postulated to result from mechanisms such that 2,3,7,8-TCDD: may increase the pool of initiated cells, either directly or indirectly; is a potent promoter based on experimental evidence in specific test systems; may be actively involved in stimulating progression of tumors from benign to malignant; and may be indirectly influencing both repair and surveillance capabilities in vivo. Such activities, if viewed as adding to events that are already underway and contributing to the background or "spontaneous" incidence rate of tumors, have been argued as reasons for considering a nonthreshold, low-dose linear type of dose-response curve as being applicable (OSTP, 1985; Crump and Howe, 1984). This would imply an approach, under the Agency's current guidance, that might be identical to that generally used for carcinogens, namely the use of the LMS model to describe a plausible upper bound on the risk. It would not be likely that such indirect effects would result in a greater response than would direct effects, although this cannot be ruled out. These issues are discussed further in section II.B.1.b. of this document and in Appendix F.

C. EVALUATION OF 2,3,7,8-TCDD AS AN "ANTICARCINOGEN"

Another attribute of chemical carcinogens that should be taken into account when attempting to understand their behavior is the activity termed "anticarcinogenesis." In some cases, chemicals have been shown to overcome background processes or their own effects at some doses to produce a net negative effect on the carcinogenic outcome of animal bioassays. Such responses could have a profound effect on expectations of the dose-response if anticarcinogenic effects were cancelling out carcinogenic effects at a given dose in some tissues. The reproducible dip in response (at low doses) to below background tumor levels in female rat liver (Kociba et al., 1978; NTP, 1982) has suggested to some observers that 2,3,7,8-TCDD may show such a phenomenon. These observations are supported by more recent data which showed that induction of liver foci were reduced at low doses of 2,3,7,8-TCDD in an initiation/promotion assay (Pitot et al., 1987). Responses in other rat tissues (i.e., uterine and breast tissue), also show decreases in background or spontaneous tumor incidence which again support the observation that there is an overall decrease in the carcinogenic response with some doses of 2,3,7,8-TCDD (Kociba et al., 1978).

The implications for an analysis of dose-response and the applicability of certain models based on the observation of a potentially "anticarcinogenic" response for 2,3,7,8-TCDD is discussed in the next section.

D. USE OF PREDICTIVE MODELS

Scientific interest in interspecies and high- to low-dose extrapolation has led to the development of a variety of predictive models, including models for estimating the likelihood of human cancer based on data from animal

studies. Selection of the appropriate model in a given set of circumstances is difficult because of a lack of knowledge of concordant events across species and at low doses. Selection is further complicated by the possibility of multiple effects affecting the carcinogenic process.

Pleiotropism, i.e., action through multiple pathways, is not an uncommon finding with molecules such as 2,3,7,8-TCDD. One has only to review the earlier experiments on multistage mouse skin carcinogenesis of 2,3,7,8-TCDD to see that, in some cases, it inhibited tumor formation by PAH initiators (DiGiovanni et al., 1977; 1980; Berry et al., 1978). It must be emphasized that the responses in multistage models are dependent on time, sequence of administration, dose, and species. Hence, inhibition under some conditions might have been predictable. This is contrasted with the two-stage liver model (Pitot et al., 1980) in which it has been shown that orally administered 2,3,7,8-TCDD enhances the tumorigenic action of DEN. In subsequent experiments at lower doses of 2,3,7,8-TCDD, a parabolic dose-response curve has been reported in the DEN/TCDD initiation-promotion protocol (Pitot et al., 1987). These results are not well understood, but they do not appear to be solely the function of enhanced metabolism or Ah receptor binding (Safe et al., 1987). Perhaps it is the result of alteration of epidermal growth factor (EGF) receptors at low doses (Madhukar et al., 1984) which displays a commonality with several steroid hormone receptors.

These findings are of importance to the approximation of human and animal health risks from exposure to 2,3,7,8-TCDD and related molecules. Mathematical modeling of physiological phenomena, especially those related to receptor function, is often conducted using the Michaelis-Menton equation (1913) as modified by Clark (1933) for the "classical" receptor model. The weight of

evidence for the most prevalent 2,3,7,8-TCDD effects falls into the category of the receptor model (Poland and Knutson, 1982). According to recent findings, hepatocarcinogenesis observed after exposure of animals to 2,3,7,8-TCDD is related to estrogen levels or to the presence of functional ovaries (Goldstein et al., 1987), and diethylnitrosamine hepatocarcinogenesis in partially hepatectomized rats is first inhibited and then promoted by 2,3,7,8-TCDD (Pitot et al., 1980; 1987). These findings indicate that 2,3,7,8-TCDD is not causing its myriad of effects in liver by a simple one-step event such as binding to the Ah receptor and subsequent induction of cytochrome P₁-450.

Risk modeling for carcinogenic xenobiotics can be segregated into three classes or types of models: (1) physiologically based pharmacokinetic (PBPK) models in which the body is considered to be a small group of physiological compartments (Hoel et al., 1983; Krewski et al., 1986; Bischoff, 1987); (2) biologically motivated models of carcinogenesis (BMCC) in which the carcinogenic process is considered to occur through a series of linked reactions that result from two or more molecular events followed by a cellular amplification by "promoter" molecules (Moolgavkar et al., 1987; Thorslund et al., 1987; Krewski et al., 1987; U.S. EPA, 1987a); and (3) the LMS model of Armitage-Doll as modified by Crump and Howe (1984) in which it is assumed that a sequence of events occur within a single cell, some of which are irreversible, leading to the neoplastic change (Armitage, 1985).

A model that appears to accommodate most of the critical components from the biological data base on 2,3,7,8-TCDD is the BMCC model, which is generally referred to as the M-V-K model (Moolgavkar and Venzon, 1979; Moolgavkar and Knudson, 1981). This model allows for several of the concepts of initiation-promotion-progression, along with the growth-stimulating role of

endogenous substrates such as hormones (Moolgavkar, 1987). Incorporation of some of the factors necessary for the PBPK model can also be done using the M-V-K model as expanded by Thorslund et al. (1987). These expansions of the M-V-K model give the risk assessor a powerful tool for looking at cancer risk mechanistically. This approach requires the use of assumptions for several critical parameters and, thus, is testable but as yet unvalidated. This approach is not available with the LMS model as originally proposed.

The LMS model might be accommodated if one hypothesizes that: (1) the initiating event is the result of an indirect action of 2,3,7,8-TCDD through modification of exogenous or endogenous compounds; (2) a population of initiated cells exist; or (3) 2,3,7,8-TCDD acts through a variety of mechanisms, some of which are, at low doses, additive to other processes related to carcinogenicity and already underway.

Recent reports have shown that 2,3,7,8-TCDD and other promoters in liver enhance stimulation of DNA synthesis in situ, and stimulate repair of O-6-methylguanine in liver DNA (Busser and Lutz, 1987; Den Englese et al., 1986). Lutz et al. (1984) presented a scheme for promoter potency based on stimulation of DNA synthesis and the assumption that cell division is a prerequisite for several stages in the carcinogenesis process. These reports indicate that 2,3,7,8-TCDD may act as a complete, indirect carcinogen, including promoter activity, despite the lack of DNA binding or direct mutagenesis. The sum of all these findings, along with the myriad of other toxic responses, suggests a complex hypothesis for 2,3,7,8-TCDD carcinogenesis in rodent liver, which is illustrated schematically in Figure 2. This hypothesis can account for the dose-response data in the bioassays and the multistage promotion experiments, as well as allow for incorporation into

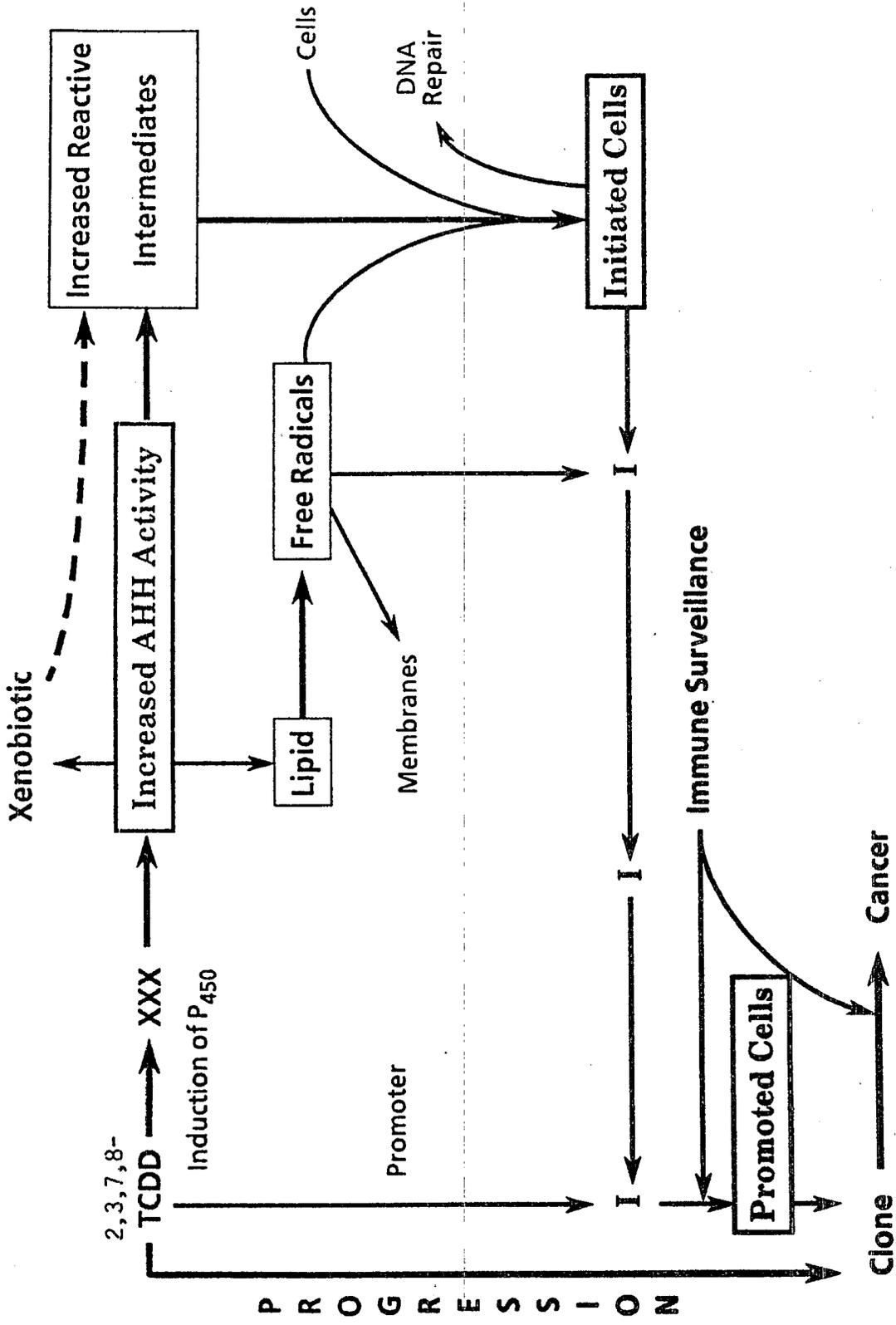


Figure 2. Potential secondary mechanisms of carcinogenic activity of 2,3,7,8-TCDD. Source: Appendix F

existing risk models, and the scheme is not inconsistent with the reports of decreased tumor formation in some tissues. If the pathway through AHH activity can be verified by demonstration of a net increase of reactive intermediates after 2,3,7,8-TCDD treatment, then the LMS model can be used. The scheme also presents several testable hypotheses that should be examined.

III. CONCLUSIONS

This re-examination of the carcinogen risk assessment for 2,3,7,8-TCDD identifies several approaches to describing the possible carcinogenic mechanisms for this chemical and reviews several different mathematical models for estimating its carcinogenic potency. However, the enormously rich data base on 2,3,7,8-TCDD is incomplete when it comes to answering the questions posed at the beginning of the analysis. The available data permit consideration of a broad array of possible scientific theories and science policy approaches when reconsidering EPA's 1985 carcinogen risk assessment for 2,3,7,8-TCDD (U.S. EPA, 1985), but they do not provide a clear basis for confidently choosing among them. The evaluation of each possible theory results in varying degrees of confidence as to their plausibility, as discussed in more detail below.

The literature review regarding 2,3,7,8-TCDD leads the Workgroup to several conclusions:

- 2,3,7,8-TCDD is a potent promoter of carcinogenesis;
- the possibility that 2,3,7,8-TCDD acts as a direct-acting, complete carcinogen cannot be eliminated;
- 2,3,7,8-TCDD may act through a secondary mechanism(s) which may affect the carcinogenic process at different stages; and
- 2,3,7,8-TCDD may act through a number of different mechanisms so that the observed effects represent an integrated composite of several mechanisms in operation.

After considering all of the data, the Workgroup has concluded that thinking about 2,3,7,8-TCDD either solely as a "promoter" or as a "complete" carcinogen is an oversimplification. Rather, while it is clear that 2,3,7,8-TCDD acts as a potent promoter, it may also affect other important carcinogenic

processes, some of which may result in a linear carcinogenic response in the low-dose region.

Schematically, this multiple mechanism hypothesis for 2,3,7,8-TCDD carcinogenicity is graphically displayed in Figure 3. The upper curve is the UCL of the LMS model, as applied in U.S. EPA (1985), in which the chemical is treated as a complete carcinogen with no distinction made for the specific contributions of initiation, promotion, or progression to the response. The low-dose behavior that is appropriately modeled by the LMS approach for the multiple mechanism hypothesis is depicted by the dotted line for the composite effect, represented here by an arbitrarily placed line. However, the magnitude of any difference between the slopes of these two lines is uncertain. Particularly from the available information, it is impossible to determine whether there is any difference at all, or if the "true" difference is negligible or substantial. The fact that the promoting behavior is taken as a major factor in the tumor response for 2,3,7,8-TCDD could argue for a greater rather than a lesser difference between the two slopes. On the other hand, because the animal tumor response observed is the net result of many processes, 2,3,7,8-TCDD potency at low doses could be characterized by the LMS upper-bound estimate, even if promotion is the predominant activity, because the linear portion of the curve would be the composite of a number of different activities acting in concert.

Quantitatively, it is not easy to fit such a hypothesis into currently available and well-accepted risk assessment models. Accordingly, the Workgroup recommends that, until either a more appropriate model is developed or additional data demonstrate that a currently available model is correct, as assessment approach that recognizes the possibility of linearity at low doses

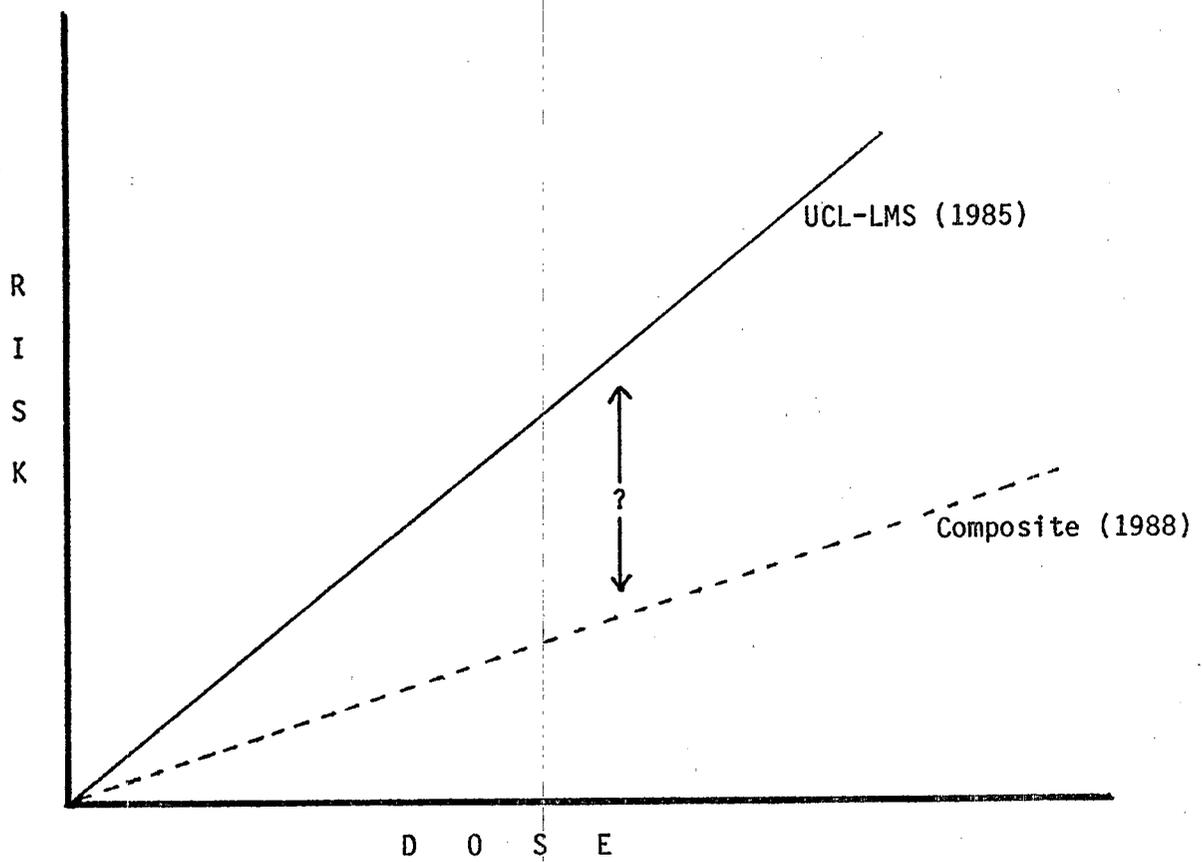


Figure 3. "Multiple mechanism" hypothesis for 2,3,7,8-TCDD carcinogenesis.

and presents estimates in terms of plausible upper bounds would be preferable as a interim approach.

The basis for these conclusions is set forth below. Section A summarizes qualitative factors relating to choosing a mathematical model, while section B reviews related quantitative considerations. Section C sets forth a rationale for a recommended cancer risk-specific dose (RSD) for 2,3,7,8-TCDD.

A. QUALITATIVE CONSIDERATIONS

Qualitatively, at least three classes of mechanisms of carcinogenic action for 2,3,7,8-TCDD have been considered in this document. First, tumors found in long-term bioassays in which 2,3,7,8-TCDD is the only known agent suggest that this agent is, at least operationally speaking, a complete carcinogen. Second, data from in vivo studies for promoter activity demonstrate that 2,3,7,8-TCDD is a potent promoter of carcinogenesis with little or no demonstrated ability to act as a direct genotoxin. Finally, an indirect impact on carcinogenic processes is suggested by studies linking 2,3,7,8-TCDD to responses such as enhancement of initiation, increased cell proliferation, antagonism of hormone-mediated responses, cytotoxicity, and in vitro transformation activity.

Despite evidence supporting each potential mechanism, 2,3,7,8-TCDD does not exhibit certain properties generally expected for each of the first two mechanisms. For example, if 2,3,7,8-TCDD directly initiated a "complete" carcinogenic response, genotoxicity or binding to DNA would be expected. The absence of these effects in studies involving this chemical does not rule out the possibility that 2,3,7,8-TCDD is a direct initiator, but it suggests that 2,3,7,8-TCDD is not a "typical" complete carcinogen. Unlike many promoting agents, 2,3,7,8-TCDD acts at low doses. (2,3,7,8-TCDD is active at doses 1000

times less than other known promoters.) Furthermore, reversibility, an oft-cited characteristic of promotion, has not and cannot easily be demonstrated because of the long half-life of 2,3,7,8-TCDD in biological systems.

In short, it appears that 2,3,7,8-TCDD has characteristics of a potent promoter, and, operationally, of a complete carcinogen. As observed previously, the Workgroup has concluded that thinking about 2,3,7,8-TCDD either solely as a "promoter" or as a "complete" carcinogen is an oversimplification. Rather, 2,3,7,8-TCDD produces a broad spectrum of biological responses that allows many hypotheses regarding the mechanism of 2,3,7,8-TCDD toxicity and carcinogenicity. Because the available data are not adequate to absolutely confirm or refute one or more of these approaches, each is considered in evaluating potential quantitative methods for estimating the risk associated with exposure to this chemical.

B. QUANTITATIVE CONSIDERATIONS

The range of potential mechanisms suggests a range of different quantitative approaches. If 2,3,7,8-TCDD is treated as a direct-acting, complete carcinogen, a model incorporating linearity at low doses would be appropriate for dose-response assessment, for the reasons mentioned in the EPA guidelines and the OSTP Cancer Principles (U.S. EPA, 1986a; OSTP, 1985). At the other end of the spectrum, if 2,3,7,8-TCDD is regarded solely as a promoter, a threshold approach to quantitative assessment may be more appropriate. And, finally, if 2,3,7,8-TCDD is regarded as an indirect carcinogen, possibly acting by multiple mechanisms in the carcinogenic process, some of which may display linear behavior at low doses, then a linearized model

could be appropriate although the slope of the response will be uncertain. It should be noted here that the 1985 estimate of the potency of 2,3,7,8-TCDD (U.S. EPA, 1985) has always been characterized as a plausible upper bound to the risk; the extent of this "overestimate" is unknown, but it may be higher than previously thought.

An assessment of several potential approaches for estimating the carcinogenic potency of 2,3,7,8-TCDD and related risk-specific doses is summarized in the following section.

1. Selection of Models

a. NOEL/Uncertainty Factor (Threshold Approaches)

If 2,3,7,8-TCDD acts solely as a promoter, the traditional toxicological approach based on a NOEL or a lowest-observed-effect-level (LOEL) may be an appropriate risk estimation approach under certain circumstances. However, while there is evidence that 2,3,7,8-TCDD acts as a promoter, the data suggest that this chemical may also act through multiple mechanisms, direct or indirect. If some of these component mechanisms were linear at low doses, then the composite dose-response curve would be expected to be linear at low doses, and a threshold approach would not be appropriate. Although 2,3,7,8-TCDD is a strong promoter, biological data and statistical limitations to the power of bioassays suggest that a threshold cannot be adequately demonstrated and may not exist. This assessment is tempered somewhat by observations both in vivo and in vitro suggesting "anticarcinogen" effects at low doses which could offset the other effects of 2,3,7,8-TCDD and possibly produce a threshold. An anticarcinogenic effect working in conjunction with a carcinogenic effect in the same tissue might result in a net response of zero over background and might be described as a threshold effect, in summary.

Until such time that some of these critical issues are resolved, the Workgroup concluded that it would not be prudent to adopt a threshold approach for estimating human cancer risk for 2,3,7,8-TCDD.

b. Sielken Approach

Sielken has produced a risk assessment with several provocative aspects; e.g., generating a maximum likelihood estimate (MLE, as opposed to a UCL), discarding the data obtained from the highest dose, using time-to-tumor information, and drawing attention to the lower-than-background response observed at the lowest dose in both the Kociba et al. (1978) and the NTP (1982) studies. While this type of exploratory analysis is interesting and raises points that should be examined more closely, the Workgroup is reluctant to adopt this approach at this time for several reasons. For example, the use of the MLE has traditionally been avoided due to its instability in the face of relatively small changes in the data (see Appendix A) and, for this reason, the UCL has generally been preferred. Crump (1987) provided a critical review of the Sielken analysis and observed that even if "the true shape of the dose response is a straight line connecting the background response and the response at the mid-dose," the probability of an MLE of zero for the linear term in the multistage model is about 1/3. He concludes that while the data are consistent with Sielken's interpretation of a higher RsD, they are also consistent with much lower RsDs, as displayed in the confidence limits.

c. M-K-V model

This model, which is based on the use of biologically-based models (see Section II.D.), represents significant progress in carcinogen risk assessment. Its use for estimating the carcinogenic potency of chemicals in general, and of 2,3,7,8-TCDD in particular, is viewed by this group as premature for several

reasons. There are concerns about its biological bases and assumptions, the statistical derivation and application of the model, the resulting large range of "best" estimates (as opposed to upper-bound estimates) for which there are no adequate criteria for selecting any estimate within the range, and the lack of use and "experience" with other chemicals. Other concerns include uncertainties and sensitivities about application of the model. Although this model has many interesting features, and the Agency will continue to encourage its development, the reasons described above and in Appendix A preclude recommendation of its use to select an RsD at this time.

d. LMS Model

Although there are many uncertainties about the mode of action of 2,3,7,8-TCDD, data from bioassays and information on possible indirect mechanisms provide some basis for assuming that this chemical might initiate the carcinogenic response. If 2,3,7,8-TCDD is both an initiator and a promoter of carcinogenesis, or if it functions in some other way as a complete carcinogen, a model that is linear at low doses would be appropriate for estimating an upper bound on the carcinogenic potency. If the chemical acts by a combination of direct and indirect mechanisms, some with the characteristic of low-dose linearity, the composite dose-response might be expected to exhibit low-dose linearity as well, but perhaps with a lower slope than previously estimated.

The EPA has elected to use the LMS model for cancer risk assessments, in general, because it has a plausible biological basis, incorporates the assumptions of nonthreshold linearity at low doses, provides a plausible upper bound to the risk, and can be used as a "yardstick" to compare the "potency" of one chemical with another. The EPA guidelines for the assessment of risk from

carcinogens point out that other models can, and should, be used if biological considerations dictate. In the case of 2,3,7,8-TCDD, some other models have been proposed (Longstreth and Hushon, 1983), but the biological basis that would justify their use is not any stronger than with the LMS model. Consequently, the Workgroup has concluded that the use of these alternative models provides no additional advantages to the risk assessment of 2,3,7,8-TCDD.

In summary, the Workgroup concludes that none of the available models adequately describe the carcinogenic behavior of 2,3,7,8-TCDD at low doses. Specifically:

- While there is evidence that 2,3,7,8-TCDD acts as a promoter, there is little evidence on which to conclude that a threshold exists. Without a more scientific basis for such a radical departure from EPA's traditional approach to the risk assessment for carcinogens, the Workgroup is unwilling to adopt a threshold approach for 2,3,7,8-TCDD.
- The innovative approaches of Sielken and Moolgavkar, Venson, and Knudson are interesting, but untested. Therefore, the Workgroup concludes that it would be imprudent to use them at this time for 2,3,7,8-TCDD.
- The available evidence suggests that reliance on the LMS model, as traditionally used by EPA, may be less appropriate for 2,3,7,8-TCDD than for many other chemicals, and that the Agency's 1985 assessment based on the LMS model may overestimate the upper bound on the risk by some unknown amount. However, a rationale for a possible linear behavior at low doses has been developed in this report, and the LMS model provides a useful and familiar context which is widely used in the Federal government when discussing risk estimates. Therefore, the Workgroup discusses its recommendation using the LMS model as a construct, that is, the plausible upper-bound estimate of risk and the risk-specific dose.

2. Selection of the RsD Range

a. Base Analysis

Application of the LMS model to estimate the carcinogenic potency of 2,3,7,8-TCDD results in a range of RsDs (10^{-6}) from 0.001 pg/kg/day to 1.2 pg/kg/day depending on the data used as the basis for the analysis and the

assumptions made in the assessment. This range would be even greater if the RfDs established in Canada, Europe, and some states in the United States were included. Moreover, it is not clear where in the range potency estimates, based on composite direct and indirect mechanisms, would fall. In fact, it is possible that such estimates may fall outside of the LMS model range described previously. The discussion in the subsequent sections attempts to narrow this wide range and provide a bound to the RsD selected.

b. Modification of Base Analysis

(1) Incorporation of Alternative Inferences

Incorporation of the factors used by the FDA for scaling from animals to humans, along with use of only the tumors of the lung, hard palate, and nasal turbinates observed in the Kociba et al. (1978) study results in an RsD (10^{-6}) of 1.2 pg/kg/day, the highest RsD we have developed based on the LMS model. This analysis excludes the tumors observed in the liver because of the strong promoter activity shown by 2,3,7,8-TCDD in this organ. However, the Workgroup gives less weight to this point on the range because (1) it excludes 90% of the response observed in the bioassay, and (2) there is controversy whether the tumors of the lung, hard palate, and nasal turbinates should be considered at all (Kociba, 1984), since they may be a localized carcinogenic response to inhaled microscopic food particles containing 2,3,7,8-TCDD. This suggestion gains support from the fact that these tumors were not observed in experiments using other routes of exposure, i.e., dermal, gavage, and intraperitoneal, while liver tumors were common to all four routes. The Workgroup concludes that there is not, as yet, sufficient evidence to accept or reject this hypothesis.

(2) Incorporation of Relative Half-Lives

The lowest RsD in the range is based on differences in the relative half-lives of 2,3,7,8-TCDD in rats and humans. The Workgroup gives less weight to this point because of numerous uncertainties about the pharmacokinetics of 2,3,7,8-TCDD, particularly the absence of information on species differences and rates of incorporation and absorption of 2,3,7,8-TCDD in different tissues and species. Similarly, the rate of release of this chemical is likely to be different from tissue to tissue and species to species. Furthermore, it is not clear how 2,3,7,8-TCDD will behave in different species, particularly humans, under conditions of chronic exposure, incorporation, and release.

(3) Alternative Dose-Response Curves

The suggestion by Hoel (1987) that AHH induction may be useful for defining the shape of the dose-response curve is interesting, but it is not clear how the results of such a calculation would be incorporated into a final risk assessment. Initially, use of AHH data to define the curve is appealing because many data points are available, AHH induction is closely related to many of the toxic effects observed in 2,3,7,8-TCDD, and AHH induction appears to be linear at low doses. However, there is no demonstrated correlation between AHH induction and tumorigenicity, and it is not apparent that the shape of the AHH dose-response curve reflects the shape of the dose-response curve for 2,3,7,8-TCDD's carcinogenic effects at low doses.

(4) Multiple Mechanisms

Qualitatively, the concept of multiple mechanisms acting in concert, or even opposition, is given added weight because it allows inclusion of much of the body of scientific data on 2,3,7,8-TCDD other than the standard bioassay data. As discussed previously, it is not unreasonable to assume that a

composite dose-response curve may, under certain conditions, exhibit linearity at low doses. However, quantitative application of this approach is limited because we do not have information on the slopes of the component curves that would be necessary to define the overall slope of the linear portion of the curve. In general, if such multiple mechanisms could be incorporated into the LMS methodology, the slope of the line would be lower (extent not quantifiable) rather than higher than that derived as a plausible upper bound for direct-acting, complete carcinogens.

(5) Different Base Assumptions

Using the same basic LMS model approach, EPA, CDC, and FDA have estimated carcinogenic RsDs (10^{-6}) for 2,3,7,8-TCDD of 0.006, 0.03, and 0.06 pg/kg/day, respectively. Several different policy-based assumptions account for the differences. For example, EPA scales from animals to humans on the basis of relative body surface area, while FDA uses relative body weights. In addition, both EPA and FDA used the 2,3,7,8-TCDD concentration in rat food as a surrogate for dose, while CDC used the concentration of the chemical in rat liver as a measure of dose. There is no obvious scientific basis for excluding any of these values from the range.

(6) Choice of RsD

As noted previously, a majority of the Workgroup has concluded that the 1985 EPA estimate of the upper-bound potency (RsD) generated from the application of the UCL LMS model to the Kociba et al. (1978) data is likely to have led to an overestimate of risk (or underestimate of the risk-specific dose). The weight of evidence indicates that a more appropriate upper-bound estimate would be obtained by a reduction of the potency by some unquantifiable amount. Therefore, in recommending a new RsD and indirectly suggesting a

change in potency, the Workgroup was confronted with the question, "How great a reduction in slope (or increase in RsD) is appropriate?"

The Workgroup concluded that there is currently no definitive scientific basis for an answer to that question. Given, however, that the question must be answered for Agency purposes, the answer should be grounded in rational, prudent science policy.

While some argument could be mounted that a threshold for the carcinogenicity of 2,3,7,8-TCDD may in fact exist, the evidence for such a contention is not compelling. Therefore, prudence dictates against adopting a simple threshold approach to setting an RsD. Hence, the Workgroup recommends against adopting a policy position similar to that of the European countries at this time.

The Workgroup encourages the type of analysis generated by Sielken and the application of the newer M-K-V model to 2,3,7,8-TCDD. These fresh looks at the problem stimulate discussion and challenge old ways of thinking. However, as noted previously, neither of these approaches is sufficiently developed nor has received sufficient standing in the critical scientific community that the Workgroup feels comfortable in recommending a potency (RsD) on this basis at this time.

The Workgroup is not convinced that the UCL LMS model is an appropriate model for estimating upper-bound cancer risks associated with exposure to 2,3,7,8-TCDD. However, without a better alternative the Workgroup has used the UCL LMS model as a construct within which to discuss the carcinogenic potency or RsD of 2,3,7,8-TCDD. The scientific evidence is consistent with, and would support, a recommended science policy position that the RsD (10^{-6}) for 2,3,7,8-TCDD be 0.1 pg/kg/day, which is associated with a q_1^* , in the UCL LMS

construct of 1×10^4 /mg/kg/day, for the following reasons:

- the scientific data indicate that the Agency's current upper bound for 2,3,7,8-TCDD may be an overestimate;
- the scientific data do not permit an estimate of the extent of the overestimate;
- all of the UCL LMS RsD estimates generated by the Federal agencies are arguably of equal scientific merit at this time;
- for strictly policy purposes, there is great benefit in Federal agencies' adopting consistent positions in the absence of compelling scientific information; and
- an order of magnitude estimate of the RsD (potency), as opposed to some more precise estimate of the risk-specific dose, helps to convey the notion that the numerical expression is only a rough estimate (the science permits no greater accuracy).

The available scientific data can give us no clearer guidance. Some of the research now underway holds the promise of clarifying the issue but not resolving it totally. While a series of considerations, based on science, may be brought to bear on the selection of the RsD, the Workgroup does not advance them as compelling scientific support for a recommended RsD (10^{-6}), which is, in this case, simply a rational and prudent science policy position. The Workgroup further recommends that the 2,3,7,8-TCDD risk-specific dose issue be examined again regularly as new information becomes available. It is felt that the rate of research on this chemical is so great and the fundamental questions relating to multistage carcinogenicity and risk are so important to Agency decision-makers that a regular re-evaluation of the science and/or science policy underlying the selection of an RsD is appropriate.

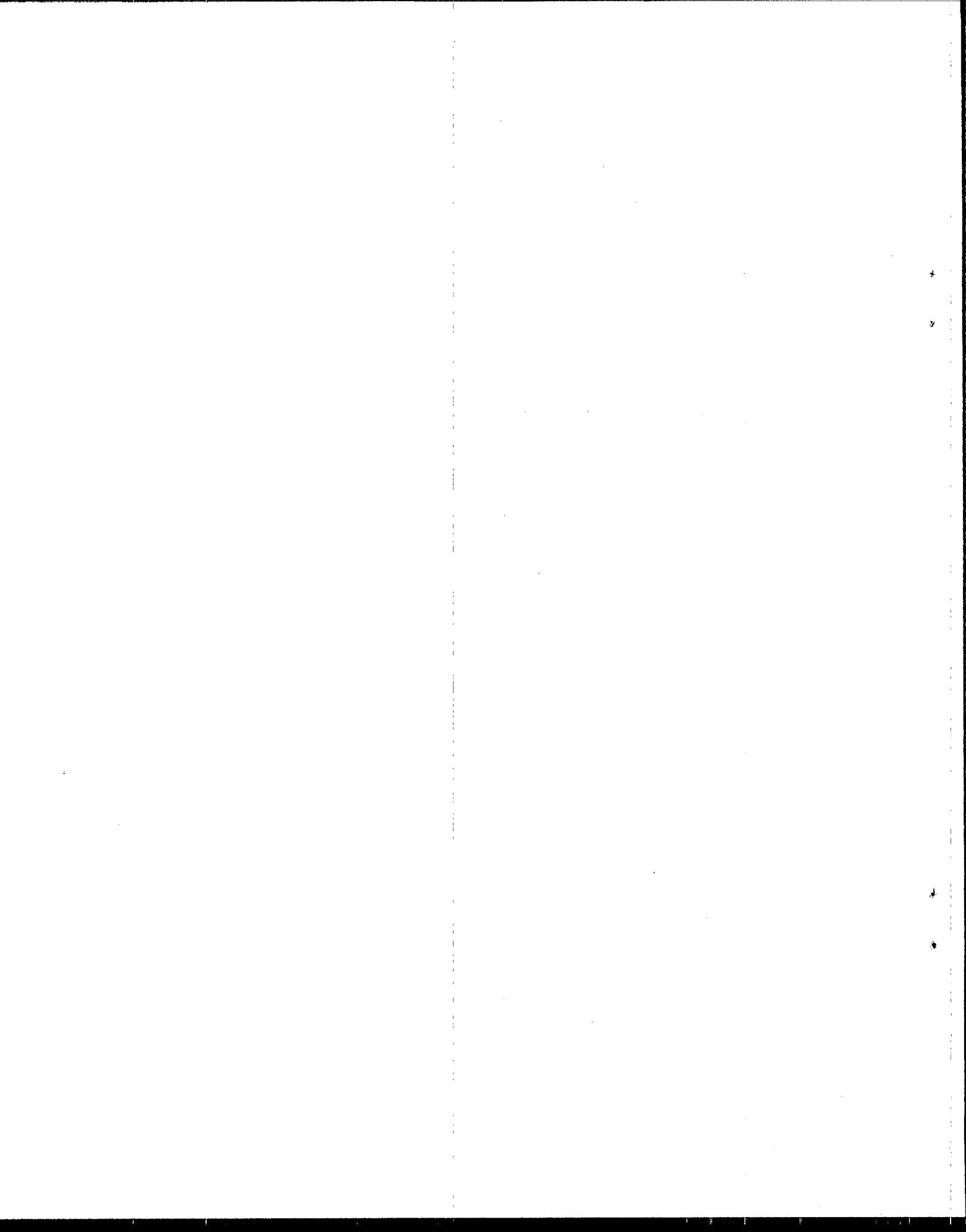
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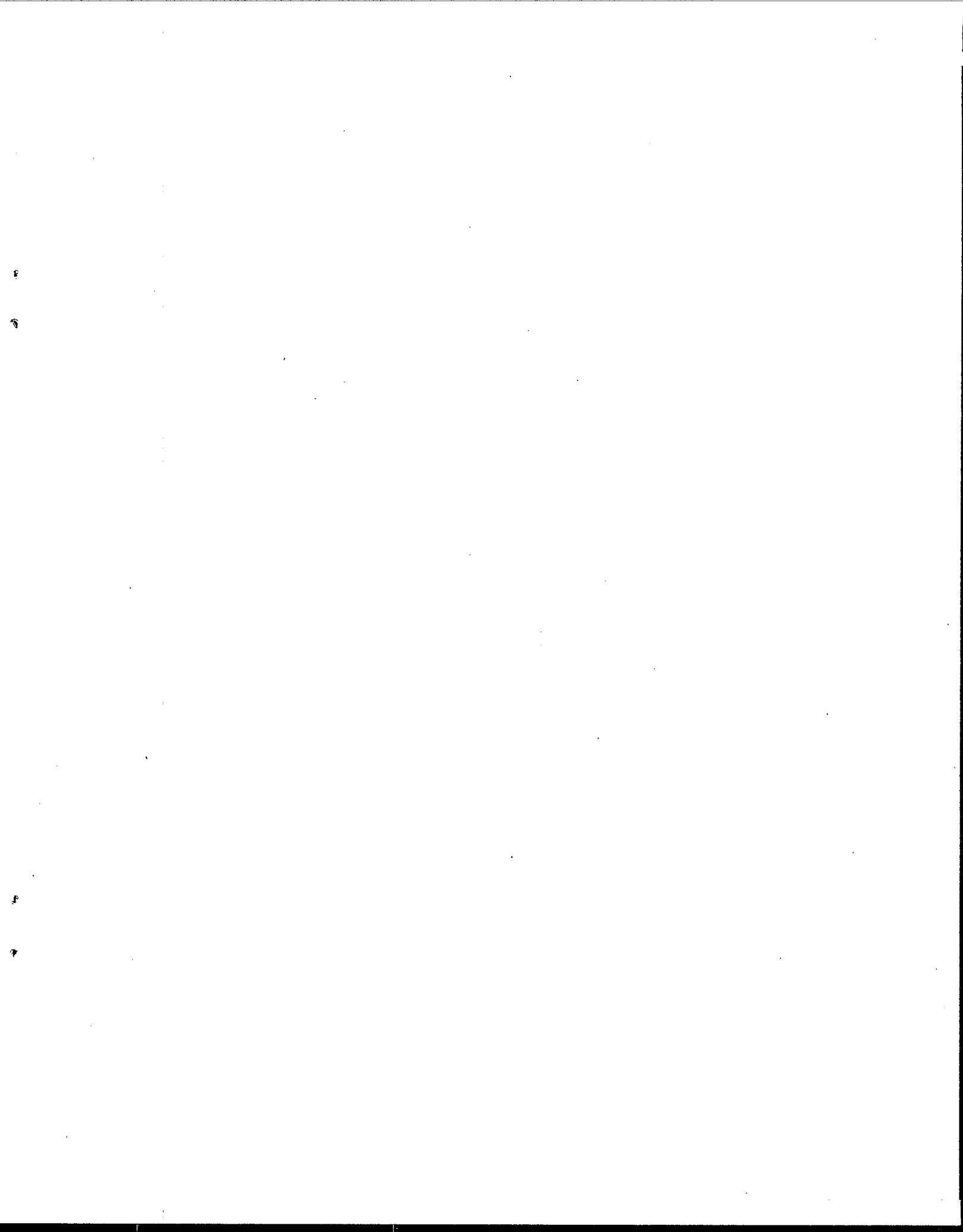
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