

History of Dioxin Regulation & Reassessment

As of May 25, 2010

- 1978** Kociba *et al.* publish what is arguably the most cited cancer bioassay for 2,3,7,8-TCDD. The authors observe an increase in liver tumors in female rats dosed at 100 ng/kg-day and report some effect at 10 ng/kg-day. A cancer rate decrease was observed in animals receiving lower doses.
- 1982** The National Toxicology Program (NTP) publishes results of a cancer bioassay for 2,3,7,8-TCDD. An increase in liver tumors was observed at 71 ng/kg-day in female rats and in mice. A decrease in cancer rate was observed in animals receiving lower doses.
- 1984** Kimbrough *et al.* propose that 1,000 ppt of 2,3,7,8-TCDD in residential soils is a "level of concern," and recommend that 1,000 ppt serve as "a reasonable level to begin consideration of action to limit exposure." The authors also state, "in residential areas, levels at or above 1,000 ppt of dioxin in soil cannot be considered safe and represent a level of concern."
- 1985 September:** EPA publishes the *Health Assessment Document for Polychlorinated Dibenzo-P-Dioxins*. Utilizing the Kociba *et al.* (1978) data, the NTP mouse data, and conservative extrapolation assumptions, the Agency concludes that human exposures to 0.006 pg/kg-day are associated with a one-in-a-million excess cancer risk. The Agency's conclusions also assume human risks at doses approximately ten million times smaller than doses that induced cancer in laboratory animals and ignore the likely existence of a threshold. The Agency regulates based on the 0.006 pg/kg-day value.
- 1988** EPA's Dioxin Workgroup recommends weakening EPA's dioxin potency 16-fold to 0.1 pg/kg-day. General agreement within the scientific community is that a substantial improvement in calculating low dose effects in humans could be made in analyzing dioxin dose-response. The use of a receptor model, which suggests a threshold effect, is widely recommended.
- 1990** A reevaluation of liver tumor data from the Kociba *et al.* (1978) study using a newer methodology concludes that some previous observations of cancer were incorrect. The reevaluation concludes that, based on this data alone, the estimates of dioxin potency should be decreased 3- to 4-fold.

The World Health Organization (WHO) concludes that the acceptable daily intake for dioxin is 10 pg/kg-day. This safe dose is almost 2,000 times greater than EPA's estimate for a one-in-a-million excess cancer rate. The WHO value is more consistent with levels accepted by other countries and the U.S. Food and Drug Administration.

1991 EPA Administrator Reilly directs the Agency to reassess dioxin health risks. Early Agency discussions suggest the use of a receptor model. EPA later rescinds this suggestion. Some EPA scientists state that the dioxin reassessment would focus on: non-cancer endpoints as well as cancer; the impact of background dioxin exposures; a large number of dioxins, furans, and PCBs; and would not likely find a threshold.

The National Institute of Occupational Safety and Health (NIOSH) conducts a cancer mortality [study](#) in a total of 5,172 workers at 12 U.S. chemical plants. Published by Fingerhut *et al.*, the study suggests that workers exposed to dioxin had a slightly greater risk of dying from cancer than the general public (230 deaths expected, 265 found). The extra cancers were mainly in the group of workers exposed to dioxin for more than 1 year (78 expected, 114 found). The authors further suggest that workers heavily exposed to dioxins in the past did seem to have a modestly increased risk of cancer in general. In addition, a group of rare cancers called soft tissue sarcomas was mentioned specifically, as was respiratory cancer. However, these reports are complicated by other potential factors that could contribute to cancer, both occupational and lifestyle.

1994 August: EPA releases the three volume draft reassessment document entitled *Health Assessment Document for 2,3,7,8-Tetrachlorodibenzo-P-Dioxin (TCDD) and Related Compounds*. The draft includes a Health Assessment Document, an Exposure Assessment Document, and a Risk Characterization. The Agency focuses on non-cancer endpoints; increases its exposure estimates by combining exposures to a variety of dioxins, furans, and PCBs; and concludes that “a broad spectrum of effects” may occur “at or near levels to which people in the general population are exposed.” The Risk Characterization (which presents the Agency’s conclusion) is not supported by the science presented in the Risk and Exposure Documents.

September: EPA launches its Dioxin Exposure Initiative (DEI), a research program to further evaluate the exposure of Americans to this class of compounds. The DEI is jointly funded and managed by EPA's Office of Research and Development and EPA's Office of Prevention, Pesticides, and Toxic Substances.

1995 December: EPA’s Science Advisory Board (SAB) reviews the draft Reassessment and concludes that EPA may have overstated the risks from dioxin, particularly at background levels. SAB recommends the EPA highlight uncertainties, incorporate a broader range of scientific opinion, and rewrite the Dose-Response and Risk Characterization chapters for re-review by the SAB (see [article](#)).

1996 EPA releases partially revised versions of the Dose-Response and Risk Characterization chapters of the Reassessment to an external stakeholder group for comment. Critical sections of the Risk Characterization document have not yet been incorporated and many sections are virtually unchanged from the previous drafts.

1997 March: EPA holds an External Peer Review Meeting on the Dose-Response chapter of the Reassessment. The draft does not incorporate many of the SAB suggestions, but does

provide a receptor model. The draft stirs disagreements among scientists representing various branches of government and among members of the scientific community.

August: The Agency for Toxic Substances and Disease Registry (ATSDR) publishes an [interim policy guideline](#) for dioxin and dioxin-like compounds in soil. ATSDR introduces a decision framework for contaminated sites. Minimum Risk Levels (MRLs) are designated as TCDD or Total Toxicity Equivalency (TEQ).

The International Agency for Research on Cancer (IARC) classifies TCDD as carcinogenic to humans (*Group 1*). The panel concludes that there is *limited evidence* in humans for the carcinogenicity of TCDD, and that there is *sufficient evidence* in experimental animals for the carcinogenicity of TCDD IARC “[Summaries & Evaluations](#).”

1998 April: EPA’s Office of Solid Waste and Emergency Response (OSWER) issues OSWER Directive 9200.4-26, [Approach for Addressing Dioxin in Soil at CERCLA and RCRA Sites](#). The Directive establishes a clean-up goal of 1,000 ppt for TCDD in residential soils, and within the range of 5,000-20,000 for commercial/industrial soils at Superfund and RCRA clean-up sites. The Directive further states that “(OSWER) does not believe it is prudent to establish new, and possibly varying precedents for Superfund or RCRA dioxin levels prior to the release of the reassessment report.”

May: WHO recommends a Total Daily Intake (TDI) range of 1 to 4 pg/kg-day for TCDD or Total TEQ (WHO Consultation [Executive Summary](#)). The TDI is established by applying an uncertainty factor of 10 to the range of lowest-observed-adverse-effect-levels (LOAELs), from 14 to 37 pg TCDD/kg-day. Because body burdens have been used to scale doses across species the use of an uncertainty factor to account for species differences of toxicokinetics is not necessary.

December: ATSDR publishes its [Toxicological Profile for Chlorinated Dibenzo-p-Dioxins](#). The MRLs are unchanged from the 1997 guideline, but a stipulation is added that the MRLs apply to TCDD or Total TEQ.

van den Berg *et al.* (1998) publish the results of a WHO meeting held to derive consensus on [Toxicity Equivalency Factors \(TEFs\)](#) for polychlorinated dibenzo-*p*-dioxins and dibenzofurans and dioxin-like polychlorinated biphenyls (PCBs) for human, fish, and wildlife assessment. The authors conclude that the TEF concept is the most “plausible and feasible approach for risk assessment of halogenated aromatic hydrocarbons with dioxin-like properties.

1999 September: The Japanese Environmental Agency and the Ministry of Health and Welfare recommend a TDI of 4 pg TEQs/kg-day based on a calculation of the daily intake for humans using a body burden of 86 ng/kg and an uncertainty factor of 10 ([guidelines](#)). End points considered are the health effects occurring after exposure during the fetal period.

2000 May: EPA releases the *Draft Exposure and Human Health Reassessment* on dioxin ([Information Sheet](#)). The Agency concludes that TCDD is a human carcinogen, and states that the lifetime all-cancer mortality risk attributable solely to the current background body burden of dioxin-like compounds could be as high as 1.3 per 100. The Agency's human cancer risk estimate is obtained from a linear dose-response model fit to the data from three epidemiology studies of TCDD-exposed chemical workers.

July: EPA releases the Consolidated Comments from the Peer Review Workshop of the Draft Dioxin Reassessment. The two-day review focuses on two parts of the draft: *Part III. Integrated Summary and Risk Characterization for 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds* and *Chapter 9: Toxicity Equivalence Factors (TEFs) for Dioxin and Related Compounds*. The reviewers provide feedback on several issues, including ambient and population exposures, TEFs, and inventory of sources.

November: The SAB Dioxin Reassessment Subcommittee convenes to review the draft "*Exposure and Human Health Assessment of 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) and Related Compounds*." The review focuses on three distinct parts of the draft document: *Part II. Chapter 8; Dose-Response Modeling; Part II. Chapter 9: TEFs for Dioxin and Related Compounds; and Part III. Integrated Summary and Risk Characterization*.

The European Union's Scientific Committee on Food establishes a temporary tolerable weekly intake of 7 pg/kg-week for TCDD or total TEQs. The Committee bases its decision on several laboratory studies that provide estimated human daily intakes ranging from 12.5 to 30 pg TCDD/kg/bw. An uncertainty factor of 3 is applied to the LOAEL-to-NOAEL extrapolation and 3 for human variability based on toxicokinetic differences. No uncertainty factor is used for interspecies extrapolation because the body burdens were used to scale doses across species.

2001 May: The European Union's Scientific Committee on Food revises ([report](#)) upward the tolerable weekly intake to 14 pg/kg-week (equivalent to 2 pg/kg-d) for TEQ in response to new data calling into question the reliability of a key dioxin health-effects study. The Joint World Health Organization/Food and Agricultural Organization Committee on Food Additives (JECFA) sets a Provisional Monthly Tolerable Intake of 70 pg/kg-month (equivalent to 2.3 pg/kg-d) for TEQ, and the United Kingdom Committee on Toxicity (UKCOT) reviews the available data and sets a TDI of 2 pg/kg-d. The various bodies achieve a consensus that these daily intake values are protective against cancer and reproductive and developmental endpoints, and the derivation of the values by each agency is based on a body burden assessment for dose-response. Each agency also concludes that even the most sensitive humans are likely to be no more sensitive than the most sensitive animal species and strains.

May: The SAB releases its [review](#) of the Reassessment, advising the Agency to make several revisions including deriving non-cancer health guidance values, or reference doses (RfDs), using the margin of exposure approach, body burden calculations, and considering the significance of naturally occurring dioxin-like compounds.

2002 April: The Government Accounting Office (GAO) releases the report [Environmental Health Risks: Information on EPA's Draft Reassessment of Dioxins](#).

In response to EPA's Reassessment, The Office of Science and Technology's Committee on the Environment and Natural Resources, Office of the President, forms the Dioxin Interagency Working Group. The workgroup is formed to assess the implications of the Reassessment for a range of federal agencies.

2003 October: EPA announces that the Agency has officially requested a National Academy of Sciences (NAS) Review Draft of the Dioxin Assessment with updates on the online "Questions and Answers about Dioxin." [The Statement of Work to the NAS Committee](#) is transmitted at this time.

The NAS' Institute of Medicine publishes [Dioxins and Dioxin-like Compounds in the Food Supply: Strategies to Decrease Exposure](#) (also called the "Green Book"). The Committee recommends increasing behavioral research on achieving dietary change and pathway intervention, or the interruption of the cycle of dioxins through forage, animal feed, and food-producing animals.

2004 October: EPA releases the National Academy of Sciences (NAS) Review Draft of EPA's *Exposure and Human Health Reassessment of 2,3,7,8-Tetrachloro-p-dioxin (TCDD) and Related Compounds*, in preparation for the first NAS panel review meeting scheduled for November 2004.

National Toxicology Program (NTP) publishes the results of a two-year [study](#) that examined dose-additive cancer effects in rodents receiving three different dioxin-like compounds and mixtures of these compounds. Dose-response curves for all cancers studied are characterized as "highly non-linear."

University of Michigan researchers begin a multi-year study entitled the [University of Michigan Dioxin Exposure Study](#) (UMDES) to determine whether elevated levels of dioxins in the soil have also caused elevated levels of dioxins in residents' bodies. The researchers perform similar measurements among residents in an uncontaminated area for comparison purposes. Results of the study indicate that dioxins in soils contribute very little to dioxins in human serum. The study will prove to be one of the largest and most relevant studies concerning the impact of dioxins in soil and dust on human body burdens.

2005 WHO expert committee convenes to re-evaluate the TEFs for dioxin-like compounds, including PCBs ([report](#)). Decisions concerning TEF values are made based on a combination of unweighted relative effect potency (REP) distributions developed by Haws *et al.* (2006). Changes are decided by the committee for 2,3,4,7,8-PeCDF, 1,2,3,7,8,-PeCDF, OCDD, OCDF, PCB 81, PCB 169, and all relevant mono-*ortho*-substituted PCBs. The committee expresses concern regarding the direct application of the TEF/total toxic equivalency (TEQ) approach to abiotic matrices such as soil, sediment, *etc.* for direct application in human risk assessment, as the TEF scheme and

TEQ methodology are primarily intended for estimating exposure and risks via oral ingestion. Application of the revised TEFs provides a modest decrease in total TEQ compared with the 1998 TEF values.

2006 July: NAS publishes its review of the Reassessment entitled *Health Risks from Dioxin and Related Compounds: Evaluation of the EPA Reassessment*. The Committee's key findings include revising approaches to dose-response modeling for cancer and non-cancer endpoints, identifying key data sets, utilizing quantitative uncertainty analysis, considering physiologically-based pharmacokinetic modeling, and using both a linear and non-linear dose-response model consistent with a receptor-mediated mechanism of action with epidemiological data and the new NTP animal bioassay data.

November: EPA releases [*An Inventory of Sources and Environmental Releases of Dioxin-like Compounds in the United States for the Years 1987, 1995, and 2000*](#). The report indicates that between 1987 and 2000 there was a 90% reduction in the releases of dioxin-like compounds from all combined sources in the U.S. Also, the study shows that burning of domestic refuse in backyard burn barrels is the largest source of dioxin emissions to the U.S. environment.

2007 July: The European Commission adopts the [second progress report](#) on the Dioxin Strategy. It summarizes the main progress over the period 2004-2006 and is supplemented by an annex containing more detailed descriptions of the developments. Among the most important progress over the period in the environmental area is the adoption of the Persistent Organic Pollutants (POP) Regulation, the development of implementation plans and the updating of legislation relating to limit values in feed and food.

2008 September: The Interagency Dioxin Workgroup posts an update to the "Questions and Answers about Dioxin."

ATSDR publishes an updated policy guideline to its 1998 [Toxicological Profile for Chlorinated Dibenzo-p-Dioxins](#). Appendix B addresses residential soil and retains the 0.05 ppb screening level for an initial comparison value for health assessments. The update also retains the preliminary remediation goal for dioxin in soil at 1 ppb.

October: EPA's Office of Solid Waste and Emergency Response (OSWER) issues OSWER Directive 9285.7-84FS, [Frequently Asked Questions on the Update to the ATSDR Policy Guideline for Dioxins and Dioxin-Like Compounds in Residential Soil](#). This Directive reasserts that the preliminary goal for dioxin in residential soil has not changed and remains 1,000 ppt. It further states that "the recommended level of 1,000 ppt is to be used pending the release of EPA's comprehensive dioxin reassessment report and cross-program assessment of the impacts of the report."

November: EPA releases a preliminary SAB member search list to address EPA's Responses to the NAS comments on the 2003 Dioxin Reassessment report.

2009 February: EPA hosts a three-day dioxin science [workshop](#) to assist the Agency's National Center for Environmental Assessment (NCEA) in responding to the NAS recommendations on the Reassessment.

May: EPA releases the "Dioxin Science Plan" for activities related to Dioxins in the environment. The plan addresses the Agency's response to the 2006 NAS recommendations; the development of interim preliminary remediation goals for dioxins in soil; the review of the University of Michigan Dioxin Exposure Study, and the use of the 2005 WHO Toxic Equivalency Factors (TEFs). The Agency sets an ambitious schedule of no later than December 31, 2009 for completing each task, and announces its intention to complete the Reassessment by end of 2010.

June: EPA releases the Dioxin Workshop Summary report containing discussions and conclusions from the Feb 18-20, 2009 workshop held in Cincinnati, Ohio.

September: EPA releases a draft document entitled [Recommended Toxic Equivalency Factors \(TEFs\) for Human Health Risk Assessments of Dioxin and Dioxin-like Compounds: External Review Draft](#). With this document the Agency recommends the use of the consensus TEF values for dioxins published in 2005 by WHO. The Agency recommends these TEFs be used for all effects mediated through aryl hydrocarbon receptor binding by dioxin-like compounds including cancer and non-cancer effects.

EPA releases its *Review of the University of Michigan Study of Dioxin Exposure in Midland, Michigan*. The Agency's criticisms of the study were that it does not include children; it does not include a sufficient number of properties with highly-contaminated soils; and that it does not represent individuals who participate in activities that may lead to elevated dioxin exposures. The EPA report is not subject to a formal review process and there is no docket established. Further, the Agency holds a one-time community meeting in Michigan, but does not provide a public comment period.

October: EPA holds a TEF Peer Review Panel. As captured in the Agency's November 4th [Peer Review Summary Report](#), the general consensus among reviewers is that additional information must be added in describing the Relative Potency (REP) variability and distribution, and that the uncertainty section of the document must provide specific direction on conducting qualitative and quantitative analysis for use of TEFs.

November: EPA [announces](#) the formation and compilation of the SAB *ad hoc* Dioxin Review Panel to review the Agency's response to the NAS recommendations concerning the 2003 Reassessment.

December: EPA releases its [Draft Recommended Interim Preliminary Remediation Goals for Dioxin in Soil at CERCLA and RCRA Sites](#). The draft document recommends a cleanup goal of 72 part per trillion (ppt) for residential uses and 950 ppt for commercial or industrial uses; the draft also proposes alternative PRGs of 3.7 ppt, and 17 ppt for residential and commercial, respectively, based on cancer at the 1E-06 risk level. These

levels are considerably more stringent than the Agency's 1998 PRG of 1,000 ppt for residential soil and 20,000 ppt for commercial soil.

2010 January: EPA establishes a special communications committee to address concerns about the safety of the food supply and other health issues expected to stem from the pending release of its revised reassessment and response to the 2006 NAS recommendations.

May: EPA releases a draft report entitled [*EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments*](#). The 1,850-page draft report is EPA's response to key comments and recommendations made by NAS in 2006 on the Agency's 2003 draft Reassessment. EPA's response establishes a cancer slope factor of 1.0×10^6 per (mg/kg-day) based on a linear dose-response model despite the NAS recommendation to use a non-linear model. It also establishes, for the first time, a reference dose (RfD) of 0.7 pg/kg-day – the amount EPA considers safe to consume daily over a lifetime without experiencing non-cancer health effects. And, as it did in the 2003 Reassessment, the Agency again determines that TCDD is carcinogenic to humans.

EPA posts an update to the "[Questions and Answers about Dioxins](#)." The update discusses the possible effects of dioxin exposure to humans, giving advice on minimizing dietary sources of dioxin, and outlining the review process for the Dioxin Reassessment.