MDH Risk Assessment: Guidance for Dioxins
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Guidance for Dioxins

The following guidance was developed by the Minnesota Department of Health (MDH) at the request of the Minnesota Pollution Control Agency (MPCA). For more information, contact the Health Risk Assessment Unit, 651/201-4899. For more information about dioxin health risks, see Development of Inhalation Benchmark for Dioxin-Like Compounds and Facts about Dioxins.

Methods for Estimating the Carcinogenic Health Risks from Dioxin-Like Compounds

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The Minnesota Department of Health (MDH) prepared this guidance in response to a request in 2003 from the Minnesota Pollution Control Agency (MPCA), and to identify a consistent approach for agencies and programs to assess the carcinogenic health risks from exposure to dioxin-like compounds. Guidance for assessing the noncancer health risks is still under development and will not be addressed in this memo. Because of the uncertainties associated with the toxicities of dioxin mixtures, MDH uses a conservative approach to evaluate potential risks. As more data become available, MDH re-evaluates and revises its risk assessment methods and procedures, as appropriate.

Dioxin-like Compounds

The term "dioxins" is used to refer to a family of complex but related chlorinated compounds with similar chemical structures and biological activity. The polychlorinated dibenzo-p-dioxins (PCDDs) include 75 individual compounds, the polychlorinated dibenzofurans (PCDFs) include 135 individual compounds, and the polychlorinated biphenyls (PCBs) include 209 individual compounds. These individual compounds are technically referred to as congeners. Based on their ability to bind to the Ah receptor and evoke a response 7 of the 75 PCDD congeners (i.e., those with chlorine substitutions in the 2,3,7, and 8 positions), 10 of the 135 PCDF congeners (i.e., those with chlorine substitution in the 2,3,7, and 8 positions), and 12 of the 209 PCB congeners (those containing 4 or more chlorines with 1 or no substitutions at the ortho position) are thought to have significant dioxin-like toxicity. The 29 compounds identified as having significant dioxin-like toxicity concerns are identified in Table 1.

Toxic Equivalence Factors (TEFs)

Dioxins interfere with a basic and ubiquitous receptor system (the Ah receptor) that regulates enzymes and other proteins. While it is believed that these 29 compounds have

a similar mechanism of toxicity not all are equally toxic. The most toxic and best-studied dioxin is 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD). The remaining 28 compounds have been assigned toxicity values relative to 2,3,7,8-TCDD. These relative toxicity values are called toxicity equivalence factors (TEFs). 2,3,7,8-TCDD is assigned a TEF of 1 and the remaining compounds are typically assigned values less than 1. The Minnesota Department of Health (MDH) recommends utilization of the World Health Organization's (WHO) 2005 TEF scheme (TEF_{WHO05}) (Van den Berg, et al., 2005) to weight each compound according to its relative toxicity for cancer risk evaluations. The TEF_{WHO05} values are shown in Table 2.

The compound specific TEF describes an order of magnitude consensus estimate derived from scientific judgment based on the examination of available experimental data. TEF estimates are generated from several sources of experimental data. The resulting range of relative potency values derived from the individual experiments for a particular compound are variable. The TEFs were primarily derived from in vivo toxicity data, which were given more weight than the in vitro and/or quantitative structure-activity relationship data. The 2005 World Health Organization Re-evaluation of Human and Mammalian Toxic Equivalency Factors for Dioxins and Dioxin-like Compounds (Van den Berg et al. 2005) should be referred to for additional information on the determination and validation of the $TEFs_{WHO05}$.

The United States Environmental Protection Agency (U.S. EPA) as well as several states, countries and international agencies have adopted the WHO 2005 TEF scheme. Utilization of the WHO 2005 TEF scheme will facilitate the comparison of environmental measurements to national and international databases.

Toxic Equivalent Concentration Calculation (TEQ)

The dioxin-like compounds exist in the environment as mixtures (i.e., a single compound is not found in isolation). Because dioxins differ in their toxic potential or potency, the toxicity of each component of the mixture must be accounted for in estimating the overall toxicity of the mixture. The evaluation of environmental dioxin mixtures consists of three simple steps. The first is a laboratory measurement of the concentration of each individual compound. Then, the measured concentration of each compound is multiplied by its corresponding TEF to produce a TCDD toxicity equivalent (TEQ) concentration. Finally, the TEQ concentrations for each compound are added together with the TEQs for each of the other compounds present to determine the total TCDD TEQ concentration in the sample. The total TCDD TEQ concentration represents the amount of 2,3,7,8-TCDD alone, that it would take to equal the combined toxic effect of the mixture.

The variability in relative potency values for individual compounds mentioned above may not significantly impact an individual risk estimate. According to the U.S. EPA draft reassessment only 5 compounds (2,3,7,8-TCDD, 1,2,3,7,8-PentaCDD, 1,2,3,6,7,8-HexaCDD, 2,3,4,7,8-PentaCDF, and PCB 126) account for 70 to 80 percent of the TCDD TEQ in the human body and food products. The relative potency variability reported in the literature for these 5 compounds is much lower than for other compounds (U.S. EPA 2003).

A number of studies have examined the toxicity of complex mixtures of dioxins and non-dioxin-like compounds in the laboratory. Some of these studies have compared the predicted (TEQ) toxicity of a mixture to the actual measured toxicity of that mixture. Other studies have compared the toxicity of individual compounds to those of the mixture in the same test system. Mixtures tested include both laboratory mixtures of individual compounds and environmental samples.

The TEF/TEQ methodology addresses the toxicity potential of complex mixture in terms of an equivalent mass of 2,3,7,8-TCDD. Although the various congeners of a mixture have relative equivalent toxicity to 2,3,7,8-TCDD, these congeners may not have the same pharmacokinetics and do not necessarily share the same environmental fate as 2,3,7,8-TCDD. The impact of an environmental mixture will likely also be affected by the ability of our bodies to absorb, metabolize and excrete the individual congeners from the environmental media (e.g. soil). For some risk assessments the differences in fate and transport of different congeners must be taken into consideration and TEQs calculated at the point of exposure to achieve more accurate assessments.

Although the use of TEFs and the TEQ approach is widespread, its use is not without controversy. The WHO has suggested that the TEF scheme and the TEQ methodology be re-evaluated every 5 years to account for new scientific information (WHO 1998). The WHO completed their most recent review of the TEFs and TEQ methodology in 2005 (Van den Berg et al., 2005). In this review they reaffirmed the use of TEFs as the best available tool for estimating the health risk of exposures to complex mixtures of dioxin-like chemicals.

Quantitative Cancer Risk Assessment

Cancer Classification:

The MDH, U.S. EPA, National Toxicology Program (NTP) and the International Agency for Cancer Research (IARC) have characterized 2,3,7,8-TCDD as a "human carcinogen". The MDH and the U.S. EPA have classified the complex mixtures of dioxin to which people are exposed as a "likely human carcinogen". The degree of certainty of the cancer hazard is dependent on the major constituents of the mixture. The consistent, suggestive evidence from epidemiology studies combined with the unequivocal evidence in animal studies and inferences drawn from mechanistic data support the characterization of complex mixtures of dioxin and related compounds as "likely" cancer hazards. "Human carcinogen" and "likely" are descriptors which are consistent with the U.S. EPA final cancer guidelines (U.S. EPA 2005). They are roughly equivalent to the terms "known" and "probable" human carcinogen contained in earlier U.S. EPA cancer guidelines (U.S. EPA 1986).

Oral Cancer Slope Factor:

The U.S. EPA's draft dioxin reassessment efforts produced two upper bound slope factors for estimating human cancer risk from exposure to dioxins:

1×10^{-3} (pg TCDD TEQ/ kg body weight/day)$^{-1}$ based on an evaluation of the human epidemiology data and 1.4×10^{-3} (pg TCDD TEQ/kg body weight/day) $^{-1}$ based on a re-evaluation of the animal data (liver cancer in female rats).

The actual shape of the low-dose exposure-response relation for animals or humans cannot be determined from the available data. For this reason U.S. EPA utilized a linear dose extrapolation model to derive an upper bound cancer potency factor. The true risk is unknown but is likely to be lower.

MDH believes that exposure to ("known" or "likely") carcinogens should be minimized where possible; this is especially true for dioxins due to existing body burden estimates. When a numerical cancer slope factor is needed to evaluate incremental risk, MDH recommends utilizing an interim cancer slope factor of 1.4×10^{-3} (pg TCDD TEQ/kg body weight/day) $^{-1}$ (i.e., 1.4×10^{6} per mg TCDD TEQ/kg/day). This value is based on EPA's draft animal-based cancer slope factor. Concerns about the quality of the exposure estimates in the human epidemiological studies preclude the quantitative use of these data in developing a cancer potency slope for dioxin; however, the results from modeling the human studies are consistent with the cancer potency slope derived by modeling data from animal studies.

In 2005 EPA issued supplemental guidance for assessing susceptibility from early-life exposures to carcinogens. The EPA draft cancer potency value for TCDD is based on an average lifetime body burden dose metric. Currently there is no established method for applying the EPA early life sensitivity factors to a potency factor that is based on lifetime body burden rather than an administered dose.

In 2006 the National Research Council (NRC) of the National Academies completed a comprehensive review of the EPA 2003 draft assessment. The NRC report contained conclusions and recommendations on how the EPA 2003 draft reassessment could be improved. EPA is currently revising the 2003 draft reassessment. Issues such as the appropriate dose-metric (e.g., body burden) for cancer and noncancer endpoints, possible modes of action, and life-stage sensitivity will be examined as part of the revision process. MDH staff will read and analyze any revisions EPA makes to the 2003 draft reassessment as well as other relevant scientific data generated since the draft reassessment (e.g., the chronic toxicological study conducted by the National Toxicology Program). MDH will update guidance and recommendations if appropriate. At this time MDH continues to recommend using our current guidance for assessing potential carcinogenic health risks from dioxin-like compounds and does not recommend application of EPA's early-life adjustment of the cancer potency.

The recommended slope factor is derived from the same study, Kociba et al., 1978, as the previous slope factor estimate (1.56E+5 per mg/kg/day). The development of the recommended slope factor utilized current methods of analysis, including the use of body burden as the dose metric for animal-to-human dose equivalence calculations (i.e., adjustments to account for the differences in half-life of dioxins in the bodies of

laboratory animals and humans), and a re-evaluation of the liver tumors in the Kociba study using the latest pathology criteria.

Inhalation Unit Risk Factor:
For bioaccumulative compounds such as the dioxins the primary exposure route of concern for long-term or chronic toxicity is ingestion rather than inhalation. Toxicological data from inhalation studies is not available for the dioxins. As stated in the MDH Statement of Need and Reasonableness (SONAR) for the Health Risk Values (HRVs) chronic ingestion studies are not, as a rule, utilized by the MDH to develop inhalation HRVs. Route-to-route extrapolation may be appropriate when sufficient toxicokinetic information is available and the critical effect would be the same regardless of how the toxicant is administered.

There is adequate evidence, in laboratory animals, that 2,3,7,8-TCDD is a multisite carcinogen capable of increasing the incidence of tumors at sites distant from the site of treatment. The limited epidemiologic evidence from occupationally exposed workers is also consistent with increased cancer risk at multiple sites.

The situations where extrapolation from an oral exposure to an inhalation exposure is inappropriate are also discussed in the SONAR:

"There are, however, situations where this extrapolation technique is inappropriate. For instance, if the critical effect is specific for the respiratory system, or if the toxicity of a chemical is expressed at or near the site of application, data from oral exposure should not be used to extrapolate to an inhalation exposure. Another case where extrapolation would be inappropriate is when the target organ for the critical effect is the liver. The liver, because of its unique structure and circulation, is subjected to much higher concentrations of ingested chemicals than other organs. In addition, the unique biochemistry of the hepatocytes can result in the generation of very different metabolic products of a toxicant in the liver than would be produced in other organs. For these reasons an extrapolation approach will not be used if the liver is the target organ for a toxicant following oral exposure."

The liver is a target organ of dioxin toxicity and the recommended oral slope factor is based on liver tumors. The MDH HRV staff were consulted regarding interpretation of the SONAR and the appropriateness of utilizing route-to-route extrapolation for dioxins. 2,3,7,8-TCDD and dioxin-like compounds undergo limited metabolism and exhibit long half-lives in the body. As a result the liver would not be subjected to significantly higher concentrations or significantly different metabolic products than other organs. Therefore, although the recommended oral slope factor is based on liver tumors, route-to-route extrapolation is acceptable.

In order to extrapolate an inhalation unit risk factor from the oral slope factor an absorption adjustment factor, inhalation rate, and body weight are necessary. These parameter values are influenced by the physical form of dioxins (e.g., particulate or vapor-phase) and the individual or population under evaluation. MDH will not

recommend default adjustment factors, inhalation rates or body weights at this time. For more information regarding MDH's recommendations for assessing inhalation risk for dioxin-like compounds see: Development of An Inhalation Benchmark for Dioxin-Like Compounds. As more data become available, MDH will re-evaluate this position and revise its recommendation as appropriate.

Information contained in the U.S. EPA draft dioxin reassessment may be a useful source of information for the MPCA. Part I, Volume 3, Chapter 4 and Volume 4, Chapter 2 of the U.S. EPA's draft reassessment provide guidance for estimating potential risks from a variety of exposure pathways, including the inhalation pathway.

Utilizing animal data and information on fate of particles in the respiratory system, U.S. EPA estimated that the fraction of 2,3,7,8-TCDD absorbed into the body ranges from 0.25 to 0.29. Although the rate of absorption of vapor-phase 2,3,7,8-TCDD into the lungs has not been studied, the U.S. EPA concluded that it seems reasonable to assume that the absorption in the vapor phase should exceed that of absorption from bound 2,3,7,8-TCDD on particulates, probably above 50%. Given the paucity of data U.S. EPA recommended that assessors not attempt any such adjustments at this point, but fully acknowledged the uncertainty. Absorption correction factors were recommended for use in the soil ingestion and soil dermal contact pathways.

A variety of inhalation rates and body weights were utilized by the U.S. EPA to estimate inhalation exposure. The specific value selected depended on the age of the subpopulation of concern and whether a central tendency or upper tendency estimate was desired.

Table 1. List of Compounds With Varying Dioxin-like Toxicity

Chlorinated Dibenzo-p-dioxins (CDDs)	Chlorinated Dibenzofurans (CDFs)	Polychlorinated Biphenyls (PCBs)
2,3,7,8-TCDD	2,3,7,8-TetraCDF	3,3'4,4'-TetraCB (PCB 77)
1,2,3,7,8-PentaCDD	1,2,3,7,8-PentaCDF	3,4,4',5-TetraCB (PCB 81)
1,2,3,4,7,8-HexaCDD	2,3,4,7,8-PentaCDF	2,3,3',4,4'-PentaCB (PCB 105)
1,2,3,6,7,8-HexaCDD	1,2,3,4,7,8-HexaCDF	2,3,4,4',5-PentaCB (PCB 114)
1,2,3,7,8,9-HexaCDD	1,2,3,6,7,8-HexaCDF	2,3',4,4',5-PentaCB (PCB 118)
1,2,3,4,6,7,8-HeptaCDD	2,3,4,6,7,8-HexaCDF	2',3,4,4',5-PentaCB (PCB 123)
1,2,3,4,6,7,8,9-OctaCDD	1,2,3,7,8,9-HexaCDF	3,3',4,4',5-PentaCB (PCB 126)

Table 1. List of Compounds With Varying Dioxin-like Toxicity		
Chlorinated Dibenzo-p-dioxins (CDDs)	**Chlorinated Dibenzofurans (CDFs)**	**Polychlorinated Biphenyls (PCBs)**
	1,2,3,4,6,7,8-HeptaCDF	2,3,3',4,4',5-HexaCB (PCB 156)
	1,2,3,4,7,8,9-HeptapCDF	2,3,3',4,4',5'-HexaCB (PCB 157)
	1,2,3,4,6,7,8,9-OctaCDF	2,3',4,4',5,5'-HexaCB (PCB 167)
		3,3',4,4',5,5'-HexaCB (PCB 169)
		2,3,3',4,4',5,5'-HeptaCB (PCB 189)

Table 2. WHO_{05} Toxic Equivalent Factors

Compound	**TEF_{WHO05}**
CDDs	
2,3,7,8-TetraCDD	1
1,2,3,7,8-PentaCDD	1
1,2,3,4,7,8-HexaCDD	0.1
1,2,3,6,7,8-HexaCDD	0.1
1,2,3,7,8,9-HexaCDD	0.1
1,2,3,4,6,7,8-HeptaCDD	0.01
1,2,3,4,6,7,8,9-OctaCDD	0.0003
CDFs	
2,3,7,8-TetraCDF	0.1
1,2,3,7,8-PentaCDF	0.03
2,3,4,7,8-PentaCDF	0.3
1,2,3,4,7,8-HexaCDF	0.1
1,2,3,6,7,8-HexaCDF	0.1
2,3,4,6,7,8-HexaCDF	0.1
1,2,3,7,8,9-HexaCDF	0.1
1,2,3,4,6,7,8-HeptaCDF	0.01
1,2,3,4,7,8,9-HeptaCDF	0.01
1,2,3,4,6,7,8,9-OctaCDF	0.0003
PCBs	
3,3'4,4'-TetraCB (PCB 77)	0.0001
3,4,4',5-TetraCB (PCB 81)	0.0003

2,3,3',4,4'-PentaCB (PCB 105)	0.00003
2,3,4,4',5-PentaCB (PCB 114)	0.00003
2,3',4,4',5-PentaCB (PCB 118)	0.00003
2',3,4,4',5-PentaCB (PCB 123)	0.00003
3,3',4,4',5-PentaCB (PCB 126)	0.1
2,3,3',4,4',5-HexaCB (PCB 156)	0.00003
2,3,3',4,4',5'-HexaCB (PCB 157)	0.00003
2,3',4,4',5,5'-HexaCB (PCB 167)	0.00003
3,3',4,4',5,5'-HexaCB (PCB 169)	0.03
2,3,3',4,4',5,5'-HeptaCB (PCB 189)	0.00003

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