Reducing Uncertainty in the Derivation and Application of Health Guidance Values in Public Health Practice

Dioxin as a Case Study

CHRISTOPHER T. DE ROSA,[a,b] HANA R. POHL,[b] HUGH HANSEN,[b] ROBIN C. LEONARD,[c] JAMES HOLLER,[b] AND DENNIS JONES[b]

[b]*Agency for Toxic Substances and Disease Registry Public Health Service, U.S. Department of Health and Human Services, Atlanta, Georgia 30333, USA*

[c]*Haskell Laboratory for Toxicology and Industrial Medicine, Newark, Delaware 19714, USA*

ABSTRACT: **We were requested by the U.S. Environmental Protection Agency (EPA) to clarify the relationships among the minimal risk level (MRL), action level, and environmental media evaluation guide (EMEG) for dioxin established by the Agency for Toxic Substances and Disease Registry (ATSDR). In response we developed a document entitled "Dioxin and Dioxin-Like Compounds in Soil, Part I: ATSDR Interim Policy Guideline"; and a supporting document entitled "Dioxin and Dioxin-Like Compounds in Soil, Part II: Technical Support Document". In these documents, we evaluated the key assumptions underlying the development and use of the ATSDR action level, MRL, and EMEG for dioxin. We described the chronology of events outlining these different health guidance values for dioxin and identified the areas of uncertainty surrounding these values. Four scientific assumptions were found to have had a great impact on this process; these were: (1) the specific uncertainty factors used, (2) the toxicity equivalent (TEQ) approach, (3) the fractional exposure from different pathways, and (4) the use of body burdens in the absence of exposure data. This information was subsequently used to develop a framework for reducing the uncertainties in public health risk assessment associated with exposure to other chemical contaminants in the environment. Within this framework are a number of future directions for reducing uncertainty, including physiologically based pharmacokinetic modeling (PBPK), benchmark dose modeling (BMD), functional toxicology, and the assessment of chemical mixture interactions.**

INTRODUCTION

The mission of the Agency for Toxic Substances and Disease Registry (ATSDR) is to prevent, or mitigate, adverse human health effects and diminished quality of life resulting from exposure to hazardous substances from waste sites, unplanned releas-

[a]Address for correspondence: C.T. De Rosa, ATSDR, Division of Toxicology, E-29, 1600 Clifton Road, Atlanta, Georgia 30333, USA. 404-639-6300 (voice); 404-639-6315 (fax).
e-mail: cyd0@cdc.com

es, and other sources of pollution present in the environment. ATSDR evaluates information from hazardous waste sites and uses this information to prepare site-specific public health assessments and consultations. Health assessors must have a knowledge of many site-related issues, including site description and history, land use, community concerns, health outcome data, environmental contaminants of concern, and completed exposure pathways. Health-based guidance values, specifically the ATSDR 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 relating to toxicity, toxicokinetics, and toxicodynamics of hazardous chemicals, ATSDR continually refines the judgment that is used in developing these values.[1,2] Nevertheless, the health assessment process involves many assumptions, limitations, and uncertainties that must be dealt with. This paper outlines some of the uncertainties encountered during development of an ATSDR interim policy guideline for dioxin and dioxin-like compounds in soil[3,4] and describes the approach taken by ATSDR to further address uncertainty in health guidance values, in consultation with its Board of Scientific Councillors.

BACKGROUND ON THE ATSDR INTERIM POLICY GUIDELINE FOR DIOXIN AND DIOXIN-LIKE COMPOUNDS IN SOIL

The ATSDR interim policy guideline for dioxin and dioxin-like compounds in soil addressed several issues.[3,4] The three primary issues evaluated were: (1) the relationship between the ATSDR action level of 1 ppb dioxin and dioxin-like compounds in residential soil and the ATSDR EMEGs, (2) concern that current analytic and sampling techniques employed for soil contaminated with dioxin and dioxin-like compounds may not be sufficiently sensitive, and (3) concern that the ATSDR action level of 1 ppb dioxin and dioxin-like compounds in residential soil may be too high.

ATSDR outlined three steps to evaluate human exposure from soil contaminated with hazardous chemicals: (1) screening for contaminants of concern, (2) evaluating potential exposure pathways, and (3) defining public health implications and actions. This approach was also used to evaluate dioxin exposure from soil. ATSDR outlined a framework that can be used by health assessors to evaluate dioxin-contaminated soil (TABLE 1). The ATSDR decisions were based on an extensive review of current literature pertaining to dioxin and dioxin-like compounds that was presented in an ATSDR draft "Toxicological Profile for Chlorinated Dibenzo-*p*-dioxins",[5] with more recent data cited and discussed in the policy paper itself.

With reference to the specific issues listed previously, the ATSDR interim policy concluded that:

1. The ATSDR action level of 1 ppb of dioxin and dioxin-like compounds expressed in toxicity equivalents (TEQs) in residential soil is consistent with the ATSDR EMEG. These values are used for distinctly different purposes in evaluating dioxin-contaminated sites (TABLE 1).

2. Currently used soil analytic methods may not be sufficiently sensitive. Determination of an appropriate analytic method should be made on a site-specific basis. Specific knowledge of different dioxin-like compounds at a given site is required in order to evaluate the adequacy of a soil-sampling protocol.
3. The ATSDR action level of 1 ppb for dioxin and dioxin-like compounds (TEQs) in residential soil is not too high. Use of the 1 ppb action level should be decided on a site-specific basis in which residential soil levels greater than 50 ppt and less than 1 ppb are further evaluated in the context of site-specific parameters.

While developing the interim policy guideline, ATSDR dealt with assumptions, limitations, and uncertainties pertaining to both health assessments in general, and to some dioxin-specific issues. Dealing with these topics was a complex and evolving experience. Because dioxin exposure is associated with effects at very low levels and a wide range of considerations was taken into account, the approach used by ATSDR in addressing these issues can serve as an example that may provide a framework for health assessment of other toxic chemicals.

TABLE 1. ATSDR decision framework for sites contaminated with dioxin and dioxin-like compounds

Screening Level	Evaluation Levels	Action Level[a]
≤ 50 ppt TEQs[b]	> 50 ppt but < 1 ppb TEQs	≥ 1 ppb TEQs
•The EMEG for TCDD is 50 ppt	Evaluation of site-specific factors, such as	Potential public health actions considered, such as
• This is based on an MRL of 1 pg/kg/day for TCDD.	• Bioavailability	• Surveillance
• For screening purposes 50 ppt TCDD is assumed to be equivalent to 50 ppt TEQs	• Ingestion rates	• Research
	• Pathway analysis	• Health studies
	• Soil cover	• Community education
	• Climate	• Physician education
	• Other contaminants	• Exposure investigations
	• Community concerns	
	• Demographics	
	• Background exposures	

[a]A concentration of chemicals at which consideration of action to interdict/prevent exposure occurs, such as surveillance, research, health studies, community education, physician education, or exposure investigations. Alternatively, based on the evaluation by the health assessor, none of these actions may be necessary.

[b]The toxicity equivalent (TEQ) of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) is calculated by multiplying the exposure level of a particular dioxin-like compound by its toxicity equivalency factor (TEF). TEFs are based on congener-specific data and the assumption that Ah receptor-mediated toxicity of dioxin-like chemicals is additive. The TEF scheme compares the relative toxicity of individual dioxin-like compounds to that of TCDD.

UNCERTAINTIES ASSOCIATED WITH THE DERIVATION OF MRLS

Areas of Uncertainty

Data Used in Various Risk Assessment Methods Are Incomplete

An incomplete database is the first source of uncertainty introduced into the risk assessment process. We may, for example, know that a certain effect occurs following oral exposure to a chemical, but can we infer from this observation that there are other routes of exposure? Similarly, extrapolation among exposure-duration categories may be difficult. Often information is available from laboratory studies in animals but relevant studies in humans are lacking. Interspecies anatomical differences (e.g., nasal turbinate in rodents, forestomach in rodents, Zymbal glands in rats, stomach in herbivores) may obviously contribute to differences in the chemical toxicity mechanism. Interspecies differences in pathophysiological responses and in pathogenesis of diseases must be also considered. For example, chronic progressive nephropathy is an age-related spontaneous disorder of rats that is more severe in males than in females and that affects certain strains more than others.[6] Chronic exposure of male rats to $\alpha_2\mu$-globulin-inducing agents results in the aggravation of chronic progressive nephropathy, characterized by increased severity and earlier onset of the disease. It has been postulated that this pathophysiology of renal disease may not be applicable to humans.

Scientific uncertainty on validity of the endpoint was also considered in the derivation of chronic oral MRL for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD). The chronic oral MRL was based on the neurobehavioral endpoint from teratology studies in monkeys (mothers exposed to dietary concentration of 5 ppt 2,3,7,8-TCDD). No significant alterations in reflex development, visual exploration, locomotor activity, or fine motor control were found.[7] In tests of cognitive function, object learning was significantly impaired, but no effect on spatial learning was observed.[8] When the monkeys were placed in social groups, altered social behavior was observed.[7,9] This lowest-observed-adverse-effect level (LOAEL) was classified as minimal—an uncertainty factor of 90 was used for MRL derivation (see TABLE 2).

Rier *et al.*[10] identified a less serious LOAEL of 5 ppt (0.00012 μg/kg/day) for moderate endometriosis. However, monkeys appear to be more susceptible to endometriosis, based on a background incidence of endometriosis (in monkeys) of 30%[10] compared with a background incidence of 10% in humans.[11] Thus, derivation of a chronic oral MRL based on endometriosis would necessitate using an uncertainty factor of at most 1 to account for the increased sensitivity of monkeys to endometriosis as compared with humans. ATSDR considered using the Rier *et al.*[10] study to calculate an oral MRL, based on the LOAEL of 0.00012 μg/kg/day divided by an uncertainty factor of 100 (10 to extrapolate from a LOAEL, 10 for human variability, and 1 for interspecies differences). This would have resulted in a computed MRL that was essentially the same as the chronic oral MRL of 1 pg/kg/day based on developmental toxicity, as described in the preceding paragraph. Moreover, (1) the clinical history for these rhesus monkeys during the 10-year period between the Schantz *et al.*[9] study and examination by Rier *et al.*[10] is unknown (not reported); (2) Boyd *et al.*[12] did not find an association between exposure to chlorinated dibenzo-*p*-dioxins (CDDs), chlorinated dibenzofurans (CDFs), or polychlorinated biphenyls

TABLE 2. Comparison of MRLs for 2,3,7,8-TCDD derived in 1989 and 1997

Year	Exposure duration	MRL in pg/kg/d	UF LOAEL/NOAEL	UF interspecies	UF sensitivity	Endpoint	See reference
1989	acute	1000	10	10	10	LOAEL for hepatic focal necrosis and hypertrophy	25
1997	acute	200	1	3	10	NOAEL for immunological effects	26
1989	intermediate adopted also as chronic	1	10	10	10	LOAEL for reproductive, abortions and developmental effects	22, 23
1997	chronic	1	3	3	10	LOAEL for neurobehavioral developmental effects	9

NOTE: The MRL is calculated as MRL = (NOAEL or LOAEL)/(UF × MF), where MRL is the minimal risk level (mg/kg/day), NOAEL is the no-observed-adverse-effect level (mg/kg/day), LOAEL is the lowest-observed-adverse-effect level (mg/kg/day), UF is the uncertainty factor (dimensionless), and MF is the modifying factor (dimensionless).

(PCBs) and endometriosis in a clinical study in women; and (3) the U.S. Environmental Protection Agency (EPA)[13] concluded that "the evidence for supporting the hypothesis that CDDs and PCBs are causally related to human endometriosis via an endocrine-disruption mechanism is very weak." Thus, even though there is information to indicate that endometriosis may also be a sensitive toxicological endpoint for 2,3,7,8-TCDD exposure, the developmental endpoint (altered social behavior) reported in the Schantz *et al.*[9] study was determined to be the most appropriate endpoint for derivation of an MRL for chronic oral 2,3,7,8-TCDD exposure.

Approach to Calculation of MRLs Is Based on Incomplete Knowledge

By definition, a minimal risk level (MRL) is an estimate of the daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.[2,14] The formula for derivation of an oral MRL is:

$$\text{MRL} = \frac{\text{NOAEL (LOAEL)}}{\text{UF} \times \text{MF}},$$

where MRL is the minimal risk level (mg/kg/day), NOAEL is the no-observed-adverse-effect level (mg/kg/day), LOAEL is the lowest-observed-adverse-effect level (mg/kg/day), UF is the uncertainty factor (dimensionless), and MF is the modifying factor (dimensionless).

Traditionally, the operational approach to lack of data has been the use of analytic steps to address the scientific uncertainty. UFs are used to account for uncertainties associated with extrapolation from a LOAEL to a NOAEL and from animal to human data, and to provide adjustments for intraspecies variability. UFs with default values of ten are usually used for all three of the previously cited categories of extrapolation. A factor of ten is used for a LOAEL, if a NOAEL was not identified, for the purposes of low dose extrapolation (i.e., to identify a biologically plausible NOAEL). This adjustment is supported by analyses of several chemicals for which at least one experimental NOAEL and LOAEL were available. These analyses indicate that dividing the lowest LOAEL by a factor of ten usually yields a value that is less than the experimental NOAEL in 95% of cases.[15,16]

Although humans are qualitatively similar to other animals with respect to health outcomes following exposures, interspecies differences do exist. Significant variations may arise from toxicokinetic and toxicodynamic differences in interactions between organisms and toxic chemicals that are species-specific. UFs of 10 have been used to offset the uncertainties surrounding these differences. Dourson and Stara[15] support the use and selection of this uncertainty factor. That support is based on empirical evidence in the literature suggesting that the tenfold reduction in animal dose is sufficient to encompass the variability between animals and humans 95% of time.

Conditions that may enhance susceptibility to adverse health effects include age, sex, genetic make-up, nutritional status, and preexisting disease conditions. UFs of 10 are usually used to derive MRLs that are protective of these sensitive subpopulations. Following an extensive literature review, Calabrese[17] concluded that the commonly used UF of 10 seems to provide protection for 80% to 95% of the human population. Recently, however, some policy makers, in order to be protective of children's health, suggest applying an additional margin of safety for exposure to infants

and children so as to account for potential toxicity and incompleteness of the database.

Combining UFs without further evaluation can lead to overestimation of the actual risk. For example, if two factors of 10 are multiplied and each factor encompasses an extrapolation at the 95% level, the product will result in an estimate that is more conservative than the 95% level (i.e., in the direction of the 99% level or greater).

Under current ATSDR methodology, default UFs of 10 are applied to extrapolate from a LOAEL to a NOAEL, for interspecies extrapolation, and for intraspecies variability. However, chemical-specific toxicity and toxicokinetic information have sometimes made it necessary and appropriate to deviate from using the standard UF of 10.[1,2] Once again, MRLs for 2,3,7,8-TCDD can be used to provide examples for decreasing uncertainty based on the available data.

A UF of 3 instead of 10 was used in computing the chronic oral MRL for 2,3,7,8-TCDD for the extrapolation from a LOAEL to a NOAEL No overt signs of toxicity were observed in the mothers or offspring, and birth weights and growth were not adversely affected by 2,3,7,8-TCDD exposure. Significant alterations were observed in play behavior, displacement, and self-directed behavior in the 2,3,7,8-TCDD-exposed offspring. 2,3,7,8-TCDD-exposed monkeys tended to initiate more rough-and-tumble play bouts and retreated less from play bouts than controls; they were less often displaced from preferred positions in the playroom than the controls; and they engaged in more self-directed behavior than controls. No other significant alterations in behavior or alterations in reflex development, visual exploration, locomotor activity, or fine motor control were noted.[7] In tests of cognitive function, object learning was significantly impaired, but no effect on spatial learning was observed.[8] In summary, only some of the results from a battery of tests showed significant changes. Therefore, the overall evaluation of seriousness of these effects was reduced.

A UF of 3 instead of 10 was used to extrapolate from animals to humans in deriving the chronic oral MRL for 2,3,7,8-TCDD. A comparison of species sensitivity suggests that even though there are wide ranges of sensitivity for some 2,3,7,8-TCDD-induced health effects, for most health effects the LOAELs for the majority of animal species cluster within an order of magnitude. Based on the weight of evidence of animal species comparisons, and human and animal mechanistic data, it is reasonable to assume that human sensitivity would fall within the range of animal sensitivity. This causes the uncertainty to be lowered. On the other hand, neurobehavioral toxicity is a recently developed discipline; not enough data are yet available to develop animal models that parallel or convincingly simulate known effects in humans. Evidence of similarities may often be concealed by inadequate testing or interpretation of data, interspecies differences in developmental maturity of the central nervous system (CNS), and differences in behavioral patterns. A UF of 3 for interspecies extrapolation acknowledges these differences and the reservations associated with them.

In contrast, a UF of 10 for human variability was not changed. A UF for intraspecies differences was introduced to account for differences in response to toxic chemicals and to protect sensitive individuals. Age, sex, genetic composition, nutritional status, and preexisting diseases may all alter susceptibility to hazardous chemicals.

The MRL was based on studies in very young animals. It is reasonable to assume that young children with developing neurological systems would be protected. However, uncertainties in the genetic make-up (e.g., differences in Ah receptors) would preclude decreasing the UF.

The level of uncertainty has also been addressed by modifying factors. For example, in the derivation of an acute oral MRL for 2,3,7,8-TCDD, a modifying factor of 0.7 was applied to adjust for the differences in higher bioavailability of 2,3,7,8-TCDD from gavage with an oil vehicle than from food. Support for this modifying factor comes from toxicokinetic studies in Sprague Dawley rats. In rats fed 0.35 or 1 μg/kg/day 2,3,7,8-TCDD in the diet for 42 days, approximately 60% of the administered dose was absorbed.[18] In contrast, 70%–84% of a single or repeated gavage dose of 0.01–50 μg/kg/day 2,3,7,8-TCDD in corn oil was absorbed in rats.[19,20] Thus, the ratio of 2,3,7,8-TCDD absorption from the diet to gavage with an oil vehicle is 0.71–0.85.

Sources of Concern

Uncertainty Factors That Are Based on Incomplete Knowledge of Substance-Specific Chemistry or Toxicology

Dioxin and dioxin-like compounds have been studied more than any other type of chemical during the last decade. Although our knowledge has increased greatly, significant scientific uncertainty remains. Increased knowledge about 2,3,7,8-TCDD toxicity was reflected in changes that MRLs underwent over the decade (TABLE 2). For example, the acute oral MRL of 1000 pg 2,3,7,8-TCDD/kg/day was based on a LOAEL of 0.1 μg/kg/day in 1989.[21] Later studies showed the toxicity of 2,3,7,8-TCDD at even lower levels, and the 1997 MRL was based on a NOAEL of 0.005 μg/kg/day (the LOAEL in this study was 0.01 μg/kg/day).[5] This would have resulted in deriving an MRL of 50 pg/kg/day, using the UF of 10 each for interspecies extrapolation and intraspecies variability. However, greater knowledge about 2,3,7,8-TCDD toxicity enabled ATSDR to lower the uncertainty and to use an MF that resulted in an MRL of 200 pg/kg/day. In summary, as an outcome the new MRL is protective but not overly conservative.

In 1989, the LOAEL of 0.001 μg/kg/day was used in deriving the intermediate-duration oral MRL of 1 pg/kg/day. At this exposure level, dilated pelvises and changes in gestational index were observed in rats,[22] and abortions were reported in monkeys.[23] A UF of 10 was used to extrapolate from animals to humans, a factor of 10 for human variability, and a factor of 10 for the use of a LOAEL. The intermediate-duration exposure MRL was adopted for chronic exposure. No UF was used to extrapolate across durations. In 1997, 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 ± 0.4 months.[9] An uncertainty factor of three was used for extrapolation from animals to humans, a factor of 10 for human variability, and a factor of three for the use of a LOAEL. In summary, although based on a lower LOAEL, the final value is the same because of the decreased uncertainty. From that, results our greater confidence in the new value.

Recognition That the Larger the Uncertainty, the Higher the Cost to Society

Discernment of real threats to public health is harder when uncertainty is high. A preeminent feature of the ATSDR mission statement is the concept of prevention. This concept extends not only to the prevention of exposure and disease, but also to diminished quality of life. Pollution and the attendant health risk potentially arising from pollution can directly impact quality of life—not only in terms of direct health effects but also in terms of lost resources.

Dioxin and other pollutants such as mercury and PCBs make significant contributions to pollutant body burdens in human populations. The primary pathway of exposure is via the diet, with fish accounting for approximately 95% of total exposure.[24] In public health practice, the precautionary principle dictates that in the face of uncertainty, larger margins of safety (sometimes referred to as margins of exposure) are invoked in the interest of public health. If potential risk is overestimated due to data limitations or gaps, natural resources may be perceived as unsafe.

Furthermore, "[t]he identification of a threshold body burden/blood serum level, below which adverse health effects are not anticipated, would help to better define potential health risks at sites contaminated with dioxin and dioxin-like compounds. However, since significant uncertainties remain regarding such levels, especially for at-risk populations by virtue of exposure or physiologic sensitivity, a threshold level cannot be identified at present".[3,4]

High social and financial cost when we try to solve every perceived problem. The same is true of hazardous waste sites and abandoned industrial sites (*brown fields*). In practice, there is a big difference in cost when cleaning up a hazardous waste site so that the final residue of dioxins is at the 10 ppb, 1 ppb, or 0.1 ppb level. Such levels may be driven by, or considered to be, artifacts of the application of uncertainty factors. Because of the limited budget for environmental clean-up, overprotection at one site may result in lack of funds for another site where the resources are needed.

UNCERTAINTIES ASSOCIATED WITH THE DERIVATION OF EMEGs

Assumptions Used in the Derivation of EMEGs

By definition, an environmental media evaluation guide (EMEG) is a media-specific comparison value that is used to select contaminants of concern at hazardous waste sites.[27] ATSDR uses EMEGs for air, water, and soil. EMEGs for water and soil are calculated from the following formula:

$$\text{EMEG} = \frac{\text{MRL} \times \text{BW}}{\text{IR}}$$

where EMEG is the environmental media evaluation guide (mg/kg), BW is the body weight (kg), and IR is the soil ingestion rate (mg/day).

The assumptions used to develop EMEGs include: (1) exposure occurs 24 hours a day for each day of the exposure period; (2) body weight is 10 kilograms (22 pounds) for a child, and 70 kilograms (154 pounds) for an adult; (3) the ingestion rate for drinking water is two liters per day for adults, and one liter for children; and (4) the ingestion rate for soil is 100 milligrams per day for adults, 200 milligrams per day for children, and 5 grams per day for a geophagic child.

These assumptions bring further inaccuracies into the process. Special attention was given to soil ingestion rates in several studies. Soil ingestion rates are assumptions that are included in the derivation of EMEGs. ATSDR uses assumptions based on a consumption of 100 mg/day for adults and 200 mg/day for children. The soil ingestion for children is based on studies[28,29] that estimated the average soil ingestion in populations of normal children. In their calculations, Kimbrough *et al.*[30] assumed that children between 1.5 and 3.5 years of age ingest about 10 g of soil daily, and their risk assessment was based on "extreme total daily dose estimates". This estimate was later disputed, and several studies were conducted to evaluate the daily intake of soil by children. One of the reports suggested that an average child ingests only about 25–40 mg of soil daily.[31] However, about 1%–2% of children are geophagic and ingest from 5 to 10 g of soil daily.[32] Uncertainties associated with this issue are acknowledged, but ATSDR[27] views ingestion rates of 100 mg/day and 200 mg/day for adults and children, respectively, to be reasonable. In the event that geophagic children are at risk, ATSDR considers this issue further in the public health assessment.

Other Limitations and Uncertainties Encountered in Developing the ATSDR Policy Guideline for Dioxin and Dioxin-like Compounds

Dioxin and dioxin-like compounds serve as good examples of the multiple uncertainties that have to be considered in deliberations on health-based guidance values. As excerpted from the De Rosa *et al.* papers,[3,4] additional limitations and uncertainties were considered in outlining the ATSDR policy guideline.

Bioavailability

Bioavailability is an integral factor in the estimation of the internal dose (or dose at target-tissue) of the chemical. The gastrointestinal absorption of 2,3,7,8-TCDD and related compounds is variable, incomplete, and is congener- and vehicle-specific. More lipid-soluble congeners, such as 2,3,7,8-tetrachlorodibenzofuran, are almost completely absorbed, however, the extremely insoluble, octachlorodibenzodioxin is less well absorbed depending on the dose regimen; high doses may be absorbed at a lower rate, whereas low repetitive doses may be absorbed at a greater rate. The only study of 2,3,7,8-TCDD bioavailability in humans was reported by Poiger and Schlatter[33] and was based on a single male in which the gastrointestinal absorption exceeded 87% when 2,3,7,8-TCDD was administered in corn oil.

Laboratory data suggest that there are no major interspecies differences in the gastrointestinal absorption of CDDs and CDFs. However, absorption of 2,3,7,8-TCDD depends on conditions and characteristics of the soil medium; in animals, absorption of 2,3,7,8-TCDD from different soils ranged from 0.5%[34,35] to 50%.[35] Absorption from a diet was 50%–60% in rats.[18] Therefore, exposure, with food as a vehicle rather than oil, relates more closely to exposure from soil. Bioavailability has to be considered when calculating the hypothetical ingestion dose.

If it is assumed that 100% of 2,3,7,8-TCDD is bioavailable, the risk may be overestimated. The health assessor should recognize that other assessors may have used different assumptions in their calculations. Kimbrough *et al.*[30] assumed 30% bioavailability from ingestion of soil, but pointed out that animal studies with contaminated Missouri soil indicated absorption up to 30%–50%.[37] Pohl *et al.*[38] assumed

40% bioavailability from soil. In contrast, Paustenbach *et al.*[39] estimated bioavailability at 10%–30%. Unless toxicokinetic studies that use soil samples from the specific site are available, it is difficult to speculate about the quantity of 2,3,7,8-TCDD and related compounds that will be absorbed. Therefore, the estimate of the actual intake has limitations.

The chronic MRL is based on studies where food was the vehicle. Results from animal studies indicate that bioavailability of 2,3,7,8-TCDD from soil varies between sites because dioxin and dioxin-like compounds bind tightly to soil—increasingly so with the passage of time and clay content of soil.[31] Therefore, 2,3,7,8-TCDD content alone may not be indicative of the potential for human health hazard from contaminated environmental materials Again, site-specific evaluation is essential.

Background Exposure

EMEGs represent an estimate of exposure dose from one source only. All relevant sources of exposure from the hazardous waste site and all possible background exposures should be included in the final evaluation of actual exposure.

Dioxin and dioxin-like compounds are known to readily enter the food chain. It has been estimated that about 98% of exposure occurs through food. It should be noted that the average background intake of TCDD and of total TEQs of dioxin and dioxin-like compounds for adults in the general population were estimated as 0.35 pg/kg/day and 1.9 pg/kg/day, respectively.[40] Furthermore, it is important to consider the background level of dioxin and dioxin-like compounds in contaminated soil. The U.S. background 2,3,7,8-TCDD soil levels ranged from undetected to 10 ppt in industrialized areas of groups of midwestern and mid-Atlantic states.[41]

Exposure from Soil by Different Routes

Kimbrough *et al.*[30] estimated that the lifetime uptake of 2,3,7,8-TCDD from soil consists of 95% from soil ingestion, 3% from soil dermal exposure (assuming 1% dermal absorption), and 2% from inhalation. Paustenbach *et al.*[39] indicated that the 1% dermal absorption proposed for 2,3,7,8-TCDD–contaminated soil may be too high. Similarly, he further lowered the estimates of inhalation intake, speculating that 2% from inhalation may be too high.

Unless indicated otherwise by the specific on-site circumstances, exposure by routes other than oral can be considered to be insignificant.

Exposure to Dioxin-like Compounds

Dioxin-like compounds, or related chemicals, are other compounds containing chlorine or bromine whose molecules are similar on shape to 2,3,7,8-TCDD and that produce similar toxic effects. These include some other dioxin congeners, some furan compounds, some PCBs, and some polybrominated biphenyls (PBBs).[42] TEQs are used to estimate toxicity of dioxin-like compounds (see TABLE 3).

Some of the assumptions for using the TEQ approach cover a well-defined group of chemicals, a broad database of information, consistency across endpoints, additivity of effects, and a common mechanism of action.[43] According to EPA guidelines for risk assessment of complex mixtures, potency-weighted additivity is assumed for mixtures in the absence of information to the contrary.[44]

TABLE 3. World Health Organization TEFs for humans, mammals, fish, and birds

Congener	Humans/mammals	Fish[a]	Birds[a]
2,3,7,8-TCDD	1	1	1
1,2,3,7,8-PeCDD	1	1	1[f]
1,2,3,4,7,8-HxCDD	0.1[a]	0.5	0.05[f]
1,2,3,6,7,8-HxCDD	0.1[a]	0.01	0.01[f]
1,2,3,7,8,9-HxCDD	0.1[a]	0.01[e]	0.1[f]
1,2,3,4,6,7,8-HpCDD	0.1	0.001	<0.001[f]
OCDD	0.0001[a]	—	—
2,3,7,8-TCDF	0.1	0.05	1[f]
1,2,3,7,8-PeCDF	0.05	0.05	0.1[f]
2,3,4,7,8-PeCDF	0.5	0.5	1[f]
1,2,3,4,7,8-HxCDF	0.1	0.1	0.1[c,f]
1,2,3,6,7,8-HxCDF	0.1	0.1[c]	0.1[c,f]
1,2,3,7,8,9-HxCDF	0.1[a]	0.1[c,e]	0.1[c]
2,3,4,6,7,8-HxCDF	0.1[a]	0.1[c]	0.1[c]
1,2,3,4,6,7,8-HpCDF	0.01[a]	0.01[b]	0.01[b]
1,2,3,4,7,8,9-HpCDF	0.01[a]	0.01[b,e]	0.01[b]
OCDF	0.0001[a]	0.0001[b,e]	0.0001[b]
3,4,4′,5-TCB (81)	0.0001[a,b,c,e]	0.0005	0.1[e]
3,3′,4,4′-TCB (77)	0.0001	0.0001	0.05
3,3′,4,4′,5-PeCB (126)	0.1	0.005	0.5
3,3′,4,4′,5,5′-HxCB (169)	0.01	0.00005	0.001
2,3,3′,4,4′-PeCB (105)	0.0001	<0.000005	0.0001
2,3,4,4′,5-PeCB (114)	0.0005[a,b,c,d]	<0.000005[b]	0.0001[g]
2,3′,4,4′,5-PeCB (118)	0.0001	<0.000005	<0.00001
2′,3,4,4′,5-PeCB (123)	0.0001[a,c,d]	<0.000005[b]	0.00001[g]
2,3,3′,4,4′,5-HxCB (156)	0.0005[b,c]	<0.000005	0.0001
2,3′,4,4′,5′-HxCB (157)	0.0005[b,c,d]	<0.000005[b,c]	0.0001
2,3′,4,4′,5,5′-HxCB (167)	0.00001[a,d]	<0.000005[b]	0.00001[g]
2,3,3′,4,4′,5,5′-HpCB (189)	0.0001[a,c]	<0.000005	0.00001[g]

[a]Limited data set.
[b]Structural similarity.
[c]Quantitative structure activity relationships (QSAR) modeling prediction from CYP1A induction (monkey, pig, chicken, or fish).
[d]No new data from 1993 WHO review.
[e]*In vitro* CYP1A induction.
[f]*In vivo* CYP1A induction after *in ovo* exposure.
[g]QSAR modeling prediction from class-specific TEFs.
SOURCE: Table derived from Van den Berg, *et al.*[45]

Limitations associated with the use of TEQs must be considered in developing health guidance values. TEQs are derived using toxicity equivalency factors (TEFs) that are constants determined from experimental studies for each congener. Although TEFs are considered to be constants, they are dependent on the specific study (endpoint, dose, and duration of exposure).

As defined, TEQs are assumed to be additive and neither synergistic nor antagonistic. In actual mixtures of dioxin and dioxin-like compounds, competitive inhibition may occur at sufficiently high doses. As with MRLs and EMEGs, biomedical judgment must be used in considering site-specific conditions that would reasonably modify the estimates to be applicable to an individual site.

CONCLUSIONS

Defining the Status Quo

In summary, this paper illustrates the use of dioxin and dioxin-like compounds to illustrate that the methodology for deriving health guidance values encompasses two kinds of uncertainty issues, both of which comprise less than certain science. The upper portion of the box in FIGURE 1, represents the area of the basic toxicology practice and endpoints used in risk assessment. This portion of the box contains the assumptions that underlies the use of traditional toxicology and, less often, epidemiology data as the starting point for estimating health guidance levels. The lower half of the box represents the traditionally applied uncertainty factors, including default values, used in the calculations.

Identifying a New Approach

To date, efforts to think "out of the box" have been almost exclusively confined to the lower half of the box (see FIGURE 2). These efforts have led to the development of analytic methodologies that refine the uncertainty factors. Although these methods have not removed all the uncertainty in health guidance values, in many cases they have increased confidence in these estimates or increased the biological plausibility of a significant effect level. Continuous decrease of factors of ten, based on greater scientific knowledge, may be one approach, as demonstrated in this paper. However, there are other methods that decrease the reliance on default values. Scientists and health assessors should be encouraged to use these methods more often.

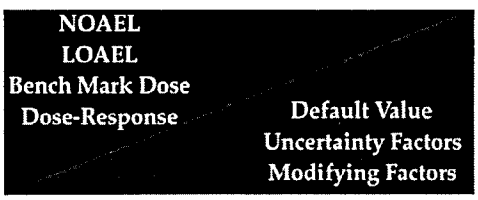

FIGURE 1. Recommendations/framework. Defining the status quo.

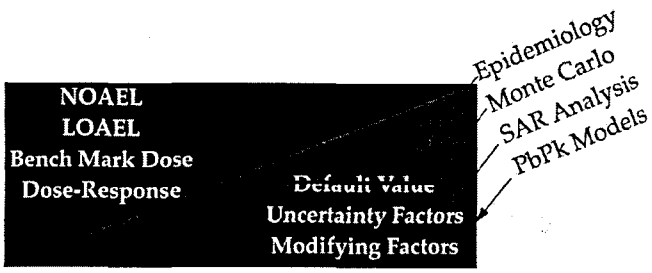

FIGURE 2. Identifying a new approach.

Two broad issues surrounding the use of these methodology refinements have been identified. The first is that complex methods have the potential to obscure the degree of uncertainty that remains after their use. The complexity of the analysis provides an artificial sense of precision. The second issue is that the refinements do not meet the criteria for a paradigm shift in scientific thinking. ATSDR envisions this exercise of refining uncertainty factors as a step out of the box for a better tool, which is then used in an essentially unchanged process. The basis of the ATSDR approach is to provide the highest level of protection for the most people in the population, recognizing that every individual in the population may not experience the same level of protection. Inherent in public health approaches is the variability of the means related to individual genotypes and variability in environmental exposures. The unchanged process, which is based on fundamental principles of toxicology, is anchored solidly in the concept of risk assessment held by the scientific community. Identifying new scientific approaches, difficult enough in itself, is probably not nearly so difficult as effecting a genuine paradigm shift among scientists and policy makers.

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Uncertainty in Risk Assessment

MARCEL VAN DEN BROECKE[a]

International Statistical Institute, Prinses Beatrixlaan 428, Voorburg, The Netherlands

The meeting from which this volume results, grew from an initiative of John C. Bailar and the International Statistical Institute to organize a cutting edge workshop on risk assessment. We were pleasantly surprised by the positive response received from industry, from academic circles, and from government agencies in Italy and elsewhere.

Why is it that a volume on risk assessment within the context of environmental and occupational safety fulfils such a clear need and has attracted papers from authors in Western Europe, the USA, Canada, Japan, and New Zealand? Because we all recognize the need to improve our understanding of the sources and nature of uncertainty in the risk assessment process, to reduce this uncertainty, and to develop policy measures accordingly.

Risk in a statistical context was defined by Bullock *et al.*, as those circumstances where the different outcomes and their probabilities are known objectively or subjectively. In the latter case, we are talking about perceived risks, and we all know how deceptive perceptions can be. Marriot is more straightforward, with the definition in his Dictionary of Statistical Terms (incidentally an ISI publication): "*risk* in statistics is a word used in its ordinary sense."

Risk, then, is the probability that something unpleasant may happen. In this volume, we focus on the necessity to assess unpleasant risks as they occur in the environment and in the work place. It is well recognized by statisticians in industry, academia, and governmental agencies that policies to assess risks and to minimize risks require a better understanding of their nature and causes than we presently have available. This is a more mature approach than to require that the probability of running risks should be zero. Desirable as that may be, we all know that there is no such thing as life without risks. I am confident that this volume will help us to understand the nature of risks so that we can manage them—if we cannot exclude them.

I want to conclude by congratulating the organizers of the workshop, specifically John C. Bailar, A. John Bailer, and Cesare Maltoni, for their excellent preparations.

[a]Address for correspondence: Marcel van den Broecke, Director of the International Statistical Institute, Prinses Beatrixlaan 428, 2273X2 Voorburg, the Netherlands. 31-70-3375737 (voice); 31-70-3860025 (fax).
e-mail: isi@cbs.nl