REGULATORY TOXICOLOGY AND PHARMACOLOGY 26, 322–329 (1997)
ARTICLE NO. RT971171

Public Health Guidance Values for Chemical Mixtures: Current Practice and Future Directions

Hana R. Pohl,[1] Hugh Hansen, and C.-H. Selene J. Chou

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

Received July 14, 1997

Agency for Toxic Substances and Disease Registry (ATSDR) utilizes chemical-specific minimal risk levels (MRLs) to assist in evaluating public health risks associated with exposure to hazardous substances. The MRLs are derived based on the data compiled from current worldwide literature searches and presented in ATSDR's toxicological profiles. These documents profile not only individual chemicals, but also groups of chemically related compounds and chemical mixtures. ATSDR took several approaches when developing MRLs for chemical mixtures. In some instances, toxicity equivalency factors were used to estimate the toxicity of the whole mixture; in other instances, the most toxic chemical was assumed to drive the health assessment for the whole mixture. Another approach was to treat the mixture as one entity and develop a health guidance value for the whole mixture. In yet another approach, each chemical of the mixture was evaluated separately and several health guidance values were developed. In the future, ATSDR will evaluate priority chemical mixtures found at hazardous waste sites. A weight-of-evidence approach, physiologically based pharmacokinetic modeling and benchmark dose modeling, and quantitative structure–activity relationships will have an impact on the development of MRLs and the assessment of chemical mixtures.

CHEMICAL MIXTURES—OVERVIEW

A growing number of chemicals are introduced into the marketplace on a weekly basis. Of the approximately 7 million total chemicals, 70,000 are in current use with more than 1,000 added each year worldwide (Newill, 1989). Until recently, research efforts have been focused primarily on the toxicology of individual chemicals. In turn, risk assessment activities have been largely concerned with individual chemical exposures, disregarding the complexities of multiple chemical exposures. The dilemma of predicting the health consequences of multiple chemical exposures is not new. The problem has been studied for more than 60 years, but the challenges presented by multiple chemical exposures remain unmet without a clear framework nor a fundamental methodology for predicting health risks to such exposures.

Although data are frequently not adequate to assess the toxic effects of individual chemicals, even less data may be available on the toxicity of chemical mixtures. For example, with the exception of epidemiological studies, most of the available toxicological data are obtained from laboratory studies, predominantly on individual chemicals. Most of these studies involve high doses to assure detection of any potential adverse responses. However, populations near hazardous waste sites are rarely exposed to individual chemicals and except for acute emergency situations, they are not exposed to high doses. Usually, exposures are to mixtures of chemicals at low doses from multiple sources and through multiple routes. The composition of such mixtures may vary with time, and human exposure levels may not be quantifiable.

The behavior of chemicals in mixtures may differ greatly from that observed for individual chemicals. Interactions of the mixture components may alter the toxicity and carcinogenicity through mechanisms such as potentiation or inhibition. Such interactions are postulated to result from chemically mediated alterations in a variety of biological processes such as absorption, distribution, metabolism, and excretion, which influence the internal dose of a chemical. These complexities open a wide variety of research areas to chemical mixtures research including pharmacokinetics, mechanistic studies, the identification of biomarkers, and development of qualitative and quantitative health assessment methods. Because toxicity data are generally not available on human health effects from exposure to specific chemical mixtures, assessment may rely on

[1] To whom correspondence should be addressed at ATSDR, Mailstop E-29, 1600 Clifton Road, Atlanta, GA 30333.

0273-2300/97 $25.00

predictive estimates of risk. Of particular concern for chemical interactions is the use of extrapolation, from *in vitro* to *in vivo,* from high dose to low dose, and from animal to human.

Section 104 of the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) as amended by Section 110 of the Superfund Amendments and Reauthorization Act (SARA) established the requirement for ATSDR to develop methods to determine the health effects of chemical mixtures found at hazardous waste sites. From its inception, the agency has been concerned about the health effects of exposure to individual chemicals. Thus, individual chemicals identified at toxic waste sites are listed in priority order based on their frequency of occurrence at hazardous waste sites, their toxicity, and the potential for exposure (ATSDR, 1996a); from this priority list, ATSDR's toxicological profiles for these chemicals are developed.

PUBLIC HEALTH GUIDANCE VALUES—CURRENT PRACTICE

ATSDR utilizes chemical-specific minimal risk levels (MRLs) to assist in evaluating public health risks associated with exposure to hazardous substances. By definition, "MRLs are estimates of daily human exposure to a chemical that are likely to be without an appreciable risk of adverse noncancer health effects over a specified duration of exposure." The MRLs are derived based on the data compiled from current worldwide literature searches and presented in ATSDR's toxicological profiles. The methodology for deriving MRLs has been described elsewhere (ATSDR, 1996b; Pohl and Abadin, 1995). Briefly, the MRL is usually based on the highest no-observed-adverse-effect level (NOAEL) or lowest-observed-adverse-effect level (LOAEL) for the most sensitive end point.

Uncertainty factors (UFs) are applied to account for intrahuman variation, interspecies extrapolation, and LOAEL to NOAEL extrapolation. Modifying factors (MFs) may be applied to reflect additional concerns not covered by the UFs.

Since their establishment, the toxicological profiles have described not only individual chemicals (for which MRLs were originally designed), but also groups of chemically related compounds and chemical mixtures. Based on available data, ATSDR dealt with these mixtures on a case-by-case basis as described in the following approaches. As summarized in Table 1, ATSDR used these four approaches:

1. Selected the most toxic chemical from the mixture and provided a health guidance based on the MRL for this chemical. Then used toxicity equivalents (TEQs) to estimate toxicity of the whole mixture.
2. Treated the mixture as one entity and developed a health guidance for the whole mixture.

TABLE 1
ATSDR's Approaches to MRLs Derivation for Selected Mixtures

MRLs for one chemical in a mixture	MRLs for the whole mixture	MRLs for several chemicals in a mixture	No MRLs derived
CDDs CDFs	PCBs PBBs Jet fuels Otto fuel II Fuel oils	PAHs	Automotive gasoline Stoddard solvent Hydraulic fluids Mineral-based crankcase oil

3. Treated each chemical from the mixture separately and developed several health guidance values.
4. Did not derive an MRL for a mixture. When considered appropriate, the most toxic chemical from the mixture was selected and assumed to drive the risk assessment.

The First Approach Was Designed to Use TEQs to Estimate Toxicity of the Whole Mixture

Chlorinated dibenzo-p-dioxins (CDDs). The basic chemical structure is a dibenzodioxin molecule that consists of two benzene rings joined at their *para* carbons by two oxygen atoms. Based on the number and position of chlorine substituents, there are 75 congeners in the CDDs group (ATSDR, 1997). The most studied congener is 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD).

ATSDR's guidance values for TCDD were based on animal studies presented in the Toxicological Profile for CDDs (ATSDR, 1997). The acute oral MRL of 70 pg/kg/day was based on the NOAEL of 0.005 μg/kg/day TCDD in mice. Decreased immunocompetence was reported at 0.01 μg/kg/day TCDD administered once by gavage in oil vehicle (Burleson *et al.,* 1996). A UF of 30 (3 for animal to human extrapolation and 10 for human variability) and an MF of 0.7 (to adjust for gavage oil route of exposure) were used for MRL calculation. The intermediate-duration oral MRL of 20 pg/kg/day was based on a NOAEL of 0.0007 μg/kg/day TCDD for decreased thymus weight in guinea pigs exposed in their feed for 90 days (DeCaprio *et al.,* 1986). Also from this study, a supporting NOAEL of the same value was identified for liver toxicity. The liver effects reported at higher levels were hepatocellular inclusions and hypertriglyceridemia. A UF of 30 was used for MRL calculation (3 for animal to human extrapolation and 10 for human variability). The chronic oral MRL of 1 pg/kg/day TCDD was based on a LOAEL for mild learning and behavioral impairment in the offspring of monkeys exposed to 0.00012 μg/kg/day TCDD in their feed

(Schantz *et al.,* 1992). A UF of 90 was used in the calculation (3 for use of a minimal LOAEL, 3 for animal to human extrapolation, and 10 for human variability).

Chlorinated dibenzofurans (CDFs). Dibenzofuran is an organic compound containing two benzene rings fused to a central furan ring. Based on the number and position of chlorine substituents, there are 135 congeners in the CDFs group (ATSDR, 1994). Oral MRLs were derived for 2,3,4,7,8-pentaCDF, the most toxic congener, in the database presented in the Toxicological Profile for CDFs (ATSDR, 1994). The acute oral MRL of 1000 pg/kg/day for 2,3,4,7,8-pentaCDF was based on a LOAEL for mild thymic lymphoid hypoplasia identified in guinea pigs following a single gavage dose in corn oil (Moore *et al.,* 1979). A UF of 1000 (10 for use of a LOAEL, 10 for animal to human extrapolation, and 10 for human variability) and MF of 3 (for lack of neurological studies in animals) were used in the calculation. The intermediate duration MRL of 30 pg/kg/day was based on a LOAEL for hepatic effects in rats exposed for 13 weeks to 2,3,4,7,8-pentaCDF in feed (Pluess *et al.,* 1988; Poiger *et al.,* 1989). The observed effects included increased serum bilirubin and decreased serum triglycerides. A UF of 1000 (10 for use of a LOAEL, 10 for animal to human extrapolation, and 10 for human variability) and MF of 3 (for lack of neurological studies in animals) were used in the calculation.

CDDs and CDFs are structurally and toxicologically related groups of chemicals that usually occur in the environment together. CDDs and CDFs are believed to act through the same Ah receptor-mediated mechanism of toxicity that has been described in detail in several publications (ATSDR, 1994, 1997; Birnbaum, 1994). To assess the risk associated with exposure to mixtures of CDDs and CDFs, the Environmental Protection Agency (EPA) (1989a) developed toxicity equivalency factors (TEFs) that compare the relative toxicity of individual CDD and CDF congeners to that of TCDD, the most toxic and extensively studied chemical from the halogenated aromatic hydrocarbons group. The TEF for TCDD is 1; all others are <1, thus indicating the lower potency of other dioxin-like compounds. TEQ is defined as the product of the concentration of an individual dioxin-like compound in a complex environmental mixture and the corresponding TCDD toxicity equivalency factor for that compound. The total TEQ is the sum of the TEQs for each of the congeners in a given mixture. Assuming additivity of the toxic response, generated TEQs can be used to estimate the toxicity of an environmental mixture containing a known distribution of CDDs or CDFs relative to that of TCDD. For existing TEFs of selected dioxin-like compounds, see the relevant toxicological profiles (ATSDR, 1994, 1997). The system was also endorsed by the World Health Organization (Ahlborg *et al.,* 1994).

Some uncertainties and limitations are still associated with the TEFs approach. Some of the assumptions for using this approach include a well-defined group of chemicals, a broad database of information, consistency across end points, additivity of the effects, and a common mechanism of action (EPA, 1989a).

The limitations associated with the use of TEQs must be considered in developing health guidance values. TEQs are derived using TEFs that are constants determined from experimental studies for each congener. Although considered constants, these factors exhibit some variability with dose, duration of exposure, and end point. As defined, TEQs are assumed to be additive. In actual mixtures of dioxin and dioxin-like compounds, competitive inhibition may occur at sufficiently high doses. However, there is a lack of knowledge regarding actual direction of possible interactions in any specific mixture of dioxin-like compounds. 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 (EPA, 1987). Because of the existing data gaps, ATSDR is adopting the additivity approach as well.

Assuming that the conditions set for the TEF system are valid, we could anticipate that the health guidance values derived for dioxin-like chemicals are similar. That is, the estimates of daily human exposure to specific congeners of dioxin-like chemicals that are likely to be without risks of adverse noncancer health effects (MRLs) should also be similar when adjusting for the relative potency in the toxicity of each specific congener. When the respective proposed MRLs for TCDD and 2,3,4,7,8-pentaCDF were expressed in TEQs and compared with each other, there was a good correlation between intermediate-duration oral MRLs, but not for acute-duration oral MRLs (Pohl and Holler, 1995). Correlation between the intermediate-duration exposure health risk assessment for TCDD and 2,3,4,7,8-pentaCDF was encouraging because these chemicals are likely to stay in the body for a long time (by ATSDR's definition, intermediate-duration exposure is between 15 and 365 days). It must be emphasized, however, that although the studies that served for derivation of these MRLs used different species (guinea pigs and rats, respectively), the toxicity end points (immunological and hepatic for TCDD and hepatic for 2,3,4,7,8-pentaCDF) were comparable. It is not clear if the correlation could hold for different end points.

The Second Approach Was to Treat the Mixture as One Entity and Develop a Health Guidance Value for the Whole Mixture

Examples are from the group of halogenated aromatic hydrocarbons and from the group of petroleum products.

Polybrominated biphenyls (PBBs). PBBs are a group of chemicals that can contain one to ten bromine

atoms attached to the biphenyl structure (ATSDR, 1995a). PBBs can exist in 209 individual congeners, but only about 42 have been synthesized. Commercial mixtures of PBBs are known as FireMaster BP-6, FireMaster FF-1, Bromkal 80, and Flammex B.

The acute oral MRL was derived from a study in rats exposed to an unspecified mixture of PBBs in lecithin liposomes by gavage for 10 days (Allen-Rowlands *et al.,* 1981). An MRL of 0.01 mg/kg/day was based on a NOAEL of 1 mg/kg/day. A UF of 100 (10 for animal to human extrapolation and 10 for human variability) was used in the calculation. Decreased serum levels of thyroid T_4 hormone were observed at $\geq$3 mg/kg/day. Decreased serum T_4 is considered adverse because of unequivocal evidence from numerous studies that the thyroid is a target of PBBs showing a spectrum of effects, including decreases in serum T_3 and T_4 hormone, thyroid enlargement, effects on the follicular cells, and accumulation of colloid droplets (ATSDR, 1995a). Although the mixture of PBBs used in the Allen-Rowlands *et al.* (1981) study was unspecified, it likely contained isomers in which bromine was present in the *meta* and *para* positions, as these isomers are known to result in thymic effects and a wasting syndrome.

Polychlorinated biphenyls (PCBs). PCBs are a group of compounds in which 1 to 10 chlorine atoms are attached to the biphenyl molecule (ATSDR, 1995b). Depending on the number and position of chlorines, there are 209 chlorobiphenyl congeners. In the United States, PCBs were manufactured under the trade name Aroclor. The number that follows the trade name (e.g., Aroclor 1242) indicates that it is a chlorinated biphenyl mixture (12) with a certain percent of chlorine content (42%).

A chronic oral MRL was derived for PCBs based on the toxicity of Aroclor 1254. The MRL of 0.02 μg/kg/day was based on a LOAEL for immunological effects in monkeys exposed to Aroclor 1254 in feed for 23 months (Tryphonas *et al.,* 1989, 1991a,b). Immunological testing of exposed monkeys revealed decreased IgG and IgM levels in response to sheep red blood cells. A UF of 300 (10 for use of a LOAEL, 3 for animal to human extrapolation, and 10 for human variability) was used in the calculation.

As described, ATSDR's MRL for PCBs was based on a commercial mixture. The decision for MRL derivation was influenced by availability of toxicological data. Most laboratory studies were performed with defined commercial mixtures. However, people are environmentally exposed to PCB mixtures of different congeneric composition than commercial mixtures. This is due to the differential partitioning and transformation of the individual congeners in the environment (ATSDR, 1995b). To estimate the health risk associated with environmental mixtures of PCBs, the TEFs method, described in this paper under related halogenated hydrocarbons, was also proposed for PCBs (Ahlborg *et al.,* 1994; EPA, 1991; Safe, 1990, 1994). Again, toxicity of individual PCB congeners was estimated relative to TCDD. All PCB congeners were given TEFs <1, thus reflecting their lower toxic potency. In addition to the limitations already described, the major drawback of this method is that it is designed only for dioxin-like compounds. Dioxin-like compounds are those containing chlorine or bromine on molecules that are shaped similarly to TCDD, produce similar toxic effects, and act through the same Ah receptor-related mechanism of action (Schierow, 1995). Some coplanar PCBs match this description; only about 13 of the total 209 PCB congeners were actually assigned a TEF value. Other PCB congeners may act through different mechanisms of toxicity. Some PCBs-induced effects, e.g., carcinogenic and behavioral, are probably not mediated by the Ah receptor (Ahlborg *et al.,* 1992; Safe, 1990). Further, it is known that, in relation to dioxins, specific PCBs appear to display an antagonistic or synergistic and therefore a nonadditive effect. The TEF approach is potentially useful for evaluating risk associated with exposure to dioxin-like compounds, because it could enable assessments that would account for specific congener composition at particular hazardous waste sites. Because of the knowledge gaps for toxicological data on individual congeners and other limitations stated previously, the method needs further development. Meanwhile, ATSDR's MRL for a specific commercial mixture (Aroclor 1254) is a screening method of choice.

From the group of petroleum products, the following mixtures were considered.

Fuel oils. Fuel oils are complex mixtures of aliphatic and aromatic hydrocarbons that are refined from crude petroleum; their composition varies with the refinery stream from which they are blended (ATSDR, 1995c). The aliphatic alkanes (paraffins) and cycloalkanes (naphthenes) are hydrogen saturated and compose about 80–90% of the fuel oils. Aromatics (e.g., benzene) and olefins (e.g., styrene and indene) constitute 10–20% and 1%, respectively, of the fuel oils. Fuel oil No. 1 (kerosene) is a light distillate that consists mainly of hydrocarbons in the C_9–C_{16} range, whereas fuel oil No. 2 is heavier with hydrocarbons in the C_{11}–C_{20} range. These fuel oils are used as residential heating oils and as diesel fuels.

There are human and animal data on the toxicological effects of fuel oils. However, the database is diverse in that the studies reported on differing fuel oils or mixtures that are not completely alike. Therefore, when deriving MRLs, the diversity was acknowledged. The MRL derived for one type of fuel product does not necessarily apply to another.

An acute inhalation MRL of 0.02 mg/m^3 for diesel fuel (fuel oil No. 2) was based on a LOAEL of 65

mg/m^3 for neurobehavioral effects (mild transient ataxia and central nervous system depression) observed in mice exposed only through the nose in a study by Kainz and White (1984). For MRL derivation, the LOAEL was adjusted for intermittent exposure and divided by a UF of 1000 (10 for extrapolation from LOAEL to NOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

An intermediate inhalation MRL of 0.01 mg/m^3 for fuel oil No. 1 (kerosene) was derived based on a LOAEL of 58 mg/m^3 for decreased blood glucose levels reported in mice exposed for 14 weeks (Starek and Vojtisek, 1986). For MRL derivation, the LOAEL was adjusted for intermittent exposure and divided by a UF of 1000 (10 for extrapolation from LOAEL to NOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

Jet fuels JP-4 and JP-7. Aviation fuels are complex mixtures of hydrocarbon compounds (paraffins, cycloparaffins, naphthenes, aromatics, and olefins) (ATSDR, 1995d). They also contain additives (e.g., antioxidants, icing inhibitors, metal deactivators) determined by the specific use of the respective fuel. Typical detailed composition of jet fuels was described elsewhere (ATSDR, 1995d).

Similar to the approach used for the fuel oils, ATSDR treated the exposure to a jet fuel as exposure to one entity. Exposure to jet fuel components, exhaust, or combustion products was not considered.

An MRL of 9 mg/m^3 was derived for intermediate-duration inhalation exposure to JP-4. The MRL was derived from a LOAEL of 500 mg/m^3 for increased hepatic toxicity in mice reported in a continuous exposure 90-day study (Air Force, 1984). The JP-4 concentration is based on the total hydrocarbon present in the vapors after the original mixture was heated to 50°C. The hepatic changes included vacuolization of cytoplasm of hepatocytes, mainly in the centrilobular region, and increased incidence of fatty degenerative changes. The LOAEL was adjusted to a human equivalent dose and divided by a UF of 300 (10 for use of a LOAEL, 3 for interspecies extrapolation, and 10 for human variability).

An MRL of 0.3 mg/m^3 was derived for chronic-duration inhalation exposure to JP-7. The MRL was based on a LOAEL of 150 mg/m^3 that caused hepatic toxicity (inflammation) in female rats (Air Force, 1991). No such effects were observed in males. The dose was adjusted to a human equivalent and to continuous exposure and divided by a UF of 300 (10 for use of a LOAEL, 3 for interspecies extrapolation, and 10 for human variability).

In the Third Approach, Each Chemical from the Mixture Was Treated Separately and Several Health Guidance Values Were Developed

Polycyclic aromatic hydrocarbons (PAHs). PAHs are a group of chemicals that are formed during the incomplete burning of some organic substances (e.g., coal, oil, gas, garbage) (ATSDR 1995e). More than 100 different PAHs are known. Some occur naturally and others are synthetic. Environmentally, people are usually exposed to a mixture of PAHs. Although information exists on complex mixtures that contain PAHs (e.g., crude oils, coal tars, complex petroleum products), it is difficult to establish the toxicity of individual components of the mixture because of the potential interactions that could take place and the presence of other toxic chemicals in these mixtures. ATSDR's Toxicological Profile for PAHs described the toxicity of 17 individual PAHs for which toxicity data were available. These PAHs were treated separately during the health risk assessment, because some of the PAHs differ with regard to toxicological effects or environmental fate. The reason for disparity is based on electron density associated with the molecule. From that arose the classification of PAHs as alternate (i.e., those having equally distributed electron density) and nonalternate (i.e., those having uneven distribution of electron density from one portion of the molecule to another). As examples, benzo[*a*]pyrene, benz[*a*]anthracene, chrysene, and dibenz[*a,h*]anthracene belong in the alternate group, whereas fluoranthene, benzo[*k*]fluoranthene, benzo[*j*]fluoranthene, and indeno[1,2,3-*c,d*]pyrene belong in the nonalternate group. The toxicological significance of this classification is that alternate and nonalternate PAHs seem to behave differently, for instance, with regard to how they are metabolized to ultimate carcinogens. For more details, see ATSDR (1995e).

From the 17 PAHs described in the profile, MRLs were derived only for acenaphthene, anthracene, fluoranthene, and fluorene. The carcinogenicity classification assigned these chemicals to group D (not classifiable as to human carcinogenicity) (IRIS, 1994). The MRLs were derived as follows.

Acenaphthene. An intermediate-duration oral MRL was based on a LOAEL of 175 mg/kg/day for absolute liver weight in mice treated daily by gavage for 90 days (EPA, 1989b). Liver weight changes, accompanied by microscopic alterations (cellular hypertrophy), were noted in higher dose groups and seemed to be dose related. Relative liver weight was significantly increased in male mice at 175 mg/kg/day, and absolute and relative weights were significantly increased in female mice at 175 mg/kg/day. The exposure level was considered a minimal LOAEL, which when divided by a UF of 300 (3 for a minimum LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability) yielded an intermediate-duration oral MRL of 0.6 mg/kg/day.

Anthracene. An MRL of 10 mg/kg/day was derived for intermediate-duration oral exposure to anthracene. The MRL was based on a NOAEL of 1000 mg/kg/day

for liver effects reported in mice exposed by gavage for 13 weeks (EPA, 1989c). The MRL was obtained by dividing the NOAEL value by a UF of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Fluoranthene. An intermediate-duration oral MRL of 0.4 mg/kg/day was based on a LOAEL of 125 mg/kg/day for liver weight changes in mice treated daily by gavage for 90 days (EPA, 1988) using a UF of 300 (3 for a minimal LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

Fluorene. Similarly, an intermediate-duration oral MRL of 0.4 mg/kg/day was based on a LOAEL of 125 mg/kg/day for liver weight changes in mice treated daily by gavage for 90 days (EPA, 1989d) using a UF of 300 (3 for a minimal LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

In contrast, MRLs were not derived for some PAHs that are probable human carcinogens (group B2) (IRIS 1994), such as benzo[*a*]pyrene, benzo[*b*]fluoranthene, and benz[*a*]anthracene. For these PAHs, the carcinogenicity should drive the risk assessment. In recent years, the TEFs methodology was recommended for assessing the risk associated with exposure to a mixture of PAHs (EPA, 1993; Nisbet and LaGoy, 1992). The toxicity of different PAHs was compared with that of benzo[*a*]pyrene, which was assigned a TEF of 1 (ATSDR, 1995e). Carcinogenicity induced by individual PAHs was the basis for TEFs designation. Similar to the TEFs system for dioxin-like chemicals, the TEFs approach for PAHs required several assumptions. These included prerequisites such as a well-characterized PAH that could serve as a reference compound for all the others in the mixture, qualitatively similar toxic effects, similar end points, additivity of toxic effect, etc. (Nisbet and LaGoy, 1992). When we calculated the TEQ values for ATSDR's MRLs, we found that the values for anthracene and acenaphthene were comparable and so were the values for fluorene and fluoranthene. However, there was a threefold difference in TEQ values between the two groups. It is important to note that the MRLs are based on the most sensitive noncancer end points. In contrast, TEFs for PAHs are based on carcinogenicity. Therefore, the TEFs method for PAHs (as currently developed) should not be used for health effects other than cancer, and derivation of separate MRLs for individual PAH compounds, as done by ATSDR, is an appropriate approach.

ATSDR Did Not Derive MRLs for Some of the Mixtures Featured in the Toxicological Profiles

These included automotive gasoline, Stoddard solvent, hydraulic fluids, and mineral-based crankcase oil. ATSDR concluded that all these mixtures can vary in chemical components and concentrations, making it difficult to apply assessments from one scenario to another. When considered appropriate, the most toxic chemical from the mixture could be selected and assumed to drive the risk assessment. An example of this approach is using benzene as a marker for the environmental exposure to automotive gasoline.

FUTURE DIRECTIONS

Development of alternative risk assessment procedures and models is a complex, data-intensive task; paucity of data is frequently the bottleneck to developing potential hazard-assessment methods or models of risk assessment of chemical mixtures, such as interaction prediction. In the process of reducing the uncertainties in public health risk assessments, improving the accuracy of MRLs, and providing interim health-based guidance values, ATSDR is considering the potential impact of physiologically based pharmacokinetic modeling, benchmark dose modeling, and quantitative structure–activity relationships on the development of MRLs. ATSDR is also assessing specific chemicals and chemical mixtures using the *in vitro* functional screening approach. In addition, a weight-of-evidence (WOE) approach (Mumtaz and Durkin, 1992) is being used to predict the toxicity of some simple chemical mixtures based on published literature and then compare these predictions with test results from animal toxicity studies. The WOE evaluation process uses individual chemical dose/response assessments and algorithms that incorporate various assumptions regarding potential chemical interactions.

CONCLUSION

At this time, ATSDR has not developed a guidance policy for development of MRLs to address each type of chemical mixture. Rather, each mixture is considered on a case-by-case approach as seen in the examples given in this paper. Developing such guidance is difficult because of the nature of different mixtures, which may be similar or dissimilar, simple or complex. Because no such guidance exists and our knowledge of chemical mixtures is continuous and evolving, consistency in the MRL process has been difficult to maintain over time. Ultimately, the criteria for evaluating the MRLs for mixtures are a balanced consideration of the science, consistent application of uncertainty factors and modifying factors, and the best combination of science and judgment in the protection of public health.

ACKNOWLEDGMENT

The authors thank Ms. Anne Olin for editorial comments.

REFERENCES

Ahlborg, U. G., Brouwer, A., Fingerhut, M. A., *et al.* (1992). Impact of polychlorinated dibenzo-*p*-dioxins, dibenzofurans, and biphenyls

on human and environmental health, with special emphasis on application of the toxic equivalency factor concept. *Eur. J. Pharmacol.* **228,** 179–199.

Ahlborg, U. G., Becking, G. C., Birnbaum, L. S., *et al.* (1994). Toxic equivalency factors for dioxin-like PCBs. *Chemosphere* **28,** 1049–1067.

Air Force (1984). Ninety-day continuous inhalation exposure to petroleum JP-4 jet fuel. In *Toxic Hazards Research Unit Annual Technical Report: 1984,* Report No. AMRL-TR-84-001, Document No. AD-A147857/7, 46–62. Aerospace Medical Research Laboratory, Aerospace Medical Division, Air Force Systems Command, Wright-Patterson Air Force Base, OH.

Air Force (1991). *Tumorigenic Evaluation of Jet Fuels JP-TS and JP-7,* Report No. AAMRL-TR-91-0020. Aerospace Medical Research Laboratory, Aerospace Medical Division, Air Force Systems Command, Wright-Patterson Air Force Base, OH.

Allen-Rowlands, C. F., Castracane, V. D., Hamilton, M. G., *et al.* (1981). Effect of polybrominated biphenyls (PBB) on the pituitary–thyroid axis of the rat (41099). *Proc. Soc. Exp. Biol. Med.* **166,** 506–514.

ATSDR (1994). *Toxicological Profile for Chlorodibenzofurans (CDFs).* U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta, GA.

ATSDR (1995a). *Toxicological Profile for Polybrominated Biphenyls (PBBs).* U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta, GA.

ATSDR (1995b). *Toxicological Profile for Selected Polychlorinated Biphenyls (PCBs).* U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta, GA. [Draft]

ATSDR (1995c). *Toxicological Profile for Fuel Oils.* U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta, GA.

ATSDR (1995d). *Toxicological Profile for Jet Fuels.* U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta, GA.

ATSDR (1995e). *Toxicological Profile for Polycyclic Aromatic Hydrocarbons (PAHs).* U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta, GA.

ATSDR (1996a). CERCLA National Priority List. *Fed. Reg.* 61 FR 18744.

ATSDR (1996b). Minimal risk levels for priority substances and guidance for derivation. *Fed. Reg.* **61**(101), 25873–25882.

ATSDR (1997). *Toxicological Profile for Chlorinated Dibenzo-p-dioxins (CDDs).* U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta, GA. [Draft]

Birnbaum, L. S. (1994). The mechanism of dioxin toxicity: Relationship to risk assessment. *Environ. Health Perspect.* **102,**(Suppl. 9), 157–167.

Burleson, G. R., Lebrec, H., Yang, Y. G., *et al.* (1996). Effects of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) on influenza virus host resistance in mice. *Fundam. Appl. Toxicol.* **29,** 40–47.

DeCaprio, A. P., McMartin, D. M., O'Keefe, P. W., *et al.,* (1986). Subchronic oral toxicity of 2,3,7,8-TCDD in the guinea pig: Comparisons with a PCB-containing transformer fluid pyrolysate. *Fundam. Appl. Toxicol.* **6,** 454–463.

EPA (1987). *The Risk Assessment Guidelines of 1986,* EPA/600/8-87/045. U.S. Environmental Protection Agency, Office of Health and Environmental Assessment, Washington, DC.

EPA (1988). *13 Week Mouse Oral Subchronic Toxicity Study—Compound: Fluranthene.* Prepared by Toxicity Research Laboratories, Ltd., Muskegon, MI, for the Office of Solid Waste, Washington, DC.

EPA (1989a). *Interim Procedures for Estimating Risks Associated with Exposure to Mixtures of Chlorinated Dibenzo-p-dioxins and Dibenzofurans (CDDs and CDFs) and 1989 Update: Risk Assessment Forum,* EPA 625/3-89/016, NTIS PB90-145756. U.S. Environmental Protection Agency, Washington, DC.

EPA (1989b). *Subchronic Toxicity Study in Mice—Compound: Acenaphthene.* Prepared by Hazleton Laboratories America, Inc. Rockville, MD, for the Office of Solid Waste, Washington, DC.

EPA (1989c). *Subchronic Toxicity Study in Mice with Anthracene.* Prepared by Hazleton Laboratories America, Inc., Rockville, MD, for the Office of Solid Waste, Washington, DC.

EPA (1989d). *Mouse Oral Subchronic Toxicity Study—Compound: Fluorene.* Prepared by Toxicity Research Laboratories, Ltd., Muskegon, MI, for the Office of Solid Waste, Washington, DC.

EPA (1991). *Workshop Report on Toxicity Equivalency Factors for Polychlorinated Biphenyl Congeners: Risk Assessment Forum.* U.S. Environmental Protection Agency, Washington, DC.

EPA (1993). *Provisional Guidance for Quantitative Risk Assessment of Polycyclic Aromatic Hydrocarbons,* ECAO-CIN-842. Environmental Criteria and Assessment Office, Cincinnati, OH.

IRIS (1994). *Integrated Risk Information System.* U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office, Cincinnati, OH.

Kainz, R. J., and White, L. E. (1984). Depressant effects associated with the inhalation of uncombusted diesel vapor. In *Advances in Modern Environmental Toxicology.* Vol. VI. Applied Toxicology of Petroleum Hydrocarbons (H. N. MacFarland, C. E., Holdsworth, J. A. MacGregor, *et al.,* Eds.). Princeton Scientific, Princeton, NJ.

Moore, J. A., McConnell, E. E., Dalgard, D. W., *et al.* (1979). Comparative toxicity of three halogenated dibenzofurans in guinea pigs, mice and rhesus monkeys. *Ann. N.Y. Acad. Sci.* **75,** 151–163.

Mumtaz, M. M., and Durkin, P. R. (1992). A weight-of-evidence approach for assessing interactions in chemical mixtures. *Toxicol. Ind. Health* **8,** 377–406.

Newill, V. A. (1989). Keynote address: Significance of risk assessment in the management of environmental exposures to chemical mixtures. *Toxicol. Ind. Health* **5,** 635–646.

Nisbet, I. C. T., and LaGoy, P. K. (1992). Toxic equivalency factors (TEFs) for polycyclic aromatic hydrocarbons (PAHs). *Regul. Toxicol. Pharmacol.* **16,** 290–300.

Pluess, N., Poiger, H., Hohbach, C., *et al.* (1988). Subchronic toxicity of some chlorinated dibenzofurans PCDFs and a mixture of PCDFs and chlorinated dibenzodioxins PCDDs in rats. *Chemosphere* **17,** 973–984.

Pohl, H., and Holler, J. (1995). Halogenated aromatic hydrocarbons and toxicity equivalency factors (TEFs) in the public health assessment perspective. *Chemosphere* **31**(1), 2547–2559.

Pohl, H. R., and Abadin, H. G. (1995). Utilizing uncertainty factors in minimal risk levels derivation. *Regul. Toxicol. Pharmacol.* **22,** 180–188.

Poiger, H., Pluess, N., and Schlatter, C. (1989). Subchronic toxicity of some chlorinated dibenzofurans in rats. *Chemosphere* **18,** 265–275.

Safe, S. (1990). Polychlorinated biphenyls (PCBs), dibenzo-*p*-dioxins (PCDDs), dibenzofurans (PCDFs), and related compounds: environmental and mechanistic considerations which support the development of toxic equivalency factors (TEFs). *Crit. Rev. Toxicol.* **21,** 51–88.

Safe, S. (1994). Polychlorinated biphenyls (PCBs): Environmental impact, biochemical and toxic responses, and implications for risk assessment. *Crit. Rev. Toxicol.* **24:** 87–149.

Schantz, S. L., Ferguson, S. A., and Bowman, R. E. (1992). Effects of

2,3,7,8-tetrachlorodibenzo-*p*-dioxin on behavior of monkeys in peer groups. *Neurotoxicol. Teratol.* **14:** 433–446.

Schierow, L. J. (1995). *Dioxin: Reassessing the Risk.* CRS Report to Congress, Environment and Natural Resources Policy Division.

Starek, A., and Vojtisek, M. (1986). Effects of kerosene hydrocarbons on tissue metabolism in rats. *Pol. J. Pharmacol. Pharm.* **38,** 461–469.

Tryphonas, H., Hayward, S., O'Grady, L., *et al.* (1989). Immunotoxicity studies of PCB (Aroclor 1254) in the adult rhesus (Macaca mulatta) monkey—Preliminary report. *Int. J. Immunopharmacol.* **13,** 639–648.

Tryphonas, H., Luster, M. I., Schiffmann, G., *et al.* (1991a). Effects of chronic exposure of PCB (Aroclor 1254) on specific and low specific immune parameters in rhesus (*Macaca mulatta*) monkey. *Fundam. Appl. Toxicol.* **16,** 773–786.

Tryphonas, H., Luster, M. I., White, K. L., *et al.* (1991b). Effects of PCB (Aroclor 1254) on non-specific immune parameters in rhesus (*Macaca mulatta*) monkeys. *Int. J. Immunopharmacol.* **13,** 639–648.