ATSDR's Guidance Values for Dioxins

H. R. Pohl, J. Holler, C.T. De Rosa

Division of Toxicology, Agency for Toxic Substances and Disease Registry, U.S. Department of Health and Human Services, Atlanta, Georgia 30333

Introduction

The Agency for Toxic Substances and Disease Registry (ATSDR) is a U.S. public health agency with a mission to prevent exposure and adverse human health effects and diminished quality of life associated with exposure to hazardous substances from waste sites and unplanned releases to the environment. Health-based guidance values, specifically ATSDR's minimal risk levels (MRLs) and environmental media evaluation guides (EMEGs), play an important role in assessing the public health implications of low-level exposures to substances found at hazardous waste sites. By staying abreast of the latest research regarding toxicity, toxicokinetics, and toxicodynamics of hazardous chemicals, ATSDR continually refines the judgment that is used in developing these values (1, 2). Dioxin and dioxin-like compounds have been studied more than any other chemicals. Increased knowledge about 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) toxicity was reflected in changes that MRLs underwent over the last decade. Although our knowledge has expanded, there remains significant scientific uncertainty. The uncertainty is reflected by the use of uncertainty factors (UFs) and modifying factors (MFs) in deriving health guidance values.

Materials and Methods

ATSDR's guidance values for chlorinated dibenzo-p-dioxins (CDDs) and chlorinated dibenzofurans (CDFs) were based on robust databases presented in ATSDR's toxicological profiles for these chemicals (3,4,5). The Toxicological Profile for TCDDs was first published in 1989; an updated document, Toxicological Profile for CDDs, was released for public comments in 1997 and finalized in 1999. The Toxicological Profile for CDFs was published in 1994. The methodology for deriving ATSDR's guidance values has been described in detail in several publications (6,7).

Results and Discussion

In 1989, the acute (14 days or less) oral MRL of 100 pg TCDD/kg/day was based on a lowest-observed-adverse-effect level (LOAEL) of 0.1 µg/kg/day for hepatotoxicity in guinea pigs (8). A UF of 10 was used for extrapolation from animals to humans, a factor of 10 for human variability, and a factor of 10 for the use of a LOAEL Later studies showed TCDD's toxicity at even lower levels. In 1999, the MRL of 200 pg/kg/day was derived for acute-duration oral exposure to TCDD. The MRL was based on a no-observed-adverse-effect level (NOAEL) of 0.005 µg/kg for immunological effects (increased susceptibility to infection) in female mice (9). A UF of 3 was used for extrapolation from animals to humans, a factor of 10 for human variability, and a MF of 0.7 was applied to adjust for the difference in higher bioavailability of TCDD via gavage with an oil vehicle in contrast to dietary exposure.

In 1989, the LOAEL of 0.001 µg/kg/day was considered for deriving the intermediate-duration (15 to 364 days) oral MRL of 1 pg/kg/day. At this exposure level, dilated pelvises and changes in gestational index were observed in rats (10) and abortions were reported in monkeys (11). A UF of 10 was used for extrapolation from animals to humans, a factor of 10 for human variability, and a factor of 10 for the use of a LOAEL. In 1997 and 1999, an MRL of 20 pg/kg/day was derived for intermediate-duration oral exposure to TCDD. The MRL was based on a NOAEL of 0.0007 µg/kg/day for immunological effects (atrophy of the thymic cortex) in Hartley guinea pigs fed TCDD in the diet for 90 days (12). Hepatotoxicity was observed at the same levels as immunotoxicity. A UF of 3 was used for extrapolation from animals to humans and a factor of 10 for human variability.

In 1989, the intermediate-duration exposure MRL was adopted for chronic exposure (365 days and more). No UF was used to extrapolate across durations. In 1997 and 1999, the chronic MRL of 1 pg/kg/day was based on a LOAEL of 0.12 ng/kg/day in monkeys administered in a diet for a total exposure of 16.2$\pm$ 0.4 months (13). An uncertainty factor of 3 was used for extrapolation from animals to humans, a factor of 10 for human variability, and a factor of 3 for the use of a LOAEL. In summary, greater knowledge about TCDD toxicity enabled ATSDR to lower the uncertainty factors and although based on a lower LOAEL, the final MRL value is the same as the original one. This decrease in uncertainty corresponds to a greater confidence in the accuracy of the MRL presented in the 1999 profile.

Independently in 1996, the Health Council of the Netherlands (14) reassessed the risk associated with dioxin and dioxin-like compounds based on recent studies and recommended a health-based exposure limit equal to 1 pg/kg/day total toxicity equivalents (TEQs). More recently, the World Health Organization (WHO) (1998) recommended a total daily intake (TDI) ranging from 1 to 4 pg/kg for TCDD or total TEQs (15). Since 1997, it is ATSDR's policy (5,16) to use health guidance values derived for TCDD for other dioxin-like compounds, expressed in total TEQs.

ATSDR also published a profile for CDFs in 1994 (4). An MRL of 0.00003 µg/kg/day was derived for intermediate-duration oral exposure to 2,3,4,7,8-pentaCDF. The MRL was based on a LOAEL for hepatic effects in rats exposed for 13 weeks to 2,3,4,7,8-pentaCDF in feed (17,18). The observed effects included increased serum bilirubin and decreased serum triglycerides. Expressed in TEQs (the toxicity equivalency factor [TEF] for 2,3,4,7,8-pentaCDF is 0.5), the MRL would be 15 pg/kg/day . This value corresponds closely with the 1999 MRL of 20 pg/kg/day for intermediate-duration oral exposure to TCDD. While these values may suggest a greater hazard attributed to 2,3,4,7,8-pentaCDF, these differences are most likely an artifact of the UFs used in deriving the MRL and the MF of 3 that was applied to adjust for lack of relevant neurological studies.

References

1. Pohl H, Abadin H, *Regul Toxicol Pharmacol*, **1995**, 22 (2):180-188.
2. De Rosa C, Pohl H, Williams M, et al., *Environ Health Perspect*, **1998**, 106 (suppl.1):369-378.
3. ATSDR. **1989**. Toxicological Profile for Tetrachlorodibenzo-*p*-Dioxin. Atlanta, GA: Agency for Toxic Substances and Disease Registry, U.S. Department of Health and Human Services.
4. ATSDR. **1994**. Toxicological Profile for Chlorodibenzofurans. Atlanta, GA: Agency for Toxic Substances and Disease Registry, U.S. Department of Health and Human Services.
5. ATSDR. **1999**. Toxicological Profile for Chlorinated Dibenzo-p-Dioxins. Atlanta, GA: Agency for Toxic Substances and Disease Registry, U.S. Department of Health and Human Services.
6. ATSDR (Agency for Toxic Substances and Disease Registry). **1996**. Minimal risk levels for priority substances and guidance for derivation. Federal Register 61 (101):25873-25882.
7. ATSDR. **1992**. Public health assessment guidance manual. Atlanta, GA: U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry. NTIS PB92-147164.
8. Turner JN, Collins DN, *Toxicol Appl Pharmacol*, **1983**, 67:417-429.
9. Burleson GR, Lebrec H, Yang YG, et al., *Fundam Appl Toxicol*, **1996**, 29:40-47.
10. Murray FJ, Smith FA, Nitschke KD, et al. , *J Chromatogr*, **1979**, 369(1):203-207.
11. Allen JR, Barsotti DA, Lambrecht LK, et al., *Ann NY Acad Sci*, **1979**, 320:419-425.
12. DeCaprio AP, McMartin DM, O'Keefe PW, et al., *Fundam Appl Toxicol*, **1986**, 6:454-463.
13. Schantz SL, Ferguson SA, Bowman RE, *Neurotoxicol Teratol*, **1992**, 14:433-446.
14. Health Council of the Netherlands. **1996**. Report on dioxins. Report available from the Health Council Secretariat.
15. Van den Berg M, Birnbaum L, Bosveld ATC, *Environ Health Perspect*, **1998**, 106 (12): 775-792.
16. De Rosa C, Brown D, Dhara R, et al., *J Clean Technol Environ Toxicol Occup Med*, **1997**, 6 (2):117-126.
17. Pluess N, Poiger H, Hohbach C, et al., *Chemosphere*, **1988**, 17:973-984.
18. Poiger H, Pluess N, Schlatter C, *Chemosphere*, **1989**, 18:265-275.