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The Precision, Uses, and Limitations of Public Health Guidance Values

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ABSTRACT

Government agencies charged with the protection of public health, such as the U.S. Environmental Protection Agency (USEPA), the Agency for Toxic Substances and Disease Registry (ATSDR), and the U.S. Food and Drug Administration (FDA), must have a reference, or comparison value, upon which to base an evaluation of potential health threat posed by any substance or chemical. The basis, or starting points, for such evaluations may have different names or acronyms, but represent more or less the same thing. These values for non-carcinogenic endpoints are called oral Reference Doses (RfDs) and inhalation Reference Concentrations (RfCs) by the USEPA, Acceptable Daily Intakes (ADIs) by the FDA, and oral and inhalation Minimal Risk Levels (MRLs) by the ATSDR. Too often, however, RfDs, RfCs, MRLs, and ADIs are construed as rigid, threshold limits, above which toxicity is likely to occur. The truth, however, is that these values actually represent levels of a potential toxicant that are highly unlikely to represent any threat to human health over a particular/specified duration of daily exposures. The more frequently these levels are exceeded and the greater the exceedance, the more likely some toxic manifestation is to occur. These guidance/reference values are most definitely not threshold values for the onset of toxicity in any exposed population. Health guidance values must be thought of in the context of their intended role as mere screening or trigger values, in which they serve as a tool for assisting in the determination of whether further evaluation of a given potential exposure scenario is warranted.

Key Words: health guidance values, precision of health guidance values, uses and limitations of health guidance values, Minimal risk levels (MRLs), Reference Doses/Concentrations (RfD/RfC), Environmental Media Exposure Guide (EMEG)

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INTRODUCTION

"If we can put men on the moon, why haven't we been able to find a cure for the common cold?" That is a question that almost all of us have heard at one time or another. The premise behind this question embellishes at the same time an appreciation of modern scientific accomplishments and a misconception that all aspects of science have advanced at the rapid rate of the space program. A similar widespread popular misconception is that modern-day health scientists and medical professionals can precisely determine at what environmental level a particular contaminant presents a clear and predictable risk to human health.

Regrettably, this is not yet the case, nor is it likely to be the case in the foreseeable future. Further, there is occasionally (which is synonymous with "all too often" in the minds of public health assessors) apparent conflict between various government agencies in identifying a precise comparison value (*i.e.*, health guidance value (HGV) or reference value) against which to weigh the risks associated with human exposure to environmental substances. It is the purpose of this paper, therefore, to provide those who use these values with a clearer understanding of what such HGVs actually mean, how they are derived, the uncertainties inherent in such a process, and by whom they are intended to be used, as well as to hopefully clear up some of the apparent discrepancies among HGVs established by various agencies of the federal government.

The Agency for Toxic Substances and Disease Registry (ATSDR) is an agency of the U.S. Public Health Service, and is charged by Congress with providing public health support to assess the risk posed by Superfund and other hazardous waste disposal sites to the health of the surrounding and otherwise impacted public. The basis of non-cancer health risk determinations rendered by ATSDR is the minimal risk level (MRL) for a chemical or other substance. The intended usage of HGVs based upon the MRL is to identify screening or trigger levels that, if exceeded, may warrant further examination of the exposure scenario and the potentially exposed population. These MRLs are intended to be used by public health officials trained in health risk assessment, and only to identify substances of concern at hazardous waste or other sites of environmental contamination. Despite their occasional misunderstanding and consequent misuse by well meaning risk assessors who view them as the panacea to health risk determination, these values provide a scientifically sound basis for decisions in the environmental health risk assessment process.

HGVs represent levels of a chemical or other substance, exposure to which would be expected to cause no adverse health effects over a specified period of time (*i.e.*, acute, intermediate, or chronic). As such, they represent neither threshold values nor levels predictive of toxicity. In addition to being duration-specific, HGVs are/may also be route-specific and/or environmental medium-specific. HGVs are associated with inherent uncertainty, which needs to be formally articulated, and therein lies a problem with blind use of reference

value numbers. Such numbers must be tied to, or viewed in, the context of site- or situation-specific exposure conditions by qualified health professionals. At ATSDR, reliance is placed upon health guidance values in the public health assessment process; but there is also invoked a broader concept defined by the Council of Environmental Quality as risk analysis, with appropriate biomedical emphasis on site-specific factors that might serve to either increase or decrease public health concern.

The ensuing portion of this paper will first focus upon two distinct types of HGVs used extensively by ATSDR: (1) the MRL, which is analogous to the reference dose (RfD) of the U.S. Environmental Protection Agency (USEPA); and (2) the environmental media evaluation guide (EMEG) that is used in ATSDR's public health assessment efforts at sites to categorize individual sites with respect to their potential human health hazard. The causes of numerical differences between HGVs used by ATSDR and the USEPA will then be discussed.

MINIMAL RISK LEVEL (MRL)

Each MRL represents a reference value for a particular substance, for a particular effect (that seen at the lowest exposure level in a study), and for a specific route of exposure. MRLs, like RfDs (Barnes and Dourson, 1988) and reference concentrations (RfCs) (USEPA, 1994), are typically based upon toxicity benchmarks identified in either controlled human clinical studies, human epidemiological studies (usually retrospective), and/or controlled studies using laboratory mammals. From such studies, the lowest dosage or treatment level at which an adverse effect is identified is termed the lowest-observed-adverse-effect level (LOAEL), and the highest level at or below which no adverse effects have been observed in that or similar studies is called the no-observed-adverse-effect level (NOAEL).

Since the experimental population or the population identified in a clinical or epidemiological study is typically not the same as the potentially exposed population to be protected by the HGV, mathematical adjustments are made to the NOAEL or LOAEL to express the uncertainties inherent in the assumptions and data based used to calculate the HGV. The overall uncertainty factor for an MRL is used to adjust the actual experimental value to account for differences in susceptibility between the test species and humans, for sensitivity differences within the human population, and to reflect the confidence in the final calculated number and the database supporting that number. The resultant effect of this on the final HGV is an estimation of a dose that is likely to be without adverse effects in sensitive individuals for a specified duration of exposure (*e.g.*, chronic in the case of an RfD or chronic MRL). The derivation of an MRL would be as follows:

$$\text{MRL} = \frac{\text{NOAEL or LOAEL or BMD}}{\text{UF}}$$

where NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, BMD = benchmark dose*, UF = uncertainty factor.

The use of physiologically-based pharmacokinetic (PBPK) modeling may decrease the uncertainty in the reference value derivation process, but only comparison of modeled results with measured biological markers of exposure and effect and/or other empirical data can evaluate the actual extent of uncertainty reduction.

MRLs and the HGVs derived from them are intended for use as screening values to identify chemicals of potential health concern at hazardous waste sites. They may also serve as trigger values to alert primary care physicians to look for symptoms of exposure. As already mentioned, they are *not* intended as precise values above which adverse health effects will occur, nor are they intended to be used to establish clean-up levels for Superfund or other hazardous waste sites. An exposure/intake level exceeding the HGV merely indicates that further evaluation of the exposure scenario and potentially exposed population may be warranted, although the more often the HGV is exceeded and the greater the magnitude of the value by which the HGV is exceeded, the greater the likelihood that an adverse health outcome will occur. Further, the relevance of an HGV to any given exposure scenario will vary from person to person and substance to substance.

ENVIRONMENTAL MEDIA EVALUATION GUIDE (EMEG)

EMEGs are media-specific in nature and are used to select contaminants that warrant further investigation in the public health assessment process (ATSDR, 1992a). They are calculated for substances for which ATSDR has developed toxicological profiles. To date, about 200 toxicological profiles have been published by the Agency, containing approximately 250 MRLs for use in EMEG development.

An EMEG is simply an allocation of an MRL to a specific environmental/exposure medium. A corresponding value based upon the USEPA reference dose is the RMEG (RfD-based Media Evaluation Guide). During EMEG (or RMEG) development, exposure assumptions are applied to the MRL (or RfD) to identify media-specific comparison values for site-specific health risk evaluation.

EMEGs and RMEGs are based upon assumptions concerning specific routes of exposure (*i.e.*, ingestion and inhalation) to allow translation of an MRL or RfD to an equivalent soil or water concentration. To get an EMEG for water, the MRL is coupled with the assumed intake rate (2 liters per day for adults), allowing a mg/L water concentration that would result in an exposure equivalent to the MRL on a total body weight basis. To get an EMEG for a particular substance in soil, soil ingestion rates of 100 mg, 200 mg, and 5,000 mg soil per day would be used for adults, children, and pica children, respectively. Although

* *Benchmark dose (BMD) is the modeled dose of a substance that corresponds to a prescribed percentage increase in the incidence of response.*

the numerical intake assumptions employed are based upon reports and studies published in the peer reviewed scientific literature, they nonetheless increase the area of uncertainty in the calculated HGV. As an agency of the U.S. Public Health Service, ATSDR places particular emphasis on the exercise of biomedical judgment in both the public health assessment process and decision making in general.

EMEGs (and RMEGs) are based on single-chemical exposure, and do not consider the effects of concurrent exposure to multiple chemicals. EMEGs are derived for all durations of exposure for which there is a corresponding MRL, since all exposure durations may be appropriate in hazardous waste site exposure scenarios. An RMEG may be calculated for only chronic exposures, since the RfD upon which they are based is developed to be protective of chronic exposure, and an attempt to back-calculate to a shorter-duration HGV might not be appropriate. An example of the calculation of an EMEG for soil ($EMEG_s$) is presented below.

$$EMEG_s = \frac{MRL \times BW}{IR}$$

where $EMEG_s$ = soil evaluation guide (ppm), MRL = minimal risk level (mg/kg/day), BW = body weight (kg), IR = ingestion rate (mg/day).

ATSDR uses these health guidance values in a hierarchy or tiered fashion in the engagement of health issues at a specific site, and the toxicological profiles play an integral role in that process. The health assessment process requires the comparison of actual measured levels of contaminants in any and all environmental media with the MRL and known or anticipated exposure parameters. It should be emphasized here, however, that as the hierarchy is traversed in going from MRL to EMEG, the reliance on default assumptions decreases and is replaced with actual site-specific information (typically empirical monitoring/sampling data, as well as occasional biological measurements from the exposed population).

As a final point of discussion before preceding to address the differences (or apparent differences) among HGVs from different government agencies, a number of factors (Table 1) which impact the relevance of the HGV to any specific site need to be mentioned. The first of these is the character-

Table 1. Factors to consider when applying HGVs.

1. Characteristics of exposed population
2. Nature of Exposure
3. Duration of Exposure(s)
4. Scientific basis of health guidance value
5. Background level of substance in environment

istics of the exposed population, which includes factors such as age, gender, general health, nutritional status, likelihood/frequency of exposures, and concurrent exposures that are coupled with site-specific concerns, such as the likelihood and frequency of exposure, as well as any concurrent exposures to other chemicals from the site or from other sources. During this evaluation process, the relevance of the toxicological endpoint used in the calculation of the HGV must be considered in light of the potentially exposed population in each situation or scenario. It must be born in mind that the scientific basis of the HGV is pivotal to any credible assessment of site or situation-specific risk.

The nature of the exposure is dependent upon, among other factors, the nature of the toxicant itself. The chemical and physical properties of the toxicant are considered as they relate to the environmental partitioning of the material as it is released from a site. The health risk assessor must look at the potential routes of exposure based on that environmental partitioning, and again try to assess the likelihood of concurrent exposure, looking at the potential for joint toxic action, focusing on mechanism of toxic action of the individual chemicals as the means of providing insight into the potential for joint toxic effects.

In terms of duration of exposure, it is important to not just look at whether it is an acute, intermediate, or chronic duration exposure, but to also look at the issue of presumed past exposures, ongoing present exposures, and the potential for future exposures. Finally, the assessor must take into account the background level of the substance in the environment.

This is an iterative approach that is consistent with the National Academy of Sciences (NAS) recommendations and is intended to screen against the possibility of false negatives early on in this tier, and to then focus resources for further evaluation for those things that are still deemed to actually merit further health evaluation.

DIFFERENCES BETWEEN MRLs AND RfDs

Although the derivation processes for MRLs and RfDs/RfCs are basically similar, there are some differences inherent in the two methods. Unlike RfDs, which represent chronic exposure values, MRLs are based upon three distinct exposure scenarios, namely acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more). These values are not intended for use in any regulatory process, but rather reflect different exposure scenarios that can be expected at or near hazardous waste sites. The MRL development process also entails internal peer review, external peer review, and an opportunity for public comment. This process is done in a very transparent fashion, and the decisions that are made regarding any internal review comment, public comment, or peer reviewer comments, become part of a legal docket that is available to the public. By contrast, the USEPA RfDs and RfCs, while undergoing extensive internal peer review, have not historically always been subjected to external peer review or public review prior to incorporation in

USEPA's Integrated Risk Information System (IRIS). It should be pointed out, however, that USEPA is currently in the process of reevaluating its policy concerning the external review of reference values.

Before proceding further, an important distinction between scientific validity and the precision of an HGV should be made here. It should be noted by all who use HGVs that while extensive peer and public review may serve to ensure the validity and acceptability of the assumptions made in calculating an HGV, the same review process does not necessarily enhance the precision of the calculated reference value.

Blending Science with Science Policy

A factor impacting HGVs and resulting in occasional apparent conflicts between MRLs, RfDs, RfCs, and/or other similar reference values is that these reference/guidance values represent a sometimes uneasy blend of science and science policy. There are issues where the uncertainties associated with the available data lead us to involve default assumptions that are actually strongly grounded in science policy. Examples of possible disagreement between, but not necessarily incompatibility of, a respective MRL and the corresponding RfD or RfC include differences in the mission-based methodological approach to mathematical derivation of the reference value, definitions of adversity, exposure assumptions for soil, the legislative mandate prompting the derivation of the number (*i.e.*, the agency mission), and (rarely) differences in interpretation of scientific data.

Methodology-Based Differences

One difference between the USEPA and ATSDR in their respective methodological approaches to deriving reference values is the reliance by ATSDR on only published data concerning comparable exposures. This is a matter of science policy, and is based upon the requirement for all studies cited in toxicological profiles (in which the MRLs are presented) to be available to the public upon request. In the case of certain pesticides, USEPA may use as the basis of an RfD or RfC unpublished studies submitted by pesticide manufacturers as part of the USEPA registration process. While the quality of the study and compliance with prescribed testing guidelines is assured by USEPA, the fact that many such studies are protected from disclosure by the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) precludes their inclusion in the toxicological profile/MRL development process, unless the pesticide manufacturer having proprietary rights to that study specifically releases the study for public availability. Since such studies often cost millions of dollars and many pesticide manufacturers do not want their studies made available to multi-national corporations who have no obligation to pay for them, permission is not always obtainable for their use and possible subsequent public disclosure. Further, on-going litigation might be influenced by public disclosure of proprietary science documents, creating an additional barrier. Hence,

one source of discrepancy is based upon the public availability of health studies.

Such an example may be seen in the case of the pesticide dichlorvos. The USEPA RfD for dichlorvos is 0.0005 mg/kg/day, based upon cholinesterase inhibition in a one-year dog feeding study by the AMVAC Chemical Corporation (AMVAC, 1990). Since this study was protected under FIFRA and was not available to the public, and since there were no published studies suitable for chronic oral MRL derivation, ATSDR did not derive a chronic oral MRL for dichlorvos. It should be pointed out that when there is a need for an assessment of possible health risk from chronic oral exposure to a substance for which there is no chronic oral MRL, an ATSDR health assessor will typically look to the RfD, as well as any intermediate oral value for the same substance, for guidance. In the case of dichlorvos, the intermediate oral MRL is 0.003 mg/kg/day, based upon a NOAEL of 0.033 mg/kg/day in a 21-day human clinical study. Dependent on the particular exposure scenario under study, a chronic HGV in the order of the RfD might well be considered.

Another methodology-based reason that may contribute to numerical inequality of HGVs is that of rounding. A case to illustrate this apparent difference is that of the pesticide methyl parathion, in which there exists a quantitative, but neither statistically nor biologically different, difference in the USEPA and ATSDR HGVs for chronic oral exposure. The study which USEPA used in deriving an RfD for methyl parathion in 1986 was a report from Monsanto Company (1984). USEPA established an RfD of 0.00025 for this pesticide, based upon a study in which rats were administered methyl parathion in their feed for two years (IRIS, 1996a). In 1992, ATSDR derived a chronic oral MRL of 0.0003 mg/kg/day (ATSDR, 1992b). While the MRL was based on an available report of the same study (Suba, 1984), there appears on the surface to be a difference in the two HGVs. This apparent difference is the result of ATSDR rounding the final HGV (MRL in this case) to one significant figure after the decimal point. Thus, 0.00025 mg/kg/day became 0.0003 mg/kg/day. The two HGVs, however, are considered by ATSDR to be, at least in a biological sense, the same. This particular example underscores the importance of viewing health guidance values in the context in which they are intended; *i.e.*, not as precise mathematical absolutes, but rather as health-based comparison values surrounded by some unquantifiable level of imprecision (albeit probably not greater than one order of magnitude). This further suggests the importance of prudent use of HGVs by trained health professionals.

A third source of apparent conflict between HGVs developed by ATSDR and USEPA that is based on differences in methodological approach concerns the "seriousness" of an effect that may be used as the basis of derivation of the HGV. ATSDR defines a "serious adverse effect" as "any effect that prevents or will prevent the organism from engaging in normal activity over a normal lifetime" (Williams and Durkin, 1995). Further, a serious adverse effect must be associated with a debilitating clinical sign or symptom, or must clearly lead to such a state at the level of the whole organism.

By policy, ATSDR will not base an MRL on an effect that the Agency deems to be "serious", while USEPA excludes as a matter of policy only "frank" effects. Serious effects, which also include frank effects such as death, irreversible paralysis, and permanent blindness, need not be irreversible or irreparable, but only reflect an effect determined to pose a serious health risk or potentially life-threatening physiological or behavioral impairment to an individual for any duration of time. An example of a serious effect that may be used as a basis of HGV derivation by USEPA, but not by ATSDR, is liver necrosis. ATSDR would argue that such an effect during the period of exposure would present a serious, or potentially serious, threat to human health, while USEPA might contend that reduction of the dose level producing this effect through the use of multiple uncertainty factors would produce an adequate level of lifetime protection against that effect. Again, this is an example of a science policy matter that may result in a difference in selection of an HGV.

A final methodological/science policy-created difference in the MRL and RfD processes concerns the use of developmental studies as a basis of a reference/health guidance value. When viewing a study in which exposure occurs *in utero* throughout gestation, or substantially throughout gestation, the USEPA considers that to represent a lifetime exposure for the fetus; hence, such a study may serve as the basis of a (chronic) RfD. ATSDR, on the other hand, looks at only the duration of actual exposure (typically less than 20 days in animal studies), and uses that exposure duration only for a comparable duration MRL (either acute or intermediate). This still would typically pose no conflict with the RfD, however, as the calculated acute or intermediate MRL (depending on the duration of the experimental exposure) would in all likelihood be very similar to, or possibly the same as, the RfD. (*i.e.,* The same study NOAEL or LOAEL would probably be divided by similar uncertainty factors for intra- and inter-species differences, with no dosage duration adjustment made by either agency) Since ATSDR would not derive a chronic MRL value greater than the acute or intermediate value, the only difference in the chronic MRL and RfD for such a substance would be if another, and more sensitive, endpoint/study were used for chronic MRL derivation.

In the case of inhalation MRLs and RfCs based upon developmental endpoints, there is also an additional difference in methodological approach. When a study used as the basis of an MRL is based upon intermittent exposures (*e.g.,* 6 hours/day, 5 days/week), USEPA makes no duration adjustment, while ATSDR adjusts for 24 hour/day, 7 days/week exposures. This can result in a difference in HGV.

An example of the latter situation is illustrated by the inhalation HGVs developed for ethylbenzene. Both ATSDR and USEPA use the same study (Andrew *et al.,* 1981), the same endpoint (developmental toxicity), and the same experimental air concentration (NOAEL of 100 ppm, equivalent to 434 mg/m^3) as a basis for their respective values. However, in this particular instance, two factors account for the difference between the intermediate inhalation MRL of 0.3 ppm (equivalent to 0.07 mg/m^3 of air) and the RfC of 1 mg/m^3 (equivalent to 4.35 ppm): (1) the use of different uncertainty factors

and (2) different science policy approaches to dosage duration adjustment for developmental effects.

To arrive at the RfD, USEPA used, according to science policy (USEPA, 1991) no adjustment for less than 24 hour/day exposure, but did apply an overall uncertainty factor of 300 (10 for intraspecies variability, 3 for interspecies differences, and 10 to adjust for the absence of multigenerational reproductive and chronic studies) (IRIS, 1996b). ATSDR, on the other hand, adjusted the 6-7 hour/day experimental exposures to an equivalent continuous (24 hour/day) exposure. ATSDR then divided by an uncertainty factor of 100 (10 each for extrapolation from animal to man and intra-human variability). The resulting difference between the two HGVs is greater than an order of magnitude. This may not be a great enough difference to pose a significant problem for an experienced health risk assessor, but may be more than enough to create a real problem for a public health official trying to communicate this to a group of concerned parents and mothers-to-be. This example again underscores the importance of the proper use of HGVs (*i.e.*, not as precise quantitive thresholds, but rather as comparison values to be used as a screening tool by trained environmental health professionals).

The important thing that the health assessor should keep in mind is that, whatever the duration-dependent application of the developmental endpoints, both provide a significant level of protection against the effect of concern, and both the MRL and the RfD/RfC must be carefully weighed against both the exposure scenario and the nature of the potentially exposed population.

Definition of Adversity

Another example of a science policy issue that may impact the calculated HGV is the definition of adversity. As is known to almost all health risk assessors who must make a call on the adversity of an effect, the distinction between adverse and not adverse is not always clear cut. The same scientific data may, for a very limited number of effects, be evaluated differently by different scientists. For example, the USEPA typically considers a significant inhibition of plasma cholinesterase (an actual measure of butyrylcholinesterase or pseudocholinesterase) activity to be an adverse effect, while ATSDR considers this same effect to be indicative only of exposure, and not of adversity. Both agencies agree on the adversity of erythrocyte and brain cholinesterase inhibition, however. In this case, the difference is one of agency science policy, and is based upon painstaking examination of the same information. An example of such a science policy decision can be illustrated in the case of the intermediate oral MRL for the organophosphorus insecticide dichlorvos. ATSDR derived the MRL on a weight-of-evidence approach in which plasma, but not erythrocyte, cholinesterase inhibition was observed in male human subjects fed dichlorvos in capsule form three times daily, with a total daily dose equivalent of 0.033 mg/kg/day (Boyer *et al.*, 1977). Since ATSDR does not consider plasma cholinesterase inhibition in the absence of clinical signs or symptoms to be adverse, this level was identified as a NOAEL for humans in

that study (ATSDR, 1996). USEPA might have considered the same daily dosage to represent an LOAEL, since significant plasma cholinesterase depression was observed.

Another example of the impact of a science policy, or former science policy, on HGV derivation is the issue of enzyme induction in the absence of evidence of histopathological damage. In early deliberations of the RfD Workgroup, microsomal enzyme induction was occasionally used as the basis of RfD development, as in the case of 1,4-dibromobenzene (IRIS, 1996c). Although that has not been the policy of the RfD/RfC Workgroup since at least 1990, that RfD remains on IRIS. In the case of 1,4-dibromobenzene, this does not pose any conflict with ATSDR, since ATSDR has not developed a toxicological profile for that substance. Both ATSDR and USEPA consider this effect to be adaptive/compensatory in nature. While ATSDR would consider this effect to be potentially adverse (as it might result in the metabolism of another chemical to which a person might be exposed to a more reactive intermediate), it would not, however, derive an MRL based on enzyme induction alone (ATSDR, 1995a). In his or her consideration of site-specific exposure scenarios, the public health assessor, on the other hand, must weigh each substance of concern present at the site both individually and in consideration of all other chemicals/substances present, since an enzyme-inducing chemical might result in the enhanced toxic action of another substance present. For example, the adversity of a substance that is metabolized *in vivo* to a reactive metabolite or intermediate that is known to cause, or is capable of causing, histopathological damage, might well be impacted by other enzyme-inducing substances present.

Differences Resulting from Legislative Mandates

As just mentioned, the programmatic needs and mission of the respective agencies play a pivotal role in the development of the methodological approaches to HGV development. The RfD or RfC may be used as a regulatory value to protect against long-term (or lifetime) exposure to a potentially toxic substance in water or air, respectively, or as the basis of a clean-up number at a toxic waste site to protect against any adverse effects of chronic exposure. The ATSDR MRL value is not intended to be used in the regulatory or site clean-up processes, but is instead intended to serve as a basis of comparison with actual measured levels of environmental exposure. Again, the role of informed biomedical judgment is crucial in HGV application in any given exposure scenario. An acute or intermediate MRL value might facilitate a determination of whether, for example, a current air level of a volatile compound would pose an immediate or future health risk to exposed populations or warrant an emergency removal action, but not necessarily be indicative of any effects associated with longer-term continuous, low-level exposure.

While the RfD is by definition a value protective of lifetime exposure to a substance, ATSDR derives separate MRLs for different specified durations of exposure. The RfD process allows for the derivation of an RfD protective of

chronic exposure from published reports of less than chronic (*e.g.*, subchronic) exposure of human or laboratory animal subjects. This is made possible with the acknowledgment of an additional area of uncertainty inherent in the extrapolation of the shorter to the longer (RfD) exposure duration. This typically reduces the calculated reference value by up to a factor of 10 below what it would be if the critical study were of chronic or lifetime duration.

ATSDR avoids that additional uncertainty by using only studies of commensurate duration with the MRL definition (*e.g.*, acute, intermediate, chronic). That is to say, an acute MRL may only be based upon a clinical human or laboratory animal study of 14 days or less exposure to the same substance. While this may serve to mitigate some of the uncertainty inherent in the HGV derivation process, it does not necessarily increase the precision of the HGV. Further, since MRLs of different duration can be based upon studies that did not necessarily test the same endpoint as used for another MRL for the same substance, a significant amount of uncertainty in individual MRLs may remain. At the same time, however, it may also serve to create apparent conflict between the RfD and an MRL. For example, the USEPA has derived an RfD of 0.06 mg/kg/day for the polycyclic aromatic hydrocarbon acenaphthene (IRIS, 1996d), based upon a 90-day study using mice. Since there was no longer duration study available, ATSDR derived no chronic oral MRL, but did establish an intermediate (15–364 days) oral MRL of 0.6 mg/kg/day (ATSDR, 1995b). To add to any ambiguity, both values are based upon the same toxicity endpoint in the very same study (USEPA, 1989). The numerical difference is based merely upon the use of identical data to derive HGVs for different exposure durations — a difference predicated upon the programmatic use of those values by their respective agencies. In fact, despite appearances, both the RfD and MRL for all naphene may well be equally valid values, and their usage in any situation must be ultimately left up to the biomedical judgment of the user.

Soil Screening Levels

Yet another source of differences, or apparent differences, between HGVs estimated by USEPA and ATSDR stems from media-specific default values for intake rates. Both ATSDR and USEPA agree on water consumption rates for adults and children, and HGVs for the air medium are given as air concentrations (either mg/m^3 or ppm), so no notable difference exists there. In the case of soil ingestion rates, however, there is some disagreement.

USEPA calculates their soil screening levels (SSLs) for non-carcinogenic effects based upon the RfD for the substance in question and an age-adjusted soil ingestion factor, with an assumed (default) ingestion rate of 200 mg soil per day for children 1 to 6 years of age and a corresponding default soil ingestion rate of 24 mg/day for ages 7–31, assuming a total lifetime exposure of 30 years (USEPA, 1996a,b). ATSDR, on the other hand, develops a separate soil comparison value (CV or $EMEG_s$) for pica children, non-pica children, and adults (chronic) using the MRLs as a basis. The exposure assumptions used by ATSDR in this process are 100 mg/day for adults, 200 mg/day for non-pica children, and 5,000 mg/day for pica children, with the estimate for maximum pica assumption based upon Calabrese *et al.* (1989).

Although these procedural (actually science policy) differences may result in quantitatively different numerical values for SSLs and soil CVs for a given substance, the differences are typically well within an order of magnitude, and actually less than 2-fold in most instances. When one considers the uncertainties inherent in such a process, regardless of the specific methodological approach taken, such a small difference (especially at fractional ppm soil concentrations) need not necessarily be considered a difference at all in the case of a public health official or health assessor using those values as a screening level, as their use is intended.

Differences in Scientific Interpretation

In rare instances, differences between HGV values, or the difference in deriving an HGV and not deriving one, are the result of differences of opinion concerning either how to address the data, the validity of the data, or the credibility of the study. One such case was illustrated previously in this paper in the discussion of ethylbenzene HGVs for inhalation based upon developmental effects. In that instance, the use of different uncertainty factors for the same study, experimental dosage, and same toxicological endpoint, contributed to a disparity between the two HGVs. Another such disagreement can also be observed in the case of the oral toxicity of ethylbenzene; however, this time the disagreement is based upon the evaluation of the appropriateness of a critical study for chronic oral HGV derivation.

USEPA (IRIS, 1996b) has derived an oral RfD for ethylbenzene based upon a 182-day study in which rats were administrated daily doses of ethylbenzene by gavage (Wolf et al, 1956). ATSDR, however, decided not to base a chronic oral MRL on that study, since it felt that the study was weak in the areas of experimental methodology, adequate reporting of the data, and lack of statistical analysis of the results (ATSDR, 1990). This is not to say that the USEPA RfD is not valid. Rather, ATSDR did not feel comfortable enough with the quality of that particular 1956 study to base an HGV (MRL or EMEG in this case) upon it. There is, however, an RMEG calculated from the RfD available for consideration by health assessors.

INTENDED USERS OF HGVs

As noted in DeRosa and Risher (1997), HGVs might well contain a disclaimer stating "CAUTION: PLEASE DO NOT TRY TO USE THIS ALONE AT HOME OR WITHOUT THE ASSISTANCE OF A QUALIFIED HEALTH EXPERT." If that word of caution were placed on each printed copy of an HGV, perhaps some of the misuse and confusion created by these numbers could be avoided. Such a warning does, however, accurately convey the message that the intended audience for HGVs or comparison values is not the general public. HGVs are intended for the use of qualified environmental and public health officials. HGVs are further intended to be used, not as standalone numbers, but in context with the broader scientific knowledge about the substance of concern and in full consideration of the potentially exposed population. Therein lies the primary problem with HGVs: misuse, or perhaps

abuse, of a scientifically legitimate reference value by an "unlicensed applicator." Those intended as primary users of the HGVs are provided in Table 2.

LIMITATIONS OF HGVs

It goes without saying that the user of an HGV should understand what that value is, but just as important in ensuring the proper use of HGVs is an understanding of what they are not. The do's and don'ts of intended HGV use are listed in Table 3. The number one rule governing the potential use of HGVs should probably be that they do *not* represent threshold levels for toxicity. It should be noted that the dosage or treatment levels used in MRL

Table 2. Intended users of health guidance values.

1.	U.S. Government scientists, medical practitioners, and public health officials
2.	State, county, and city environmental and public health departments
3.	Fire departments and other local or state emergency management offices
4.	Private sector organizations involved in mitigation activities at hazardous waste sites

Table 3. Do's and don'ts of applying HGVs

May be properly used as:	
1.	Screening values to identify substances/chemicals of concern at hazardous waste sites
2.	Substance-specific trigger levels to identify possible need for further investigation of potential exposure scenarios
3.	To identify populations at potential risk
4.	For use in computing other HGVs (*e.g.*, use of oral MRL for soil ingestion screening levels)
May not be used as:	
1.	Threshold levels for a toxic effect
2.	Predictors of toxicity at any given level above the HGV
3.	Absolute values (since there is an inherent area of uncertainty surrounding them)
4.	Screening values for all effects and populations (without first evaluating the relevance of the critical effect upon which the HGV is based *vis a vis* the potentially exposed populations)

and RfD/RfC derivation are appropriately called "no observed" effect levels, and not "no observable" effect levels, as they are descriptive only of the dosing conditions in a specific scientific study, and are not meant to imply a threshold level for a specific effect. It should also be noted that the NOAEL focuses only on the dose representing the NOAEL and does not incorporate information on the slope of the dose-response curve or higher doses at which effects are observed. Further, the spacing of the doses in the critical study influence the level identified as the NOAEL. Consequently, a wide dose spacing may result in a NOAEL that considerably underestimates the actual threshold for a non-cancer effect. A second limitation of the NOAEL approach is that identification of a NOAEL is based upon a statistical test of a hypothesis that the response rate at a particular dose is equal to the response rate of a control group (Dourson, 1993). As the sample size is increased, the test becomes more sensitive, making it more likely that the null hypothesis will be rejected. This tends to push the NOAEL toward a lower value as the size of the sample population is increased.

These observations serve to illustrate that the NOAEL/LOAEL approach to human health risk guidance value derivation does not, and is not intended to, provide an absolute prediction of a toxicity threshold, above which toxic effects are likely to occur. On the contrary, an HGV merely represents a level at or below which adverse effects are unlikely to occur during or following a specified period of exposure. There is no inherent presumption or implication that occasional excursions above that level will necessarily lead to a manifestation of toxicity, although the risk of experiencing adverse health effects will be expected to increase with increasing frequency and magnitude of excursions above that level.

Alternate approaches to the traditional NOAEL/LOAEL method, such as the benchmark dose approach (Crump, 1995) which allows selection of a specific (*e.g.*, 1%, 5%, 10%) percent response level within the experimental dose range, are being employed in health risk assessment with increasing frequency. Such approaches have advantages over the traditional approach, but typically have requirements for larger and better data bases and are actually extensions of the NOAEL/LOAEL approach with a little more flexibility for the application of biomedical judgment at multiple steps in the process, rather than just in effect selection and estimation of uncertainty. In reality, it may be that there is no "one size fits all" methodological approach to health risk assessment, just as the ultimate HGV likewise represents no "one size fits all" number.

Why One Size Doesn't Fit All

The primary, and very pragmatic, reason why HGVs cannot represent a one-size-fits-all approach is that in public health practice, just as with clothing, one size *does not* fit all equally well. Just as not all individuals wear the same size shoe, shirt, or trousers, not all persons share the same sensitivity to toxic injury from a given substance. This can be clearly illustrated by the dinner guest who

suffers slightly slurred speech after only one pre-dinner martini, while the hosts can drink two or three and seem unaffected; or by two friends, one of whom suffers from extreme springtime allergies, while the other, who lives just next door, never has any of those same troublesome symptoms.

The fact is that no two of us are exactly alike (with the possible exception of genetically identical siblings). In the science of risk assessment, this is known as intraspecies or intrahuman variability. This makes application of a "one size fits all" reference or health guidance value in real-life exposure scenarios perhaps not fully protective, unless those values are geared toward the most sensitive group or population. Conversely, an exposure level that will be broad enough to encompass even the most susceptible sub-populations will certainly be protective of less sensitive/more tolerant individuals, but might be inordinately stringent compared to the actual amount of exposure restriction necessary to afford protection to them. Similarly, an HGV that is based upon the endpoint methemoglobinemia in infants would not necessarily be appropriate for a geriatric population. This requires the judicious evaluation of the entire exposure scenario, a deliberative process which we term biomedical judgment. This wide variability in susceptibility within the human species, as well as the differences between various mammalian species and limitations of the data base from which seemingly precise reference values are derived, are all reflected in the MRL or other HGV.

Therefore, when it comes to the application of such conservative health guidance values, scientific judgment must be exercised in determining any reference value's suitability for the exposed population in question. Since HGVs are typically protective of the most sensitive sub-population that might be exposed, the use of biomedical judgment assumes an irreplaceable role. Biomedical judgment is just as fundamental as the MRL or RfD/RfC in defining plausible exposure ranges of concern, organized into a weight of evidence presentation of the extent of any existing health risk to a particular exposed population.

Other Differences

There are other minor differences that hinge on interpretation of scientific data by groups of experts in the field of toxicology and health risk assessment. One such case is the pesticide disulfoton, for which the USEPA has an RfD of 0.00004 mg/kg/day and ATSDR has a chronic oral MRL of 0.00006 mg/kg/day. Both reference values were based upon the same endpoint (acetylcholinesterase inhibition), the same disulfoton concentration (1 ppm in feed), and the same species from the same study (Hayes, 1985). The minor difference between the MRL and the RfD results from the manner in which the exposure doses were calculated.

Although USEPA frequently uses food consumption data provided by the study authors, this was not the case for the disulfoton RfD. In this instance, USEPA multiplied the analytical dietary concentration of 0.8 ppm by the reference rat food consumption factor of 0.05 to arrive at an experimental

LOAEL of 0.04 mg/kg/day, which was then divided by an uncertainty factor of 1,000 to arrive at an RfD. ATSDR, however, multiplied the analytical concentration of 0.8 ppm by the equivalent dose of 0.08 mg/kg/day calculated by the author from actual food consumption and body weight data to get an experimental LOAEL of 0.06 mg/kg/day, and then applied an uncertainty factor of 1,000 to get their MRL of 0.00006 mg/kg/day (ATSDR, 1995c). The resultant numerical difference between the two HGVs, therefore, represents a judgment-based scientific difference of opinion on how the experimental dose should be calculated on a unit body weight per day basis. However, it is extremely doubtful that anyone involved in the calculation of either the RfD or the MRL would dispute the validity of the other number. Numerically the two values are clearly different, but both are still surrounded by sufficient uncertainty (on the order of 1,000-fold) to make actual quantification of any *real* biologically based difference (and we doubt that there is any) virtually impossible to determine.

SUMMARY

MRLs and EMEGs are numbers representing arithmetically estimated safe levels of exposure, and are in no way intended to be construed as precise values. These guidance values are not intended to be considered as representing a threshold for toxicity, but rather are intended to serve as trigger levels to suggest that further evaluation of a site may be warranted. MRLs and EMEGs are not intended for use of the general population, but rather by public health officials trained in the biomedical sciences. When evaluating the appropriateness of their usage in a given situation, the final decision should be guided by full consideration of the potentially exposed population, all reasonable possible exposure scenarios, and the relevance of the toxicity endpoint upon which the MRL is based.

The use of both an MRL and the RfD for a particular substance might well be totally appropriate at the same site. The MRL and the RfD/RfC values are functions of the respective agency missions, and differences in value do not necessarily imply either disagreement concerning science nor an increased level of precision of one vs. the other.

While small differences in assumed intake rates, most typically soil ingestion rates, may combine with small differences between an MRL and its corresponding RfD to provide even a larger difference between guidance values, the resultant HGVs (*e.g.*, SSL and soil CV) rarely vary significantly from a biological perspective. The old popular adage that "little things mean a lot" may be true in everyday life, but small differences in HGVs defined by various government agencies may mean far less, if anything at all, from a scientific perspective.

FINAL COMMENTS

Despite primarily subtle or scientifically inconsequential differences in HGVs emanating from different government agencies, the fact that any differ-

ences even exist raises questions in the public eye about the validity of any two guidance values derived for similar purposes. Government agencies charged with the protection of public health and the environment are very cognizant of this, and are continually striving to both enhance the science of health risk assessment and to reach a meeting-of-the-minds on issues of science whenever possible. Interagency groups such as the Mid-Level Managers' Forum have been working for some time in resolving such differences. The ATSDR Interagency MRL Workgroup has representation both from the USEPA and the National Institute of Environmental Health Science, as well as occasional representation from other federal organizations. The USEPA RfD/RfC Workgroup* has also had participation from other agencies, including routine participation by ATSDR and the U.S. Food and Drug Administration (FDA), as well as representation by expert scientists from the U.S. Department of Agriculture (USDA) in deliberations concerning nutritionally essential trace elements. And recently ATSDR and USEPA have formed a joint workgroup to address, and resolve wherever possible, differences in soil screening values for environmentally contaminated soils.

In both the public interest and the interest of science, such interagency efforts will continue to vigorously address, and hopefully eventually resolve, differences (or apparent differences) in health guidance values to create not only a safer environment, but also a more confident public.

REFERENCES

AMVAC. 1990. AMVAC Chemical Corporation. MRID No. 41593101; HED Doc. No. 008178. Paper held by the U.S. Environmental Protection Agency, Office of Pesticide Programs. Washington, D.C. 20460.

Andrew, F.D., Buschbom, R.L., Cannon, W.C. et al. 1981. Teratologic assessment of ethylbenzene and 2-ethoxyethanol. Richland, WA: Battelle Pacific Northwest Laboratory. PB83-208074.

ATSDR (Agency for Toxic Substances and Disease Registry). 1996. Toxicological Profile for Dichlorvos (Draft for Public Comment). U.S. Department of Health and Human Services. Public Health Service. Agency for Toxic Substances and Disease Registry. For public comment period ending February 20, 1996.

ATSDR (Agency for Toxic Substances and Disease Registry). 1995a. Guidance for the Development of Set 9 Toxicological Profiles. Agency for Toxic Substances and Disease Registry. Atlanta, GA.

ATSDR (Agency for Toxic Substances and Disease Registry). 1995b. Toxicological Profile for Polycyclic Aromatic Hydrocarbons (PAHS) (Update). U.S. Department of Health and human Services. Public Health Service. Agency for Toxic Substances and Disease Registry. August 1995. Atlanta, GA.

ATSDR (Agency for Toxic Substances and Disease Registry). 1995c. Toxicological Profile for Disulfoton. U.S. Department of Health and Human Services. Public

* Activities of the USEPA RfD/RfC Workgroup have been suspended while that agency is developing its IRIS program.

Health Service. Agency for Toxic Substances and Disease Registry. September 1992. August 1995. Atlanta, GA.

ATSDR (Agency for Toxic Substances and Disease Registry). 1992a. Public Health Assessment Guidance Manual. PB92-147164. Agency for Toxic Substances and Disease Registry. March 1992. Atlanta, GA.

ATSDR (Agency for Toxic Substances and Disease Registry). 1992b. Toxicological Profile for Methyl Parathion. U.S. Department of Health and Human Services. Public Health Service. Agency for Toxic Substances and Disease Registry. Atlanta, GA.

ATSDR (Agency for Toxic Substances and Disease Registry). 1990. Toxicological Profile for Ethylbenzene. U.S. Department of Health and Human Services. Public Health Service. Agency for Toxic Substances and Disease Registry. December 1990. Atlanta, GA.

Barnes, D.G. and Dourson, M. 1988. Reference Dose (RfD): Description and use in health risk assessments. *Reg. Toxicol. and Pharmacol.* **8,** 471-486.

Boyer, A.C., Brown, L.J., Slomka, M.B., and Hine, C.H. 1977. Inhibition of human plasma cholinesterase by ingested dichlorvos: effect of formulation vehicle. *J. Toxicol. Appl Pharmacol.* **41,** 389-394.

Calabrese, E.J., Pastides, H., Barnes, R. et al. 1989. How much soil do young children ingest: an epidemiologic study. *Regul. Toxicol. Pharmacol.* **10,** 123-137.

Crump, K. S. 1995. Calculation of benchmark doses from continuous data. *Risk Analysis* **15,** 79-89.

DeRosa, C. T. and Risher, J.F. 1997. The use of health guidance values in public health practice. *J. Toxicol. Environ. Health.* In press.

Dourson, M.L. 1993. Overview to alternatives to benchmark dose. EPA-ILSI Workshop on Benchmark Dose, Washington, D.C. September 23, 1993.

Hayes, R.H. 1985. Chronic feeding/oncogenicity study of technical disulfoton (Di-Syston) with rats. Study no. 82-271-01. Mobay Chemical Corporation, Corporate Toxicology Department, Stilwell, Kansas.

IRIS (Integrated Risk Information System). 1996a. Methyl Parathion. I. Chronic health hazard assessments for noncarcinogenic effects. Integrated Risk Information System. Micromedex, Inc., Vol. 29.

IRIS (Integrated Risk Information System). 1996b. Ethylbenzene. I. Chronic health hazard assessments for noncarcinogenic effects. Integrated Risk Information System. Micromedex, Inc., Vol. 29.

IRIS (Integrated Risk Information System). 1996c. 1,4-Dibromobenzene. I. Chronic health hazard assessments for noncarcinogenic effects. Integrated Risk Information System. Micromedex, Inc., Vol. 29.

IRIS (Integrated Risk Information System). 1996d. Acenaphthene. I. Chronic health hazard assessments for noncarcinogenic effects. Intergated Risk Information System. Micromedex, Inc., Vol. 29.

Monsanto Company. 1984. MRID No. 000139023, 00143965, 00145507. Paper held by U.S. Environmental Protection Agency, Office of Pesticide Programs, Washington, D.C.

Suba, L.A. 1984. Additional information to support the registration of methyl parathion: Two year chronic feeding study of methyl parathion in rats. Monsanto Agricultural Products Company, St. Louis, MO.

USEPA (U.S. Environmental Protection Agency). 1994. Methods for Derivation if Inhalation Reference Concentrations and Application of Inhalation Dosimetry. EPA/600/8-90/066F. Oct. 94. U.S. Environmental Protection Agency. Office of Health and Environmental Assessment. Washington, D.C. 20460.

USEPA (U.S. Environmental Protection Agency). 1991. Environmental Protection Agency. Guidelines for Developmental Toxicity Risk Assessment; Notice. Federal Register, Vol. 56, No. 234, Thursday, December 5, 1991.

USEPA (U.S. Environmental Protection Agency). 1996a. Soil Screening Guidance: Technical Background Document. 9355.4-17A, EPA/540/R-95/128, PB96-963502, May 1966. United States Environmental Protection Agency. Office of Solid Waste and Emergency Response, Washington, D.C.

USEPA (U.S. Environmental Protection Agency). 1996b. Soil Screening Guidance: Users' Guide. 9355.4-23, EPA/540/R-96/018, PB96-963505, April 1996. United States Environmental Protection Agency. Office of Solid Waste and Emergency Response, Washington, D.C.

Williams, M.D. and Durkin, P. 1995. Guidance for Assessing Adverse Health Effects and Using Severity of Effects in the Derivation of MRLs. U.S. Department of Health and Human Services. Public Health Service. Agency for Toxic Substances and Disease Registry. Division of Toxicology. October 2, 1995.

Wolf, M.A., Rowe, V.K., McCollister, D.D., Hollingsworth, R.L., and Oyen, F. 1956. Toxicological studies of certain alkylated benzenes and benzene. *Arch. Ind. health.* **14,** 387-398.