OFFICE OF THE
SCIENCE ADVISOR
GUIDANCE

CHAPTER 9

A TOXICITY EQUIVALENCY FACTOR
PROCEDURE FOR ESTIMATING
2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN
EQUIVALENTS IN MIXTURES OF
POLYCHLORINATED
DIBENZO-P-DIOXINS
AND POLYCHLORINATED
DIBENZOFURANS
ABSTRACT

Hazardous waste sites and facilities in California frequently contain mixtures of polychlorinated dibenzo-p-dioxins (PCDDs) and/or polychlorinated dibenzofurans (PCDFs). There are 210 possible isomers of PCDDs and PCDFs, but only several have received extensive toxicological testing. The most potent isomer is 2,3,7,8 tetrachloro dibenzo-p-dioxin (TCDD). With several exceptions, the toxicity and potency of the remaining structural isomers remains unknown.

Three approaches have been developed in an attempt to fill this data void: The first, DHS-TEF, developed by the California Department of Health Services (DHS 1986b), the second, EPA-TEF/87, developed by the U.S. Environmental Protection Agency (U.S. EPA 1987), and the last, NATO/CCMS I-TEF/88 developed, by an international scientific committee convened under the auspices of the North Atlantic Treaty Organization (NATO/CCMS 1988a, b). The first and last approaches assumed that only isomers in which the 2,3,7,and 8 positions were occupied with chlorines are of toxicologic concern. Various portions of the toxicity database were used by each approach to calculate a Toxicity Equivalency Factor (TEF) for each isomer of concern. The TEF permits conversion of PCDD and PCDF concentrations into a toxicologically equivalent concentration of 2,3,7,8-TCDD.

Unfortunately, each approach utilized different portions of the toxicity database. Consequently, TEF values can differ substantially between the three approaches. The NATO/CCMS I-TEF/88 approach provided the most extensive use of the database compared to its two predecessors, DHS-TEF and EPA-TEF/87. Subsequently, U.S. EPA abandoned the EPA-TEF/87 approach and endorsed the I-TEF method of NATO/CCMS for use within the Agency.

The Department of Toxic Substance Control (DTSC) will use the I-TEF method developed by NATO/CCMS and endorsed by U.S. EPA in assessing the risks of PCDDs and PCDFs. Guidance and rationale for use of the I-TEF method is provided in this guidance document. Use of the I-TEF method will minimize regulatory differences between DTSC and U.S. EPA, as well as standardize procedures within DTSC.

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# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>SECTION</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABSTRACT</td>
<td>................................................................. i</td>
</tr>
<tr>
<td>TABLE OF CONTENTS</td>
<td>............................................................................................................ ii</td>
</tr>
<tr>
<td>LIST OF FIGURES</td>
<td>........................................................................................................ iv</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>........................................................................................................ iv</td>
</tr>
<tr>
<td>LIST OF APPENDIXES</td>
<td>...................................................................................................... iv</td>
</tr>
<tr>
<td>ABBREVIATIONS AND ACRONYMS</td>
<td>........................................................................................................ v</td>
</tr>
<tr>
<td>1 INTRODUCTION</td>
<td>........................................................................................................ 1</td>
</tr>
<tr>
<td>1.1 PURPOSE</td>
<td>.......................................................................................................... 1</td>
</tr>
<tr>
<td>1.2 APPLICATION</td>
<td>.................................................................................................. 1</td>
</tr>
<tr>
<td>1.3 LIMITATIONS</td>
<td>.................................................................................................. 1</td>
</tr>
<tr>
<td>2 BACKGROUND</td>
<td>............................................................................................................ 2</td>
</tr>
<tr>
<td>3 TOXICITY OF PCDDs AND PCDFs</td>
<td>............................................................................. 3</td>
</tr>
<tr>
<td>3.1 2,3,7,8-TCDD</td>
<td>.......................................................... 3</td>
</tr>
<tr>
<td>3.1.1 Animal Carcinogenicity</td>
<td>.......................................................... 3</td>
</tr>
<tr>
<td>3.1.2 Developmental and Reproductive Toxicity</td>
<td>......................................... 4</td>
</tr>
<tr>
<td>3.1.3 Human Chronic Toxicity</td>
<td>.......................................................... 5</td>
</tr>
<tr>
<td>3.1.4 Other PCDDs and PCDFs</td>
<td>........................................................................... 5</td>
</tr>
<tr>
<td>3.2 Dose-Response - Cancer Endpoints</td>
<td>.......................................................... 5</td>
</tr>
<tr>
<td>3.3 Dose Response - Developmental and Reproductive Toxicity</td>
<td>........................................... 6</td>
</tr>
<tr>
<td>3.4 Data Gaps</td>
<td>........................................................................................................... 6</td>
</tr>
<tr>
<td>4 ESTIMATING TOXICITY OF TO A MIXTURE OF PCDDs AND PCDFs</td>
<td>................................................. 7</td>
</tr>
<tr>
<td>4.1 THE TOXICITY EQUIVALENCY FACTOR (TEF APPROACH)</td>
<td>........................................... 7</td>
</tr>
<tr>
<td>4.1.1 California Department of Health Services</td>
<td>.......................................................... 7</td>
</tr>
<tr>
<td>TEF (DHS-TEF)</td>
<td>............................................................................................................... 7</td>
</tr>
<tr>
<td>4.1.2 U.S. Environmental Protection Agency</td>
<td>.......................................................... 8</td>
</tr>
<tr>
<td>TEF (TEF/87)</td>
<td>............................................................................................................... 8</td>
</tr>
<tr>
<td>4.1.3 TEFs Developed by North Atlantic Treaty</td>
<td></td>
</tr>
</tbody>
</table>
### SECTION | PAGE
--- | ---
1.1 TECHNICAL GUIDANCE FOR USE OF I-TEFs | 9
1.1.1 Selection of an Interim TEF Method for Use | 9
1.1.2 Use of TEFs | 10

2 ESTIMATING HEALTH RISKS ASSOCIATED WITH EXPOSURE TO A MIXTURE OF PCDDs AND PCDFs | 11
2.1 CANCER RISK | 11
2.2 NON-CANCER RISK | 11
2.3 ADMINISTERED VS ABSORBED DOSE | 12
2.4 EXAMPLES OF RISK CALCULATION USING TEFs | 12
2.5 SUMMARY OF RISKS | 13

REFERENCES | 14
LIST OF FIGURES

F1  Chemical Structures of PCDDs and PCDFs ................................................................. 18

LIST OF TABLES

T1  PCDD and PCDF Isomers - Number of Chlorines per Substitution Type ............... 19
T2  Interim Toxicity Equivalency Factors ...................................................................... 20
T3  Interim Toxicity Equivalency Factors (I-TEFs/89) ................................................ 21
T4  Calculation of 2,3,7,8-TCDD Toxicity Equivalents from PCDDs/PCDFs
    in an Environmental Soil Sample ........................................................................... 22

LIST OF APPENDICES

A1  Cancer Risk from Ingestion of Contaminated Soil ............................................... 23
A2  Cancer Risk from Skin/Contact with Contaminated Soil ...................................... 25
A3  Cancer Risk from Inhalation of Contaminated Soil ............................................... 28
ABBREVIATIONS AND ACRONYMS

CAG - Carcinogen Assessment Group at U.S. Environmental Protection Agency
DHS - California Department of Health Services
IRIS - Integrated Risk Information System: U.S. Environmental Protection Agency's on line computer database for hazardous chemicals
NATO/CCMS - North Atlantic Treaty Organization, Committee on the Challenges of Modern Society
NTP - National Toxicology Program
PCDD - polychlorinated dibenzo-p-dioxin
PCDF - polychlorinated dibenzofuran
RfD - Reference dose: an exposure level which is not likely to cause significant non-cancer adverse health effects.
TCDD - 2,3,7,8-tetrachlorodibenzo-p-dioxin
TEF - Toxicity Equivalency Factor
TRAS - Toxicology and Risk Assessment Section, Technical Services Branch, California Department of Toxic Substances Control
TSCP - Toxic Substances Control Program, California Department of Health Services
U.S. EPA - U.S. Environmental Protection Agency
kg - kilogram
g - gram, one thousandth of a kilogram, 1x10^{-3} kg
mg - milligram, one-millionth of a kilogram, 1x10^{-6} kg
ug - microgram, one-billionth of a kilogram, 1x10^{-9} kg
ng - nanogram, one-trillionth of a kilogram, 1x10^{-12} kg
pg - picogram, one-quadrillionth of a kilogram, 1x10^{-15} kg
ppm - parts per million
ppb - parts per billion
ppt - parts per trillion
A TOXICITY EQUIVALENCY FACTOR PROCEDURE FOR ESTIMATING  2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN EQUIVALENTS IN MIXTURES OF POLYCHLORINATED DIBENZO-P-DIOXINS AND POLYCHLORINATED DIBENZOFURANS

2 INTRODUCTION

2.1 PURPOSE

This guidance is intended to document Department of Toxic Substances Control (DTSC) implementation of the I-TEF/89 method endorsed by the U.S. EPA. Other documents should be consulted for background information and detailed guidance for the development and use of Toxicity Equivalency Factors (TEFs) (DHS, 1986b; U.S. EPA, 1987, 1988a, 1989a; NATO/CCMS, 1988a, b).

2.2 APPLICATION

Use of the I-TEF/89 procedure as described in this document and as illustrated with examples in Table 4 and Appendices 1 through 3 ensures that consistent estimates of 2,3,7,8-TCDD equivalents can be calculated for a mixture of PCDDs and PCDFs. Estimates of the concentration of 2,3,7,8-TCDD equivalents in soil, air and water can be derived using the I-TEF procedure for all state-lead sites, but issuance of this guidance does not affect exposure or risk assessments in progress or completed before the date of this publication.

2.3 LIMITATIONS

More toxicological and/or mechanistic research is necessary in order to provide an accurate assessment of risks posed by PCDDs and PCDFs. Thus, DTSC anticipates that the I-TEF/89 approach is an interim procedure, and the method will be updated periodically to reflect both gains in scientific knowledge and consistency with U.S. EPA procedures.

3 BACKGROUND
2,3,7,8-tetrachlorodibenzo-p-dioxin, commonly called "TCDD" or "dioxin," is the most potent animal carcinogen, reproductive and developmental toxin tested to date.

TCDD belongs to a family of organic chemicals which consist of two benzene rings connected to one another by two oxygens, as shown in Figure 1. Positions 1-4 and 6-9 on either of the benzene rings can be substituted with up to eight chlorines per molecule, to yield eight sub-classes with a total of 75 possible isomeric forms of the basic dioxin molecule. Chlorine substitutions at these positions can yield 2-mono, 10-di, 14-tri, 22-tetra, 14-penta, 10-hexa, 2-hepta, and 1-octa-chlorodibenzo-p-dioxin isomers (Table 1). Any of these are commonly referred to as "polychlorinated dibenzo-p-dioxins" (PCDDs).

A closely-related family of compounds, the polychlorinated dibenzofurans (PCDFs), consists of two benzene rings adjoined by a central furan ring, as shown in Figure 1. Substitution of chlorines at the 1-4 and/or 6-9 positions can yield up to a total of 135 possible isomers, including 4-mono, 16-di, 28-tri, 38-tetra, 28-penta, 16-hexa, 4-hepta, and 1-octadibenzofuran (Table 1). Any of these are commonly referred to as PCDF. None of the PCDFs have been tested for carcinogenic potential.

Initially, 2,3,7,8-TCDD was the only isomer of toxicologic concern, due to its presence as a manufacturing byproduct in the herbicide 2,4,5-trichlorophenoxyacetic acid. Additional concern was raised following two separate incidents: (1) Times Beach, Missouri, in 1971, when horses and dogs died as a result of application of TCDD-contaminated waste oil as a dust suppressant on dirt roads and in a horse arena, and (2) an industrial accident in Seveso, Italy, in 1976, in which a reaction vessel in a herbicide plant exploded and released an estimated 1.7 kg of TCDD over a town of 220,000 inhabitants.

Since then, PCDDs as well as PCDFs have been found to originate from other sources, such as: (1) technical grade pentachlorophenol used by numerous wood preservative treatment facilities; (2) fly ash from municipal garbage incinerators; and (3) other combustion sources. In many cases, the amount of other PCDDs and PCDFs released into the environment greatly exceed that of 2,3,7,8-TCDD. As a consequence, these compounds are ubiquitous in the environment, and are routinely detected as "background" contaminants in human adipose tissue. With the exception of 2,3,7,8-TCDD and a mixture of 1,2,3,6,7,8 and 1,2,3,7,8,9-hexachloro dibenzo-p-dioxins, the carcinogenic potential of PCDDs and PCDFs is largely unknown.

Various scientific groups have attempted to relate the toxic potency of PCDDs and PCDFs to that of 2,3,7,8-TCDD by use of information in the toxicity database for this class of compounds. The most recent effort is the "I-TEF/89" method developed by U.S. EPA in conjunction with scientists from other industrialized countries under the auspices of the North...
Atlantic Treaty Organization's Committee on Challenges in Modern Society (NATO/CCMS). The I-TEF/89 method provides TEFs which can be used to calculate the concentrations of PCDDs and PCDFs in terms of an equipotent concentration of 2,3,7,8-TcDD.

4 TOXICITY OF PCDDs AND PCDFs

The Cal/EPA cancer potency factor (q₁) for 2,3,7,8-TcDD is 1.3 x 10⁵ (mg/kg/day)⁻¹ based on animal studies in which TCDD was administered via the oral route. The Reference Dose (RfD) for TCDD for noncancer effects is 1.0 x 10⁻⁹ mg/kg/day based on studies in which TCDD was administered to animals by the oral route (U.S. EPA 1985a).

4.1 2,3,7,8-TCDD

The PCDD isomer having four chlorines, one each in the 2,3,7, and 8 position, is 2,3,7,8-tetrachloro dibenzo-p-dioxin, commonly referred to as "TCDD." 2,3,7,8-TCDD is the most potent animal carcinogen, reproductive/developmental toxin and teratogen known. The toxicity of 2,3,7,8-TCDD has been extensively studied, and the results are summarized in numerous criteria documents and journal reviews (Fishbein et al., 1987; Kimbrough et al., 1984; NATO/CCMS, 1988a, b; U.S. EPA, 1984, 1984a, 1985a, 1985b, 1989a).

4.1.1 Animal Carcinogenicity

2,3,7,8-TCDD was carcinogenic in male and female rats and mice (Kociba et al., 1978; NTP, 1980). Both studies were independently reviewed by the DTSC, Toxicology and Risk Assessment Section (TRAS) (DHS-TSCP, 1991). 2,3,7,8-TCDD was also carcinogenic in male hamsters (Rao et al., 1988).

• Kociba et al. Study

Malignant tumors occurred in Sprague-Dawley rats receiving 2,3,7,8-TCDD in the feed at dose levels equivalent to 0.1, 0.01, 0.001, or 0 ug/kg body weight/day for two years. Four sites were involved:

1. Squamous cell carcinoma of the hard palate/nasal turbinates in both males and females;
2. Squamous cell carcinoma of the tongue in males;
3. Squamous cell carcinoma of the lung in females; and
• National Toxicology Program (NTP) Study

Malignant tumors occurred in both Osborne-Mendel rats and B6C3F1 mice receiving 2,3,7,8-TCDD twice weekly by gavage in a corn oil:acetone vehicle (9:1). In rats and male mice, weekly dose levels were 0.5, 0.05, 0.01, or 0 ug/kg body weight/week, whereas weekly dose levels in female mice were 2.0, 0.2, 0.04, or 0 ug/kg body weight/week.

In rats, the prevalence of thyroid follicular cell adenomas was significantly increased in males, with a non-significant trend for increase noted in females. In females, the prevalence of neoplastic nodules of the liver was significantly increased. No similar changes were observed in males.

In mice, the prevalence of thyroid follicular cell adenomas in females was significantly increased, with no similar findings in males. Both males and females showed a significant increase in the prevalence of hepatocellular carcinomas.

• Rao et al. Study

Malignant tumors occurred in male Syrian golden hamsters after intraperitoneal or subcutaneous injection with 2 or 6 doses, one dose every 4 weeks, of 50 or 100 ug/kg body weight of 2,3,7,8-TCDD. Twenty one percent of the animals receiving 6 doses of 100 ug/kg bodyweight developed a very rare tumor, squamous cell carcinoma of the facial skin, within 12-13 months of the beginning of the experiment. None of the controls or low dose animals had tumors. The induction of these very rare tumors by 2,3,7,8-TCDD in hamsters, the animal most resistant to 2,3,7,8-TCDD toxicity, argues for 2,3,7,8-TCDD having complete carcinogen activity, and not being solely a promoter.

• Discussion

2,3,7,8-TCDD produced malignant tumors at a total of five different sites in the first two studies (Kociba et al., 1978, and NTP, 1980). Identical target organs were found in both rats and mice in the second study as well as in male and female rats of the first study. Particularly striking was the increased prevalence in both rats and mice, of thyroid follicular cell tumors.
which historically have a relatively low spontaneous rate for this tumor type.

The EPA classifies 2,3,7,8-TCDD as a probable human carcinogen (classification B2) and considers 2,3,7,8-TCDD to be the most potent chemical carcinogen and reproductive toxin yet evaluated by the EPA (U.S. EPA, 1989). There is adequate evidence from animal experiments that 2,3,7,8-TCDD functions as a complete carcinogen, not just as a promoter of carcinogenicity, (Rao et al., 1988; Bayard, 1989; Holder and Menzel, 1989). Support for the B2 classification includes observations that extremely low doses of 2,3,7,8-TCDD induce tumors, some of which are malignant, in multiple species of experimental animals, at multiple tumor sites, and that the spectrum of tumors induced by 2,3,7,8-TCDD in animals includes rare types of tumors.

4.1.2 Animal Developmental and Reproductive Toxicity

2,3,7,8-TCDD is the most potent reproductive toxin known, causing decreases in fertility, litter size, gestation survival, postnatal survival and postnatal body weight in rats administered relatively low levels of 2,3,7,8-TCDD in a three generation study (Murray et al., 1979). 2,3,7,8-TCDD is the most potent teratogenic and fetotoxic agent tested to date; these data have been reviewed in detail by U.S. EPA scientists in the EPA Health Assessment Document (U.S. EPA, 1985a), as well as in the dioxin Applied Action Level document (DHS-TSCP, 1990d and 1991).

4.1.3 Human Chronic Toxicity

Currently, there is no evidence that PCDDs pose a significant health risk to humans via environmental exposure. Numerous cases of human exposure including industrial accidents, use of dioxin-contaminated herbicides, and illegal disposal, have not clearly documented cancer or adverse reproductive effects in humans (Bond et al., 1989; Bertazzi et al., 1988; Hoffman et al., 1988; Mastroiacovo et al., 1988; Ott et al., 1987; Stehr-Green et al., 1988; Stockbauer et al., 1988; Webb et al., 1987).

The carcinogenic potency of 2,3,7,8-TCDD in animals, when compared on a molar basis, is greater than 50,000,000 times the potency for vinyl chloride, and 50 times the potency of aflatoxin B₁. Both of these are known human carcinogens (U.S. EPA, 1988d). Therefore, it is prudent to consider PCDDs
and PCDFs as probable human carcinogens in the absence of definitive mechanistic or human epidemiological data to prove otherwise.

### 4.1.4 Other PCDDs AND PCDFs

The only other 2,3,7,8-substituted PCDD tested for carcinogenicity to date was a 1:2 mixture of 1,2,3,6,7,8- and 1,2,3,7,8,9-hexachlorodibenzo-p-dioxin, termed "HeCDD" (NTP, 1980). This mixture was carcinogenic in male and female rats and mice, producing malignant and benign liver cell cancer (IRIS, 1990).

In rats, there was a dose-related increase in hepatocellular neoplastic nodules and carcinomas in both sexes, with the increase achieving statistical significance in females. In mice also, there was a dose-related increase in hepatocellular adenomas and carcinomas, which reached significance in males. No other tumor types were noted in the IRIS database.
4.2 DOSE-RESPONSE - CANCER ENDPOINTS

- **2,3,7,8-TCDD**

  The Carcinogen Assessment Group of U.S. EPA (CAG) used data of Kociba et al (1978) to calculate a "cancer potency factor" for 2,3,7,8-TCDD via low-dose extrapolation using the GLOBAL79 version of the linearized multistage model. Detailed discussions of the data sets utilized, the rationale for use, and values obtained are located in Section 11 and Appendix B of the Health Assessment Document for 2,3,7,8-TCDD (U.S. EPA, 1985a). The oral potency factor obtained was $1.5 \times 10^5$ kg-day/mg.

- **Hexachlorodibenzo-p-Dioxin (HeCDD): Mixture of 1,2,3,6,7,8- and 1,2,3,7,8,9 Isomers, 1:2**

  A mixture of two 2,3,7,8-substituted isomers of HeCDD was carcinogenic in rats and mice (NTP, 1980). As noted above, CAG used these results to calculate a cancer potency factor of $6.2 \times 10^2$ kg-day/mg from these data (U.S. EPA 1990).

4.3 DOSE RESPONSE - DEVELOPMENTAL AND REPRODUCTIVE TOXICITY

2,3,7,8-TCDD is the most teratogenic agent tested to date. Numerous reviews are available for guidance (Fishbein, 1987; Silbergeld, 1987; U.S. EPA, 1984 and 1985a).

The Reference Dose (RfD) for developmental toxicity can be calculated from the lowest observed adverse effect level of 0.001 ug/kg/day in rats (Murray et al., 1979) in conjunction with a thousand-fold uncertainty factor. Based on these figures, the oral RfD is $1 \times 10^{-9}$ mg/kg/day (U.S. EPA, 1985a).

4.4 DATA GAPS

It is unlikely due to problems of time and expense that the extensive research conducted on 2,3,7,8-TCDD will be conducted on the remaining 209 PCDD and PCDF isomers. Therefore, much scientific research effort into the dioxin problem is focused upon mechanistic studies, but even these studies will take considerable time. Other relevant research would include testing the biological/toxicological response to complex environmental mixtures of PCDDs and PCDFs (U.S. EPA, 1989a).
The void of toxicity information for most of the 210 possible isomeric forms of PCDDs and PCDFs limits assessment of risk. The available database indicates that only those isomers having one chlorine each in the 2,3,7, and 8 positions are of toxicologic significance relative to 2,3,7,8-TCDD. This assumption enabled reduction of the number of isomers of concern from 210 to less than 20.

By default, the other isomers could be considered equipotent to 2,3,7,8-TCDD for risk assessment. However, potency data for non-cancer endpoints, such as acute, subchronic, reproductive, developmental, and immunotoxicity, as well as receptor binding or mechanistic data, suggest that the other 2,3,7,8-substituted isomers are moderately-to-substantially less potent than 2,3,7,8-TCDD. With 2,3,7,8-TCDD, however, cancer was the most sensitive endpoint of toxicity. Whether the carcinogenic potency of the other isomers is equal to or less than that of 2,3,7,8-TCDD remains unknown, except for HeCDD as discussed above.

5 USE OF THE TOXICITY EQUIVALENCY FACTOR (TEF) APPROACH FOR ESTIMATING TOXICITY OF A MIXTURE OF PCDDs AND PCDFs

The Department recommends use of the TEF approach to calculate 2,3,7,8-TCDD toxic equivalents. As several estimates of toxic equivalents exist, their origins and use is documented below:

5.1 THE TOXICITY EQUIVALENCY FACTOR (TEF) APPROACH

The TEF represents a ratio of the toxicity of a 2,3,7,8-substituted PCDD or PCDF isomer to that of 2,3,7,8-TCDD. With use of TEFs, the concentration of PCDD or PCDF isomers may be converted to equipotent concentrations of 2,3,7,8-TCDD. For example, the potency of a PCDF having a TEF of 0.05 and present in soil at a concentration of 100 ppm, would be equivalent of that of 2,3,7,8-TCDD at a concentration of 5 ppm.

5.1.1 California Department of Health Services TEF (DHS-TEF)

In the absence of a toxicity database, the California Air Resources Board requested in 1986 that the Department of Health Services (DHS) develop a method for assessment of cancer risks from PCDDs and PCDFs formed by combustion (DHS, 1986b). The data set used for development of DHS-TEFs consisted solely of the laboratory rodent bioassays with 2,3,7,8-TCDD and the hexachlorodibenzo-p-dioxin mixture. None of the remaining database for
PCDDs and PCDFs, such as acute, developmental, reproductive, immune system toxicity, or in vitro, mechanistic, or receptor binding studies, was considered for TEF development.

The DHS-TEF method (Table 2) assumed that:

- 2,3,7,8-substituted tetra-CDF, penta-CDDs, and penta-CDFs were equipotent to 2,3,7,8-TCDD,
- 2,3,7,8-substituted hexa- and hepta-CDDs and CDFs had 3% of the potency of 2,3,7,8-TCDD, and
- Octa-CDD, octa-CDF, and non-2,3,7,8-substituted CDDs and CDFs have zero potency relative to 2,3,7,8-TCDD.

The DHS-TEF approach was based on little data and is not recommended.

5.1.2 U.S. Environmental Protection Agency TEF (TEF/87)

Subsequently, the EPA adopted a TEF approach that differed significantly from that of DHS (U.S. EPA, 1987). The EPA approach (Table 2) utilized, in addition to the rodent bioassay data, data from acute, subchronic, developmental, immunotoxicity, reproductive, and in vitro toxicity studies as well as mechanistic investigations of PCDDs and PCDFs. Much of the data utilized in establishing the above TEFs (EPA, 1987) is believed to have little or no relevance to classical mechanisms of cancer induction. However, there is also considerable controversy as to the exact mechanism of cancer induction by 2,3,7,8-TCDD. 2,3,7,8-TCDD acts as a promoter of carcinogenicity and also as a complete carcinogen. Therefore, there may be some merit in considering toxicity other than cancer data in establishing TEFs for PCDDs and PCDFs. Also, it is often necessary to use TEFs not only to assess cancer risks but also to determine risks for other toxicities (such as developmental or reproductive toxicity) in humans exposed environmentally to mixtures of PCDDs and PCDFs.

Although the biochemical mechanisms leading to the toxic response resulting from exposure to PCDDs and PCDFs are not known in detail, there is considerable information now available, as summarized by EPA (U.S. EPA, 1989)... "experimental data have accumulated which suggest that an important role in the development of systemic toxicity resulting from exposure to (PCDDs and PCDFs) is played by an intracellular protein, the Ah receptor, the putative product of a gene locus designated Ah. This receptor binds halogenated polycyclic aromatic molecules, including PCDDs and PCDFs. It has been
postulated that the Ah locus controls several pleiotropic responses: a limited, but widely expressed gene complex that includes the structural genes for aryl hydrocarbon hydroxylase expression, and, in a few organs, such as skin and thymus, a second gene complex regulating cell proliferation and differentiation...(Although) A recent review concludes that there are inconsistencies across species in the Ah receptor being the sole mechanism of toxicity of (PCDDs and PCDFs), the data suggest that the binding of these compounds to the receptor is in some way related to some of the biological effects seen in experimental animals."

5.1.3 TEFs Developed by North Atlantic Treaty Organization/Committee on the Challenges of Modern Society (NATO/CCMS)

In 1989, a NATO Committee on the Challenges of Modern Society (NATO/CCMS) refined, extended and modified the EPA TEF/87 approach (NATO/CCMS, 1988). It should be noted that the NATO/CCMS dioxin committee was composed of scientists from participating countries, including Canada, Federal Republic of Germany, Italy, The Netherlands, Great Britain, and the United States. The U.S. EPA was instrumental in bringing this group together, and in obtaining an international consensus on the TEF approach. Like the EPA approach, the International TEFs (ITEF/88) developed by the NATO/CCMS committee (NATO/CCMS, 1988) utilized, in addition to the laboratory animal carcinogenicity data, data from acute, subchronic, developmental, immunotoxicity, reproductive, and \textit{in vitro} toxicity studies as well as mechanistic investigations of PCDDs and PCDFs.

5.1.4 U.S. Environmental Protection Agency TEF (I-TEF/89)

In April 1989, the EPA determined that it would revise the EPA-TEFs/87, and adopted as agency interim policy the NATO/CCMS ITEF/88 method. The EPA I-TEF/89 represents the TEFs derived from the entire database (Table 3).

5.2 TECHNICAL GUIDANCE FOR USE OF TEFs

Use the I-TEF/89 procedure to calculate 2,3,7,8-TCDD Toxicity Equivalents as an estimate of exposure to mixtures of PCDDs and PCDFs. The I-TEF/89 values are shown in Table 3, and the use of the TEF procedure for estimating the exposure to mixtures of PCDDs and PCDFs is illustrated with an example in Table 4.

5.2.1 Selection of an Interim TEF Method for Use
Three factors were considered in recommending adoption of the I-TEF/89 values to replace the DHS-TEF approach:

- The DHS-TEF method was a major attempt to define the carcinogenic potency of PCDDs and PCDFs in the absence of data. However, acute, developmental, reproductive, in vitro, immunotoxicity, and mechanistic data were not utilized in derivation of TEF values in the DHS-TEF approach. As a result, the DHS-TEF method has received considerable criticism.

- More of the database was utilized in derivation of TEFs in the EPA TEF/87 approach. The NATO/CCMS method refined and expanded on EPA TEF/87 procedure. U.S. EPA adopted the I-TEF/88 method and endorsed it for Agency use. The I-TEF/89 approach represents the "state of the science," with TEFs derived from the entire database.

- Use of the I-TEF/89 procedure by DTSC would minimize conflicting risk assessments not only between DTSC and U.S. EPA, but also within DTSC itself.

5.2.2 Use of I-TEFs

The I-TEF/89 values from U.S. EPA are given in Table 3. These TEF values shall be used for calculation of PCDD and PCDF potency relative to that of 2,3,7,8-TCDD. The concentration of PCDD or PCDF is multiplied by the TEF to convert the PCDD or PCDF level to an equipotent concentration of 2,3,7,8-TCDD. The product is often referred to as a "TCDD equivalent."

6 USE OF I-TEFs FOR ESTIMATING HEALTH RISKS ASSOCIATED WITH EXPOSURE TO A MIXTURE OF PCDDs AND PCDFs

To estimate health risks associated with exposure to a mixture of PCDDs and PCDFs, use the concentration determined by the TEF procedure, and the Cancer Potency Factor and the RfD for 2,3,7,8-TCDD. The use of the TEF procedure for estimating the health risks associated with exposure to mixtures of PCDDs and PCDFs is illustrated with examples in Appendices 1-6.

6.1 CANCER RISK
The cancer potency factor listed by U.S. EPA for 2,3,7,8-TCDD (U.S. EPA, 1990) will be used to assess cancer risk posed by PCDDs and PCDFs. Such cancer risks are calculated by multiplying the average daily intake (in mg/kg/day) of 2,3,7,8-TCDD toxicity equivalents in the media by the cancer potency factor.

The oral cancer potency factor derived by U.S. EPA is $1.5 \times 10^5$ kg-day/mg as listed on page B-18 of the Health Effects Assessment Summary Tables (U.S. EPA, 1991). No information was available in the IRIS database for 2,3,7,8-TCDD, presumably due to re-evaluation by U.S. EPA of the scientific basis and methods used in derivation of this cancer potency factor.

The cancer potency factor used for the risk assessment must be current. If an inhalation or dermal cancer potency factor is not available, it is appropriate to use the oral cancer potency factor, adjusted, if necessary, for incomplete absorption as described in Section 7.2.2.3 below. Guidance for this effort can be obtained from the TRAS.

6.2 NON-CANCER RISK

In estimating non-cancer hazards posed by a mixture of PCDDs and PCDFs, it is appropriate to use the Reference Dose (RfD) for 2,3,7,8-TCDD (1 pg/kg-day) derived by the U.S. EPA (1985a, 1989a). This RfD is currently based on reproductive/developmental toxicity. It is important to ensure that the RfD employed is current at the time of writing of the risk assessment, since this value may be updated by either TRAS or U.S. EPA.

In estimating non-cancer hazards posed by inhalation of or dermal contact with an environmental medium containing a mixture of PCDDs and PCDFs, it is appropriate to adjust for absorption differences as discussed in Section 5.3 below. Guidance for this effort can be obtained from the TRAS.

6.3 ADMINISTERED vs ABSORBED DOSE

The current U.S. EPA oral cancer potency factor and the RfD tentatively proposed by TRAS for 2,3,7,8-TCDD are based upon administered dose and not absorbed dose. In the pivotal animal studies, 2,3,7,8-TCDD was administered in the feed.

Therefore, prior to correcting for incomplete absorption from an environmental medium of concern, it is necessary to adjust the current EPA 2,3,7,8-TCDD cancer potency factor or TRAS RfD by factoring in the ratio of absorbed dose to administered dose.
from the laboratory animal studies from which the cancer potency factor or the RfD were derived. Guidance for this effort can be obtained from the examples provided in Appendices 1-3.

6.4 EXAMPLES OF RISK CALCULATION USING TEFs

Appendices 1-3 provide detailed examples for the calculation of cancer risk according to three exposure scenarios:

- Ingestion of contaminated soil from such activities as mouthing behavior in children, hand-to-mouth activities such as smoking, and poor hygienic practices such as not washing hands before either preparing or eating food;

- Dermal absorption, that is, absorption of contaminants from soil adhering to skin, through the skin and into the body;

- Inhalation of wind-blown soil ("fugitive dust") with absorption of contaminants through the respiratory tract.

6.5 SUMMARY OF RISKS

Total Risk may be calculated by summation of individual risk from each exposure pathway, as shown in the examples in Appendices 1-6:

- **Total Cancer Risk**
  
  Risk from Oral Ingestion (Appendix 1) = $1.8 \times 10^{-7}$
  Risk from Dermal Absorption (Appendix 2) = $6.0 \times 10^{-8}$
  Risk from Soil Inhalation (Appendix 3) = $8.9 \times 10^{-9}$
  
  Total = $2.5 \times 10^{-7}$

REFERENCES


U.S. EPA. 1990. Integrated Risk Information System (IRIS). File for 2,3,7,8-TCDD.


FIGURE 1

CHEMICAL STRUCTURES
POLYCHLORINATED DIBENZO-p-DIOXINS
POLYCHLORINATED DIBENZOFURANS

Polychlorinated dibenzo-p-dioxins (PCDDs)

Polychlorinated dibenzofurans (PCDFs)
Taken from page 4 of NATO/CCMS, 1988b.
**TABLE 1**

**PCDD AND PCDF ISOMERS\(^a\)**  
**NUMBER OF CHLORINES PER SUBSTITUTION TYPE\(^b\)**

<table>
<thead>
<tr>
<th>SUBSTITUTION TYPE</th>
<th>1-Cl</th>
<th>2-Cl</th>
<th>3-Cl</th>
<th>4-Cl</th>
<th>5-Cl</th>
<th>6-Cl</th>
<th>7-Cl</th>
<th>8-Cl</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PCDDs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One chlorine each in 2,3,7,8 positions</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Others</td>
<td>2</td>
<td>10</td>
<td>14</td>
<td>21</td>
<td>13</td>
<td>7</td>
<td>1</td>
<td>0</td>
<td>68</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>75</td>
</tr>
<tr>
<td><strong>PCDFs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One chlorine each in 2,3,7,8 positions</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Others</td>
<td>4</td>
<td>16</td>
<td>28</td>
<td>37</td>
<td>26</td>
<td>12</td>
<td>2</td>
<td>0</td>
<td>125</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>135</td>
</tr>
</tbody>
</table>

Total possible PCDDs and PCDFs = 210

Total non-2,3,7,8-CDDs and -CDFs = 193

Total 2,3,7,8-CDDs and -CDFs = 17

---

\(^a\)PCDD = polychlorinated dibenzo-p-dioxin  
PCDF = polychlorinated dibenzofuran

\(^b\)From page 4 of USEPA, 1988b
## TABLE 2

### COMPARISON OF TOXICITY EQUIVALENCY FACTORS

Toxicity Equivalency Factor Scheme

<table>
<thead>
<tr>
<th>COMPOUND</th>
<th>DHS-TEF</th>
<th>EPA-TEF/87</th>
<th>I-TEF/89</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mono-, Di-, and Tri-CDDs</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>TCDD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2,3,7,8 chlorines)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>(others)</td>
<td>0</td>
<td>0.01</td>
<td>0</td>
</tr>
<tr>
<td><strong>PeCDD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2,3,7,8 chlorines)</td>
<td>1.0</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>(others)</td>
<td>0</td>
<td>0.005</td>
<td>0</td>
</tr>
<tr>
<td><strong>HxCDD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2,3,7,8 chlorines)</td>
<td>0.03</td>
<td>0.04</td>
<td>0.1</td>
</tr>
<tr>
<td>(others)</td>
<td>0</td>
<td>0.0004</td>
<td>0</td>
</tr>
<tr>
<td><strong>HpCDD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2,3,7,8 chlorines)</td>
<td>0.03</td>
<td>0.001</td>
<td>0.01</td>
</tr>
<tr>
<td>(others)</td>
<td>0</td>
<td>0.00001</td>
<td>0</td>
</tr>
<tr>
<td><strong>OCDD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
<td>0.001</td>
</tr>
<tr>
<td>Mono-, Di-, and Tri-CDFs</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>TCDF</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2,3,7,8 chlorines)</td>
<td>1.0</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>(others)</td>
<td>0</td>
<td>0.001</td>
<td>0</td>
</tr>
<tr>
<td><strong>PeCDF</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1,2,3,4,7,8 chlorines)</td>
<td>1.0</td>
<td>0.1</td>
<td>0.05</td>
</tr>
<tr>
<td>(2,3,4,7,8 chlorines)</td>
<td>1.0</td>
<td>0.1</td>
<td>0.5</td>
</tr>
<tr>
<td>(others)</td>
<td>0</td>
<td>0.001</td>
<td>0</td>
</tr>
<tr>
<td><strong>HxCDF</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2,3,7,8 chlorines)</td>
<td>0.03</td>
<td>0.01</td>
<td>0.1</td>
</tr>
<tr>
<td>(others)</td>
<td>0</td>
<td>0.0001</td>
<td>0</td>
</tr>
<tr>
<td><strong>HpCDF</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2,3,7,8 chlorines)</td>
<td>0.03</td>
<td>0.001</td>
<td>0.01</td>
</tr>
<tr>
<td>(others)</td>
<td>0</td>
<td>0.00001</td>
<td>0</td>
</tr>
<tr>
<td><strong>OCDF</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Key: CDD = chlorinated dibenzo-p-dioxin; CDF = chlorinated dibenzofuran; TCDD = tetraCDD; PeCDD = pentaCDD; HxCDD = hexaCDD; HpCDD = heptaCDD; OCDD = octaCDD; TCDF = tetraCDF; PeCDF = pentaCDF; HxCDF = hexaCDF; HpCDF = heptaCDF; OCDF = octaCDF.
### TABLE 3

**1989 EPA INTERIM TOXICITY EQUIVALENCY FACTORS (I-TEFs/89)**

<table>
<thead>
<tr>
<th>CONGENER</th>
<th>TEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>POLYCHLORINATED DIBENZO-p-DIOXINS</td>
<td></td>
</tr>
<tr>
<td>Tetra-CDD (chlorines in the 2,3,7,8 positions)</td>
<td>1.0</td>
</tr>
<tr>
<td>Tetra-CDD (chlorines not in 2,3,7,8 positions)</td>
<td>0</td>
</tr>
<tr>
<td>Penta-CDD (chlorines in the 2,3,7,8 positions)</td>
<td>0.5</td>
</tr>
<tr>
<td>Penta-CDD (chlorines not in 2,3,7,8 positions)</td>
<td>0</td>
</tr>
<tr>
<td>Hexa-CDD (chlorines in the 2,3,7,8 positions)</td>
<td>0.1</td>
</tr>
<tr>
<td>Hexa-CDD (chlorines not in 2,3,7,8 positions)</td>
<td>0</td>
</tr>
<tr>
<td>Hepta-CDD (chlorines in the 2,3,7,8 positions)</td>
<td>0.01</td>
</tr>
<tr>
<td>Hepta-CDD (chlorines not in 2,3,7,8 positions)</td>
<td>0</td>
</tr>
<tr>
<td>Octa-CDD</td>
<td>0.001</td>
</tr>
</tbody>
</table>

| POLYCHLORINATED DIBENZOFURANS | |
| Tetra-CDF (chlorines in the 2,3,7,8 positions) | 0.1 |
| Tetra-CDF (chlorines not in 2,3,7,8 positions) | 0 |
| Penta-CDF (chlorines in the 2,3,4,7,8 positions) | 0.5 |
| Penta-CDF (chlorines in the 1,2,3,7,8 positions) | 0.05 |
| Penta-CDF (chlorines not in 2,3,7,8 positions) | 0 |
| Hexa-CDF (chlorines in the 2,3,7,8 positions) | 0.1 |
| Hexa-CDF (chlorines not in 2,3,7,8 positions) | 0 |
| Hepta-CDF (chlorines in the 2,3,7,8 positions) | 0.01 |
| Hepta-CDF (chlorines not in 2,3,7,8 positions) | 0 |
| Octa-CDF | 0.001 |
Four chlorines must be in the 2,3,7,8-positions for toxicity.
### TABLE 4

**CALCULATION OF 2,3,7,8-TCDD TOXICITY EQUIVALENTS FROM PCDDs/PCDFs IN AN ENVIRONMENTAL SOIL SAMPLE\(^a\)**

<table>
<thead>
<tr>
<th>Soil Sample</th>
<th>2,3,7,8-TCDD</th>
<th>2,3,7,8-TCDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congener</td>
<td>Toxic. PCDD/F</td>
<td>Toxic. Equiv.</td>
</tr>
<tr>
<td></td>
<td>Concen. (pg/kg)</td>
<td>(I-TEFs/89) (pg/kg)</td>
</tr>
<tr>
<td>TCDDs</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>PeCDDs</td>
<td>0.5</td>
<td>100</td>
</tr>
<tr>
<td>HxCDDs</td>
<td>0.1</td>
<td>160</td>
</tr>
<tr>
<td>HpCDDs</td>
<td>0.01</td>
<td>19</td>
</tr>
<tr>
<td>OCDD</td>
<td>0.001</td>
<td>25</td>
</tr>
<tr>
<td>TOTAL PCDDs</td>
<td>28,800</td>
<td>404</td>
</tr>
<tr>
<td>TCDFs</td>
<td>0.1</td>
<td>40</td>
</tr>
<tr>
<td>PeCDFs</td>
<td>0.05</td>
<td>20</td>
</tr>
<tr>
<td>1,2,3,7,8-</td>
<td>0.5</td>
<td>200</td>
</tr>
<tr>
<td>2,3,4,7,8-</td>
<td>0.1</td>
<td>280</td>
</tr>
<tr>
<td>HxCDFs</td>
<td>0.1</td>
<td>16</td>
</tr>
<tr>
<td>HpCDFs</td>
<td>0.01</td>
<td>40</td>
</tr>
<tr>
<td>OCDF</td>
<td>0.001</td>
<td>40</td>
</tr>
<tr>
<td>TOTAL PCDFs</td>
<td>45,600</td>
<td>596</td>
</tr>
</tbody>
</table>

\(^a\) Only those congeners that are chlorinated in the 2,3,7,8 positions are listed in the table.
APPENDIX 1

CANCER RISK FROM INGESTION OF CONTAMINATED SOIL

1. GASTROINTESTINAL ABSORPTION OF 2,3,7,8-TCDD

Scientists at U.S. EPA, TRAS, and contractors for TRAS-TSCP reviewed a number of studies in animals examining the gastrointestinal absorption of 2,3,7,8-TCDD from ingestion of contaminated soil, ingestion of 2,3,7,8-TCDD in the feed, and gastric intubation of 2,3,7,8-TCDD dissolved in organic materials such as corn oil. Results of these studies are critiqued elsewhere (pp. 120-126 of U.S. EPA, 1988a; Section 7 of U.S. EPA 1985a; Review No. 1, pp. 7-11, and Reviews No. 6-10 of TRAS, 1990d).

The data indicated that gastrointestinal absorption of 2,3,7,8-TCDD administered by intubation in corn oil was about 80%. Bioavailability of 2,3,7,8-TCDD administered in soil was 25% to 50% of that of 2,3,7,8-TCDD administered in corn oil, based on comparison of toxicologic endpoints used for derivation of TEFs by NATO/CCMS. Therefore, the reviewing scientists concluded that the amount of 2,3,7,8-TCDD absorbed from soil represented 20% to 40% of the dose of 2,3,7,8-TCDD ingested.

2. CORRECTION FOR ABSORPTION OF 2,3,7,8-TCDD BETWEEN DIFFERENT MEDIA

A bioavailability factor is calculated as the ratio of the bioavailability of 2,3,7,8-TCDD in the media of concern for each exposure route, divided by the bioavailability of 2,3,7,8-TCDD by the route used in the animal study from which the cancer potency factor was derived. The cancer potency factor for 2,3,7,8-TCDD was based on tumor prevalence in rats receiving 2,3,7,8-TCDD mixed into the feed. Gastrointestinal absorption of 2,3,7,8-TCDD from the feed was estimated to be 50% to 60% (Fries and Marrow, 1975); 50% will be used here. In comparison, the absorption of 2,3,7,8-TCDD ingested in soil was estimated to be 40%. Absorption differences such as these may need to be corrected for in calculation of soil ingestion risk.

Correction can be achieved by dividing the percentage of 2,3,7,8-TCDD absorbed from soil by that absorbed from the feed, to yield a "gastrointestinal absorption factor" (GAF):

\[
GAF = \frac{\text{Percent absorbed from soil}}{\text{Percent absorbed from feed}} = \frac{40\%}{50\%} = 0.8
\]
3. DAILY SOIL CONSUMPTION

For the purposes of this exercise only, daily soil consumption will be assumed to be 100 mg/day. Guidance for use of this or other values can be found elsewhere (Sedman, 1989; Calabrese et al., 1989; TRAS, 1990c; U.S. EPA, 1989a).

4. CANCER RISKS

Cancer hazards are assumed to have no threshold dose below which there is no risk. Much controversy surrounds this concern regarding certain animal carcinogens, including dioxins (U.S. EPA, 1988c and 1988d). For this example, however, no threshold will be assumed. The cancer potency factor in this exercise is used to estimate the risk of ANY exposure level, no matter how small. Specific guidance for nonthreshold effects as well as development and use of cancer potency ("slope") factors is given in Section 7.3 of the Human Health Evaluation Manual (U.S. EPA, 1989b), the Technical Standard for low-dose extrapolation (DHS-TSCP, 1990b), as well as numerous references provided by each of these documents.

In general, cancer risk may be estimated as follows:

\[ \text{Risk} = \frac{\text{Exposure} \times \text{Cancer Potency Factor} \times \text{Bioavailability Factor}}{\text{Average Lifetime Body Weight}} \]

5. GENERAL ASSUMPTIONS FOR RISK CALCULATION

Lifetime exposure = 70 years
Average lifetime body weight = 70 kg
Cancer potency factor for 2,3,7,8-TCDD = 1.56x10^5 kg·day/mg (U.S. EPA, 1990)
Exposure = Soil ingestion x TCDD equivalents
Bioavailability factor = GAF

6. CALCULATION OF ESTIMATED RISK

\[ \text{Risk} = \frac{\text{Soil Ingestion} \times \text{TCDD Eq.} \times \text{Cancer Potency Factor} \times \text{GAF}}{\text{Body Weight}} \]

When:
Soil Consumption = 100 mg soil/day
TCDD Equivalents, from the example in Table 4, 1,000 pg TCDD Eq. per kg soil = $1 \times 10^{-6}$ mg/kg = $1 \times 10^{-12}$ mg/mg soil Cancer Potency Factor = $1.56 \times 10^5$ kg-day/mg GAF = 0.8 Body Weight = 70 kg

Therefore:

\[
\text{Risk} = \frac{100 \text{ mg/day} \times 1 \times 10^{-12} \text{ mg/mg} \times 1.56 \times 10^5 \text{ kg-day/mg} \times 0.8}{70 \text{ kg}}
\]

Risk = $1.8 \times 10^{-7}$
APPENDIX 2

CANCER RISK FROM SKIN CONTACT WITH CONTAMINATED SOIL

1. DERMAL ABSORPTION OF 2,3,7,8-TCDD

Scientists at U.S. EPA, TRAS, and contractors for TRAS-TSCP reviewed a number of studies in animals examining the gastrointestinal absorption of 2,3,7,8-TCDD from ingestion of contaminated soil, ingestion of 2,3,7,8-TCDD in the feed, gastric intubation of 2,3,7,8-TCDD dissolved in organic materials such as corn oil, and dermal absorption. Results of these studies are critiqued elsewhere (pp. 120-126 of U.S. EPA, 1988; Section 7 of U.S. EPA 1985a; Review No. 1, pp. 7-11, and Reviews No. 6-10 of DHS-TSCP, 1990d).

The data indicated that dermal absorption of PCDDs from skin contact with soil is 0.9% in adults and 1.8% in children. The range of values cited was 0.07% to 3% of the administered dose. These results were derived by comparing various endpoints obtained after treatment by oral intubation vs skin contact with contaminated soil.

2. CORRECTION FOR ABSORPTION OF 2,3,7,8-TCDD BETWEEN DIFFERENT MEDIA

In general, a bioavailability factor is calculated as the ratio of the bioavailability of 2,3,7,8-TCDD in the media of concern for each exposure route, divided by the bioavailability of 2,3,7,8-TCDD in the vehicle used in the animal study from which the cancer potency factor was derived. The cancer potency factor for 2,3,7,8-TCDD was based on tumor prevalence in rats receiving 2,3,7,8-TCDD mixed into the feed. Gastrointestinal absorption of 2,3,7,8-TCDD from the feed was estimated to be 50% to 60% (Fries and Marrow, 1975); 50% will be used here. In comparison, the dermal absorption of soil-borne 2,3,7,8-TCDD in contact with skin was estimated to be 0.9% in adults and 1.8% in children, with values ranging from 0.07% to 3%.

Absorption differences such as these need to be corrected for in calculation of risk from dermal absorption of soil-borne chemicals. Correction can be achieved by dividing the maximal percentage of soil-borne 2,3,7,8-TCDD absorbed through the skin by that absorbed from the feed, to yield a "dermal absorption factor" (DAF):

\[
\text{Percent absorbed from soil} = 3% \\
\text{DAF} = \frac{\text{Percent absorbed from soil}}{\text{Percent absorbed from feed}} = \frac{3}{50} = 0.06
\]

DAF = 0.06
3. AMOUNT OF DAILY SKIN CONTACT WITH SOIL

For the purposes of this exercise only, the amount of soil coming in contact with, or adhering to, skin is assumed to be 450 mg/day. Specific guidance for use of this figure, or derivation of different values based on other age, activity, and time-weighted exposure scenarios, can be found elsewhere (Sedman, 1989; U.S. EPA, 1989b; DHS-TSCP, 1990c).

4. CANCER RISKS

Cancer hazards are assumed to have no threshold dose below which there is no risk. Much controversy surrounds this concern regarding certain animal carcinogens, including dioxins (U.S. EPA, 1988c and 1988d). For this example, however, no threshold will be assumed. The cancer potency factor in this exercise is used to estimate the risk of ANY exposure level, no matter how small. Specific guidance for nonthreshold effects as well as development and use of cancer potency ("slope") factors is given Section 7.3 of the Human Health Evaluation Manual (U.S. EPA, 1989b), the Technical Standard for low-dose extrapolation (DHS-TSCP, 1990b), as well as numerous references provided by each of these documents.

In general, cancer risk may be estimated as follows:

\[
\text{Risk} = \frac{\text{Exposure} \times \text{Cancer Potency Factor} \times \text{Bioavailability Factor}}{\text{Average Lifetime Body Weight}}
\]

5. GENERAL ASSUMPTIONS

- Lifetime exposure = 70 years
- Average lifetime body weight = 70 kg
- Cancer potency factor for 2,3,7,8-TCDD = 1.56x10^5 kg-day/mg
  (U.S. EPA, 1990)
- Exposure = daily skin/soil contact x TCDD equivalents
- Bioavailability factor = DAF

6. CALCULATION OF ESTIMATED RISK

\[
\text{Risk} = \frac{\text{Skin Soil Contact} \times \text{TCDD Eq.} \times \text{Cancer Potency Factor} \times \text{DAF}}{\text{Body Weight}}
\]

When:
- Skin/Soil Contact = 450 mg soil/day
- TCDD Equivalents, from the example in Table 4, 1,000 pg TCDD
Eq. per kg soil = \(1 \times 10^{-6}\) mg/kg = \(1 \times 10^{-12}\) mg/mg soil
Cancer Potency Factor = \(1.56 \times 10^5\) kg-day/mg
DAF = 0.06
Body Weight = 70 kg

Therefore:
\[
\text{Risk} = \frac{450 \text{ mg/day} \times 1 \times 10^{-12} \text{ mg/mg} \times 1.56 \times 10^5 \text{ kg-day/mg} \times 0.06}{70 \text{ kg}}
\]
\[
= 0.60 \times 10^{-7}
\]
\[
= 6.0 \times 10^{-8}
\]
APPENDIX 3

CANCER RISK FROM INHALATION OF CONTAMINATED SOIL

1. INHALATION ABSORPTION OF 2,3,7,8-TCDD

In the absence of data, absorption of TCDD is assumed to be 100% of the dose inhaled.

2. CORRECTION FOR ABSORPTION OF 2,3,7,8-TCDD BETWEEN DIFFERENT MEDIA.

In general, a bioavailability factor is calculated as the ratio of the bioavailability of 2,3,7,8-TCDD in the media of concern for each exposure route, divided by the bioavailability of 2,3,7,8-TCDD in the vehicle used in the animal study from which the cancer potency factor was derived. The cancer potency factor for 2,3,7,8-TCDD was based on tumor prevalence in rats receiving 2,3,7,8-TCDD mixed into the feed. Gastrointestinal absorption of 2,3,7,8-TCDD from the feed was estimated to be 50% to 60% (Fries and Marrow, 1975); 50% will be used here. In comparison, the absorption of 2,3,7,8-TCDD via inhalation of contaminated soil is assumed to be 100%.

These absorption differences must be corrected for in calculation of risk from inhalation of soil contaminated with PCDDs. Correction is achieved by dividing the percent absorbed by inhalation by that absorbed from feed, to yield an "inhalation absorption factor (IAF):"

\[
\text{IAF} = \frac{\text{Percent of inhaled dose absorbed}}{\text{Percent absorbed from feed}} = \frac{100\%}{50\%} = 2.00
\]

3. AMOUNT OF DUST INHALED PER DAY

For the purposes of this exercise only, the dust concentration in air is assumed to be 100 \(\text{ug/m}^3\), and the respiration rate is assumed to be 20 \(\text{m}^3/\text{day}\). Therefore, the quantity of dust inhaled per day is:

\[
100 \text{ug/m}^3 \times 20 \text{m}^3/\text{day} = 2,000 \text{ug/day} = 2 \times 10^{-3} \text{mg/day}
\]

Specific guidance for derivation of different values based on other age, activity, and time-weighted exposure scenarios, can be found elsewhere (U.S. EPA, 1989a; DHS-TSCP, 1990a).
4. CANCER RISKS

Cancer hazards are assumed to have no threshold dose below which there is no risk. Much controversy surrounds this concern regarding certain animal carcinogens, including dioxins (U.S. EPA, 1988c and 1988d). For this example, however, no threshold will be assumed. The cancer potency factor in this exercise is used to estimate the risk of ANY exposure level, no matter how small. Specific guidance for nonthreshold effects as well as development and use of cancer potency ("slope") factors is given Section 7.3 of the Human Health Evaluation Manual (U.S. EPA, 1989b), the Technical Standard for low-dose extrapolation (DHS-TSCP, 1990b), as well as numerous references provided by each of these documents.

In general, cancer risk may be estimated as follows:

\[
\text{Risk} = \frac{\text{Exposure} \times \text{Cancer Potency Factor} \times \text{Bioavailability Factor}}{\text{Average Lifetime Body Weight}}
\]

5. GENERAL ASSUMPTIONS

Lifetime exposure = 70 years
Average lifetime body weight = 70 kg
Cancer potency factor for 2,3,7,8-TCDD = \(1.56 \times 10^5\) kg-day/mg
(U.S. EPA, 1990)
Exposure = Soil inhalation x TCDD equivalents
Bioavailability Factor = IAF

6. RISK FROM INHALATION OF SOIL CONTAINING PCDDs

\[
\text{Risk} = \frac{\text{Soil Inhalation} \times \text{TCDD Eq.} \times \text{Cancer Potency Factor} \times \text{IAF}}{\text{Body Weight}}
\]

When:
Soil Inhalation = \(2.0 \times 10^{-3}\) mg/day
TCDD Equivalents, from the example in Table 4, 1,000 pg TCDD
Eq. per kg soil = \(1 \times 10^{-6}\) mg/kg = \(1 \times 10^{-12}\) mg/mg soil
Cancer Potency Factor = \(1.56 \times 10^5\) kg-day/mg
IAF = 2.00
Body Weight = 70 kg
Therefore:

\[
\text{Risk} = \frac{2,000 \times 10^{-3} \text{ mg/day} \times 1 \times 10^{-12} \text{ mg/mg} \times 1.56 \times 10^{5} \text{ kg-day/mg} \times 2.00}{70 \text{ kg}}
\]

\[
= 0.89 \times 10^{-8}
\]

\[
= 8.9 \times 10^{-9}
\]