Approaches to Determining "Unreasonable Risk to Health"

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Executive Summary

The Safe Drinking Water Act (SWDA) allows public water systems to receive variances or exemptions from the National Primary Drinking Water Regulations, as long as the variance or exemption does not result in an "unreasonable risk to health" (URTH). In 1990, the U.S. Environmental Protection Agency (U.S. EPA) developed draft guidance that compares risk assessments for cancer and non-cancer endpoints and considers exposure duration when determining URTH. Using its existing approaches for assessing risk posed by drinking water contaminants, EPA has determined that URTH is a *range* from the maximum contaminant level (MCL) to a chemical-specific upper bound value. These chemical-specific values are presented in the draft guidance. EPA (U.S. EPA, 1990; Zavaleta, 1992) recommended the following decision rules for determining URTH when the chemical has non-cancer effects:

1. URTH equals the MCL, if the MCL is based on acute toxicity. (EPA considers that in this situation there is usually little margin of safety above the MCL. However if there is a greater margin of safety above the MCL, scientific judgment should be used to set an URTH that exceeds the MCL.)

2. URTH equals the longer-term HA for a child if the MCL is based on subchronic or chronic toxicity. EPA considers this to be adequately protective of potentially sensitive subpopulations. EPA noted that the DWEL could be used if data are not available to calculate a longer-term HA.

EPA (U.S. EPA, 1990; Zavaleta, 1992) recommended the following decision rules when the chemical causes cancer:

1. URTH equals the MCL, if the MCL is set at or above the 10^{-4} cancer risk.

2. URTH equals a water concentration that gives a 10^{-4} cancer risk, if the MCL is less than the 10^{-4} cancer risk

3. URTH equals 10 times the MCL, if the contaminant is a Group C carcinogen and the MCL includes an additional safety factor of 10 to account for this.

EPA (U.S. EPA, 1990; Zavaleta, 1992) also recognized that some contaminants have both noncancer and cancer effects and therefore, may have risk values based on both types of effects. In these cases, the noncancer and cancer effects should be compared before a final URTH value is determined. For example, the longer-term HA (or DWEL) should be compared to the water concentration that gives a 10^{-4} cancer risk (or 10 times the MCL); URTH equals the lower of these values.

However, EPA recognizes that States may determine that URTH is above this range based on site-specific factors such as site-specific exposure, including past exposure, population sensitivity, or volatility of the contaminant. Therefore, this paper focuses on methods that States

may use to incorporate more data to assess URTH on a site-specific basis. The methods are presented as a series of Tiers that require an increasing amount of specialized expertise. Tier 1 methods are approaches that can be applied easily based on readily available information, and require little or no specialized knowledge. Tier 1 includes (1) straightforward application of the draft U.S. EPA guidance; (2) review of recent evaluations of the contaminant to determine whether the existing drinking water guidelines are based on current science, and if the use of current science would allow an exemption to be granted; and (3) an examination of the imprecision of the risk values used as the basis for the maximum contaminant level (MCL). Tier 2 methods require additional input from an experienced toxicologist/risk assessor, but can be completed without substantial mathematical or other specialized expertise. Tier 2 includes (1) consideration of the percentage of exposure to the contaminant that results from drinking water (i.e., the relative source contribution); (2) examination of exposure parameters (e.g., water consumption and body weight); and (3) investigating whether the public water system serves the sensitive population that the underlying risk value was designed to protect. Tier 3 methods require expert analysis, and may be time-intensive, but have the advantage that the analysis results can be incorporated into cost-benefit analyses. The steps included in tier 3 are mathematical modeling methods, the general concepts of which are described in the body of this white paper. These sophisticated mathematical methods do not lead directly to a determination of an URTH level, but results of these analyses can be used by a risk manager to determine what level of risk is acceptable, as well as to compare the costs of achieving a certain water concentration with the health benefits of doing so.

Introduction

The Safe Drinking Water Act (SDWA) allows public water systems to receive variances or exemptions from the National Primary Drinking Water Regulations, as long as the variance or exemption does not result in an "unreasonable risk to health" (URTH). However, the SDWA does not specify how an unreasonable risk to health shall be determined, leaving the U.S. Environmental Protection Agency (U.S. EPA) latitude in defining URTH and in setting URTH levels for drinking water contaminants. Therefore, the purpose of this paper is to describe the approaches U.S. EPA has taken to define URTH and to recommend how additional information and new research methods can be used on a case-by-case basis to further support, or improve, the methods for determining URTH.

Congress passed the SDWA in 1974 with the goal of protecting public health by regulating the nation's public drinking water supply (U.S. EPA, 1999a). It has been amended twice since then, in 1986 and 1996. While the original act focused on safe drinking water at the tap, the amendments passed in 1996 added language dealing with source protection, operator training, funding for water system improvements, and public information (U.S. EPA, 1999a).

The SDWA authorizes the U.S. EPA to set national standards for water to protect against both man-made and naturally occurring contaminants. The EPA then works with States and water systems to make sure the standards are met (U.S. EPA, 1999a). The SDWA does not apply to private wells that serve less than 25 people or have less than 15 connections (Zavaleta, 1992; U.S. EPA, 1999a). The SDWA allows the EPA to relinquish control of regulation enforcement and oversight of regulations and standards to states and territories. States can apply to the EPA for primacy. States, or the EPA as the primacy agent, must make sure water systems test for contaminants, review plans for system improvements, conduct on-site inspections, provide training and technical assistance, and take action against public water systems not meeting standards (U.S. EPA, 1999a). All states except Wisconsin and the District of Columbia, have received primacy.

When originally passed in 1974, the SDWA recognized that some public water systems could not comply with some standards by the time they become effective, and it established means by which water systems could acquire additional time to come into compliance. Under section 1415 of the SDWA, states with primacy may grant variances to public water systems that serve up to 3,300 people (Zavaleta, 1992; U.S. EPA, 2003a). Small systems, which serve up to 10,000 people, may be granted a variance with the approval of the EPA (U.S. EPA, 2003a). Variances may be granted if a water system cannot afford to comply with a rule, and if the PWS installs EPA-approved variance technology (U.S. EPA, 2003a). There are three basic types of variances and exemptions. A general variance may be granted due to the poor quality of a PWS's source water, if the standard cannot be met even after applying the best available technology (BAT) (Fensterheim, 2001). Small system variances can be granted if EPA, in consultation with the states, determines that the BAT to achieve a standard is unaffordable. When the variance is granted, a schedule for compliance is established. This schedule may include interim control levels and a schedule for implementation of control measures. Exemptions may be granted to a PWS to allow them more time to come into compliance with a standard. Exemptions may be granted if there are compelling reasons, including cost and the inability to restructure or make

management changes (Fensterheim, 2001). An exemption is granted for one year, with an extension for an additional two years, if needed. After the exemption period expires, the PWS must be in compliance (U.S. EPA, 2003a). However, systems serving less than 500 people may apply for additional 2-year renewals after demonstrating good faith to come into compliance. Variances and exemptions are granted under the condition that they will not pose an unreasonable risk to health (URTH).

Assessing Health Risks for Water Contaminants: The First Step in Developing Drinking Water Standards

Before describing approaches for evaluating URTH, it is useful to first briefly review the methods used by the U.S. EPA to develop safe drinking water standards. In this process, the EPA first reviews and critically evaluates the data regarding the potential health effects for a contaminant. EPA evaluates the potential for drinking water contaminants to cause cancer and non-cancer effects, and derives drinking water standards based on overall evaluation of cancer and non-cancer effects. Unless otherwise specified, chemicals that affect health, but do not cause cancer, are believed to have a "safe dose", and if the exposure stays below this dose, then the chemical will not harm health. This safe dose is called a threshold. For chemicals that cause cancer, it is assumed that there is no safe dose, so that any exposure no matter how small can result in cancer. Therefore, these chemicals are said to act without a threshold.[1]

Noncancer

The first step to develop a drinking water standard based on noncancer effects is to determine the "safe dose", which is known as a Reference Dose (RfD) (formerly called the Acceptable Daily Intake, or ADI). The RfD is defined as "an estimate of an exposure, designated by duration and route, to the human population (including susceptible subgroups) that is likely to be without an appreciable risk of adverse health effects over a lifetime" (U.S. EPA, 2002a). The RfD is derived by reviewing all of the scientific data available on the chemical. The goal is to identify both the most sensitive harmful health effect (called the critical effect[2]) that occurs following exposure to the chemical and the lowest dose of the chemical that causes this effect. The RfD is intended to protect sensitive individuals and different life stages as well as the general population.

Because the RfD is designed to be safe following lifetime exposure, it is most often derived from chronic (lifetime) studies or subchronic studies (usually defined as studies including at least 1/10 of the lifespan). Depending on the data available for the chemical, the RfD may be derived from either the highest dose that has no effect (called a "no observed adverse effect level", or NOAEL) or the lowest dose that causes a harmful effect (called the "lowest observed adverse effect level", or LOAEL). If enough data are available, then the RfD can be derived using

[1] However, recent thinking in the EPA and elsewhere suggests an approach that considers mode of chemical action and harmonization of cancer and noncancer risk assessment (U.S. EPA, 2002a, 2003b). As this suggestion is further explored, the distinction between these two types of endpoints may break down, including the thought that all carcinogenic do not have thresholds, and that all noncancer endpoints have thresholds. The approaches to evaluate URTH that we describe can account for this eventual harmonization.

[2] EPA defines the critical effect as "the first adverse effect, or its known precursor, that occurs to the most sensitive species as the dose rate of an agent increases."

mathematical equations that predict the dose of a chemical that will cause a specific effect (e.g,, the dose that will cause 10% of the population to have liver effects). This prediction is called a "benchmark dose" (BMD), and it is derived from fitting a curve to the dose-response data. The NOAEL, LOAEL, or BMD is then divided by uncertainty factors (UF) that account for extrapolation from incomplete data, as described below. Thus, the RfD is calculated as follows:

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

Professional judgment is used to select which uncertainty factor will be used to calculate the RfD, considering the entire database on the chemical's toxicity and toxicokinetics. EPA recognizes five areas of variability or uncertainty in the development of RfDs (U.S. EPA, 2002a; Felter et al., 1997; Haber et al., 2001). These areas are:

UF_H Intraspecies variability. This factor accounts for the variation in sensitivity among the members of the human population. Therefore, use of this factor protects sensitive members of the human population.

UF_A Interspecies extrapolation. This factor accounts for the uncertainty involved in extrapolating from animal data to humans (interspecies variation).

UF_S Subchronic to chronic extrapolation. This factor accounts for the uncertainty involved in basing the RfD on a NOAEL from a study that was conducted for less than the entire lifetime of the test animals. This factor can be modified if there are some data suggesting that effects following a lifetime of exposure will not be more sever. Such data might include information on progression of effects, toxicokinetics, and transience of the endpoint.

UF_L LOAEL to NOAEL. This factor accounts for the uncertainty involved when the RfD is based on a LOAEL rather than a NOAEL. It may be modified if the chemical's effect is minimally severe.

UF_D Database completeness. This factor accounts for the uncertainty that arises when not all possible areas of toxicity have been studied – i.e., when the database is missing important studies. In the absence of human data, EPA considers a complete database to include systemic toxicity studies in two species, developmental toxicity studies in two species, and a multigeneration toxicity study. The implications of the lack of various study types were investigated by Dourson et al. (1992).

Note that some of these factors are used to account for uncertainty and others are used to account for variability in populations. Uncertainty is defined as the lack of information, and can be reduced by acquiring additional information. Three of the factors account for uncertainty in the RfD due to the absence of data: UF_S, UF_L, UF_D. Additional information can remove the need for

these uncertainty factors. In contrast, variability describes differences inherent in the biology of animals and people. Additional data can be used to quantify this variability, and improve the precision of the estimate, but the variability cannot be removed. Thus, the interspecies and intraspecies uncertainty factors describe true variability – biological differences between animals and humans, or variability in the human population – although there may also be uncertainty regarding the size of this variability.

Typically, a value of 1, 3, or 10 is used for each uncertainty factor discussed above[3]. If the data are sufficient so that a given area of uncertainty is completely addressed, then a value of 1 is used for that area of uncertainty. For example, if the database contains chronic studies, then a value of 1 is used for UF_S. On the other hand, if data for a given area of uncertainty is missing, then a value of 10 is used for that area of uncertainty. For example, if the database does not contain useful human studies, then a value of 10 is used for UF_A. When the uncertainty in one area is not large enough to warrant a full value of 10, an intermediate factor of 3 is often used, as approximately one half $\log_{10}$ unit (i.e., the square root of 10). For example, if a RfD is derived from a LOAEL, the default for UF_L is 10, but a smaller factor may be used if the LOAEL is based on a mild effect. Similarly, if the database for a chemical is judged to be complete, UF_D is 1, but the lack of just one key study would result in a UF_D of 3.

The value of the composite uncertainty factor used to derive a RfD is obtained by multiplying the values for the five individual factors. For example consider that the following individual factors were chosen for a given chemical: $UF_A = 10$; $UF_H = 10$; $UF_S = 1$; $UF_L = 1$; $UF_D = 3$. The total UF used to calculate the RfD for this chemical is 10 x 10 x 1 x 1 x 3, or 3,000. However, this rule becomes complicated when there are four or more areas of uncertainty. Risk assessors recognize that some overlap exists among the uncertainty factors, and that the potential for overprotection increases substantially as the number of uncertainty factors increases. Therefore, if there are four or more areas of uncertainty, then two areas of uncertainty will be combined within one 10-fold factor (Dourson et al., 1996; EPA, 2002a). For example, if there are four full areas of uncertainty, simple math would indicate that the composite uncertainty factor is 10,000. However, due to the overlap in uncertainty factors, the correct composite value is 3,000. If the composite uncertainty factor exceeds 3,000, then the database generally does not support development of an RfD (U.S. EPA, 2002a), although some early assessments used a composite uncertainty factor of 10,000.

Other organizations, such as the U.S. Agency for Toxic Substances and Disease Registry (ATSDR), International Programme for Chemical Safety/World Health Organization (IPCS/WHO), Health Canada, and the Netherlands National Institute of Public Health and Environmental Protection (RIVM) use methods similar to those of the U.S. EPA for deriving safe doses. All of these organizations use default factors of 10 for interspecies extrapolation and intraspecies variability, but there are some differences in how they apportion other areas of uncertainty. Some organizations also include factors for such issues as the nature of the toxicity

[3] The uncertainty for UF_H and UF_A is often broken into toxicokinetic and toxicodynamic components, reflecting a chemical's disposition and the chemical's effect on the target tissues, respectively. The International Program on Chemical Safety/World Health Organization (IPCS/WHO) has developed guidelines on the use of data to develop chemical-specific values for the toxicokinetic and toxicodynamic components of UF_H and UF_A (IPCS, 2001); these guidelines are being discussed by the U.S. EPA (2002a).

(e.g., severe, irreversible effects, such as teratogenicity), or the potential for interactions with other chemicals, and several are considering, or are using, chemical specific data to adjust default values of 10 when appropriate. In general, safe doses are not developed when the total uncertainty factor exceeds 10,000.

Assessment of Carcinogens

As for the contaminants that have noncancer effects, setting drinking water standards for contaminants that cause cancer involves a thorough review of all of the available data on the contaminant. However, rather than determining a "safe dose", the goal for assessing carcinogens is to understand the data that describe how the chemical may be causing cancer and, if possible, give an estimate of the cancer risk that is associated with a given chemical dose. Because cancer risk assessment is so complex, U.S. EPA issued guidelines for cancer risk assessment in 1986 (U.S. EPA, 1986) and is in the process of updating and modifying those guidelines (U.S. EPA, 1999b; 2003b). The recent draft guidelines emphasize that risk assessors provide of a general description of how the chemical causes cancer (called mode of action) and evaluate whether cancer observed in experimental animals following exposure to a contaminant is relevant to humans. Risk assessors also consider mode of action in determining how to predict human cancer risk from the doses that cause cancer in experimental animals.

Although new assessments are currently being conducted using the draft guidelines, many old assessments conducted using EPA's old guidelines have not been updated. Therefore, this text presents the cancer assessment methods under both sets of guidelines. Under the 1986 guidelines, EPA assumed that no threshold exists for chemicals that cause cancer, unless data existed to show that this assumption was not true. Therefore, any exposure to a carcinogenic chemical could result in cancer (U.S. EPA, 1986). Under the 1986 guidelines, the EPA considered all of the available data to describe the potential of a chemical to cause cancer in humans, according to the following scheme:

- Group A: Human Carcinogen. Sufficient evidence exists from studies in humans to support a causal association between exposure to the chemical and human cancer.

- Group B: Probable Human Carcinogen. Sufficient evidence of carcinogenicity in animals with limited (Group B1) or inadequate (Group B2) evidence in humans.

- Group C: Possible Human Carcinogen. Limited evidence of carcinogenicity in animals in the absence of human data.

- Group D: Not Classified as to Human Carcinogenicity. Inadequate human and animal evidence of carcinogenicity or for which no data are available.

- Group E: Evidence of Noncarcinogenicity for Humans. No evidence of carcinogenicity in at least two adequate animal tests in different species or in both adequate epidemiologic and animal studies.

Under the 1986 guidelines, if a chemical is classified as either Group A, B, or C, mathematical models are used to estimate excess cancer risk associated with a given dose of ingested chemical, (in units of mg/kg-day). The models actually predict the 95% upper confidence limit as a dose estimate. This means that the true risk to humans, while not identifiable, is not likely to exceed the upper confidence limit estimate and, in fact, may be lower or even zero. The data used in these estimates usually come from lifetime-exposure studies in animals. In order to predict the risk for humans from animal data, animal doses must be converted to equivalent human doses by adjusting for the different surface area of the test animal and humans. In determining the risk associated with ingestion of the contaminant in drinking water, it is assumed that the average adult human body weight is 70 kg and that the adult human consumes two liters of water per day. These are somewhat health-protective assumptions, since, for example, most adults in the U.S. consume less than two liters of tap water per day.

In the new draft guidelines (U.S. EPA, 1999b; 2003b)[4], EPA replaces the Group A to E categories with a narrative that describes the evidence regarding a chemical's potential for causing cancer and describes the conditions under which the chemical may cause cancer. The standard descriptors suggested by EPA are described below:

- Carcinogenic to humans. This descriptor is appropriate when there is convincing human evidence demonstrating that exposure to the chemical causes cancer in humans. This descriptor is also appropriate even if no convincing human studies are available, as long as the following conditions are met:
  - there is compelling and convincing studies where exposure to the chemical causes cancer in animals
  - the mode of action and associated key events[5] have been identified in animals
  - the key events have been observed in human populations that show evidence of an association between exposure to the chemical and cancer.

- Likely to be carcinogenic to humans. This descriptor is appropriate when the available tumor effects and other key data are adequate to demonstrate carcinogenic potential to humans.

- Suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential. This descriptor is used when human or animal studies suggest that a chemical causes cancer in humans, but the studies are not good enough for a strong conclusion that the chemical causes cancer in humans. It is not appropriate to predict cancer risk for these chemicals. The following are examples of situations that suggest a chemical causes cancer:
  - a marginal increase in tumors that may be exposure-related
  - tumors observed only in a single study

[4] EPA is in the process of finalizing its revised Guidelines for Carcinogen Risk Assessment, but the basic structure does not appear likely to change. As of the writing of this white paper, the July 1999 *Draft Revised Guidelines for Carcinogen Risk Assessment* serve as EPA's interim guidance to EPA risk assessors preparing cancer risk assessments until final Guidelines are issued. More recent draft guidelines were released in March 2003 (U.S. EPA, 2003b). These guidelines differ from the 1999 draft primarily in providing additional guidance regarding the approach for nonlinear low-dose extrapolation (see below), and in explicitly addressing children's risk.

[5] The key event is a precursor event that must occur in order for cancer to develop.

- the only tumors observed are ones that commonly occur spontaneously in one sex of one species.

- Data are inadequate for an assessment of human carcinogenic potential. This descriptor is used when available data are inadequate to draw conclusions about the likelihood of a chemical to cause cancer in humans, either because of the lack of pertinent or useful data, or because of conflicting data.

- Not likely to be carcinogenic to humans. This descriptor is used when the available data are considered robust for deciding that there is no basis for human hazard concern.

In EPA's draft guidelines, describing a chemical's mode of action is an integral part of preparing the cancer narrative. The guidelines direct that the entire body of data regarding a chemical's mode of action be compared against a set of criteria that help prove the relationship between the chemical's actions and the formation of tumors; the data for each tumor type are evaluated separately. Generally, chemicals are determined to have one of two broad categories of mode of action: genotoxic and nongenotoxic. If a chemical is determined to have a genotoxic mode of action, data show that the chemical causes cancer by reacting with DNA, the genetic material in the cell, resulting in mutations that give rise to tumors. If a chemical is determined to have a nongenotoxic mode of action, data show that it causes cancer without affecting the DNA. In the case of a nongenotoxic chemical, the guidelines require that the key event (the event that must occur in order for cancer to develop) be identified. This key event then becomes part of the narrative descriptor. For example, a chemical may be "not likely to be carcinogenic to humans" at doses that do not cause cytotoxicity (cell death), but "likely to be carcinogenic to humans" under conditions that cause cytotoxicity.

Under the draft guidelines, a two-step process is used to estimate the cancer risk. In the first step, the experimental data are evaluated and mathematical equations are used to predict the dose of a chemical that will cause a specific effect (e.g, the dose that will cause 10% increase in the incidence of tumors). This dose is called the LED_{10} (lower bound on the effective dose corresponding to 10% risk). As described for the 1986 guidelines, the models actually identify the 95% lower confidence interval on this dose (upper confidence interval on risk), which is used as a health-protective estimate. In the second step, the LED_{10} is used to describe the cancer risk of the chemical at environmentally relevant doses. This process is called "low-dose extrapolation", and the methods used depend on the chemical's mode of action. If the chemical has a genotoxic mode of action, or if the mode of action is not known, the cancer risk at environmental doses calculated by drawing a straight line between the LED_{10} and zero dose. The cancer risk is calculated directly from the slope of the straight line. If the chemical has a nongenotoxic mode of action, a safe dose (i.e., a dose at which the key event does not occur) is calculated from the LED_{10}, using uncertainty factors in an approach analogous to the development of the RfD.

Drinking Water Health Advisories and Guidelines

Once EPA has estimated risk values for noncancer toxicity and carcinogenicity, it then considers the populations (children vs. adults) exposed to the chemical in drinking water as well as the

duration of exposure. Based on information on both toxicity and exposure, EPA develops a set of health advisories and drinking water guidelines that specify the concentration of a chemical in water that should not result in harmful health effects under different conditions of exposure. EPA develops a "drinking water equivalent level" (DWEL) as well as one-day, ten-day, longer-term, and lifetime health advisories (HAs). The DWEL and the lifetime HA are then used to develop final drinking water standards as well as determine URTH. In addition, the shorter-term health advisory values are used as informal guidance to municipalities and other organizations when emergency spills or contamination situations occur.

The DWEL is calculated from the RfD, and thus applies to lifetime exposure. The DWEL represents the drinking water concentration that gives an adult a dose of chemical equivalent to the RfD, assuming that the adult does not take in the chemical from other sources such as food or air. Therefore, an adult who drinks water with a chemical present at this concentration for a lifetime is not anticipated to develop adverse, noncarcinogenic health effects. The DWEL is derived as follows:

$$\text{DWEL (mg/L)} = \frac{(\text{RfD}) \times \text{BW}}{\text{WI}}$$

where:

BW = 70-kg adult body weight

WI = Drinking water intake (2 L/day)

Similar methods are used to calculate Health Advisory (HA) values for noncancer effects. HAs are determined for lifetime exposures as well as for exposures of shorter duration (1-day, 10-day, and longer-term).

The HAs for exposures of less than a lifetime are calculated using an equation similar to the RfD and DWEL; however, the NOAELs or LOAELs are derived from acute (typically 2 weeks or less, but may be as much as 30 days) or subchronic (13 weeks, or 10% of the lifetime, for a rodent study) studies and identify a sensitive noncarcinogenic endpoint of toxicity. The HAs are derived as follows:

$$\text{HA} = \frac{\text{NOAEL, LOAEL or BMD x BW}}{\text{UF x WI}}$$

Using this equation, the following drinking water HAs are developed for noncarcinogenic effects:

- 1-day HA for a 10-kg child ingesting 1 L water per day. Ideally, the 1-day HA is developed from a single exposure toxicity study, but continuous exposure up to 5 days may be used.
- 10-day HA for a 10-kg child ingesting 1 L water per day. When developed from animal studies, the study duration should be 30 days or fewer.

- Longer-term HA for a 10-kg child ingesting 1 L water per day. This is developed from a study where exposure was for approximately 10% of the lifetime.
- Longer-term HA for a 70-kg adult ingesting 2 L water per day. This is developed from a study where exposure was for approximately 10% of the lifetime.

The lifetime HA is calculated from the DWEL and takes into account exposure from sources other than drinking water. The lifetime HA becomes the maximum contaminant level goal (MCLG) for a chemical that is not a carcinogen. For noncarcinogens, the lifetime HA is calculated as the product of the DWEL and the relative source contribution (RSC). The RSC is the fraction of the total exposure allocated to drinking water. The default RSC is 20%, and accounts for potential sources of exposure aside from drinking water, such as from ambient air and from food (U.S. EPA, 2000). For class C carcinogens, EPA's policy is to base the lifetime HA on the noncancer endpoint, but to include an additional safety factor of 10 to account for possible carcinogenicity of the chemical.

Note that the exposure assumptions used to develop the longer-term HA for a child result in a large degree of health protection. First, the longer-term HA is designed to be protective for exposures that last as long as 7 years (10% of the human lifetime), yet the body weight used to estimate this HA, 10 kg, is the weight of a small 1-year-old child. Second, the water ingestion rate used to estimate this HA, 1 L/day, greatly overestimates the amount of water actually consumed by children. For a 10 kg child, a water ingestion rate of 1 L/day corresponds to drinking 100 mL/kg BW-day. However, 95% of children age 1-10 only drink 64 mL /kg BW-day or less of water (U.S. EPA, 2002b). This means that the water ingestion rate is very health protective for children more than 1 year of age, and somewhat higher drinking water concentrations than the longer-term child HA are likely to also be protective for children.

EPA Approach to Setting Drinking Water Standards

After reviewing the data available, EPA sets a maximum contaminant level goal (MCLG), which is the maximum level at which no known or anticipated adverse health effects will occur and will allow for an adequate margin of safety (U.S. EPA, 2003a). MCLGs are non-enforceable public health goals. They consider only public health and do not take into account cost, the detection limits for the contaminant, or the available treatment technology. MCLGs represent the ideal drinking water level that public water systems should strive to achieve. As noted above, the MCLG for non-carcinogens is the same as the lifetime HA. For genotoxic carcinogens, or carcinogens for which a linear approach to low-dose extrapolation is used, the MCLG is set at zero. For carcinogens for which a nonlinear approach is used for low-dose extrapolation, the MCLG is set using an approach similar to that used for noncarcinogens (U.S. EPA, 2003a). For microbial contaminants, the MCLG is set at zero; this is because it is assumed that ingestion of even one protozoa, bacterium, or virus may lead to adverse health effects. EPA is conducting studies to see if certain microbial contaminants may have a safe level above zero, but so far none have been determined (U.S. EPA, 2003a).

Often, the MCLG is set at a level that is not realistic to achieve. For this reason, the EPA establishes an enforceable standard; most often this is a maximum contaminant level (MCL) (U.S. EPA, 2003a). The MCL is the maximum permissible level of a contaminant in water,

which is delivered to any user of the PWS (U.S. EPA, 1990). The MCL is set as close to the MCLG as is feasible. Feasible is defined by the SDWA to mean "feasible with the use of the best technology, treatment techniques, or other means which the Administrator finds available (taking cost into consideration) after examination for efficacy under field conditions and not solely under laboratory conditions" (Fensterheim, 2001). If there is no reliable method that is economically and technically feasible to measure a contaminant at extremely low levels, a treatment technique (TT) may be set instead of an MCL (U.S. EPA, 2003a). A treatment technique is an enforceable procedure that public water systems must follow to ensure control of a contaminant (U.S. EPA, 2003a). MCLs for non-threshold contaminants are set as close to zero as feasible, generally falling in the excess cancer risk range of 10^{-4} to 10^{-6} (U.S. EPA, 1990). Once the EPA has established an MCL or TT, public water systems have 18 months (unless otherwise specified) to come into compliance (Zavaleta, 1992).

EPA Approaches to URTH

When Congress passed the SDWA in 1974, it did not specify what constituted an unreasonable risk to health (Zavaleta, 1992), leaving EPA to develop guidance for determining URTH. This guidance has evolved slowly. In 1979, EPA developed guidance to assist states in determining URTH (U.S. EPA, 1979). Four criteria were considered in the evaluation of the unreasonableness of risk: the degree to which the MCL will be exceeded, the duration of the requested variance or exemption, historical data, and the type of population exposed (Zavaleta, 1992). In light of these criteria, URTH was generally considered to be any concentration that was two times the MCL. However, this approach did not take into account the toxicity or other properties of the contaminant (Zavaleta, 1992).

After the 1986 SDWA amendments, EPA reevaluated the 1979 URTH guidance and released a new draft guidance document in 1990. In this draft guidance, EPA incorporated contaminant toxicity information by using the same risk assessment methodologies to determine URTH values as were used to determine other drinking water criteria. The 1990 draft guidance compares risk assessments for cancer and non-cancer endpoints and considers exposure duration when determining URTH (U.S. EPA, 1990; Zavaleta, 1992[6]). EPA noted that, while ideally the variance or exemption period would be shorter than a lifetime, in reality past exposure to the contaminant might not be known. Therefore, EPA recommended that variances and exemptions not exceed seven years when the URTH is based on non-cancer endpoints. Using EPA's process, URTH is a *range* from the MCL to an upper bound of chemical-specific values presented in the draft guidance. However, EPA recognizes that States may determine that URTH is above this range based on site-specific factors such as site-specific exposure, including past exposure, population sensitivity, or volatility of the contaminant.

EPA (U.S. EPA, 1990; Zavaleta, 1992) recommended the following decision rules for threshold contaminants.

1. URTH equals the MCL, if the MCL is based on acute toxicity. (EPA considers that in this situation there is usually little margin of safety above the MCL. However if there is a

[6] In Zavaleta (1992) the URTH values are called "short-term acceptable risk (STAR)" levels. However the approach is the same as that taken in EPA's 1990 draft guidance.

greater margin of safety above the MCL, scientific judgment should be used to set an URTH that exceeds the MCL.)

2. URTH equals the longer-term HA for a child if the MCL is based on subchronic or chronic toxicity. EPA considers this to be adequately protective of potentially sensitive subpopulations. EPA noted that the DWEL could be used if data are not available to calculate a longer-term HA.

EPA (U.S. EPA, 1990; Zavaleta, 1992) recommended the following decision rules for non-threshold contaminants:

1. URTH equals the MCL, if the MCL is set at or above the 10^{-4} cancer risk.

2. URTH equals a water concentration that gives a 10^{-4} cancer risk, if the MCL is less than the 10^{-4} cancer risk

3. URTH equals 10 times the MCL, if the contaminant is a Group C carcinogen and the MCL includes an additional safety factor of 10 to account for this.

EPA (U.S. EPA, 1990; Zavaleta, 1992) also recognized that some contaminants have both noncancer and cancer effects and therefore, may have risk values based on both types of effects. In these cases, the noncancer and cancer effects should be compared before a final URTH value is determined. For example, the longer-term HA (or DWEL) should be compared to the water concentration that gives a 10^{-4} cancer risk (or 10 times the MCL); URTH equals the lower of these values.

In its final rule for arsenic, EPA (2002) proposed a different approach for setting an URTH value for arsenic. This approach was based on an extension of a policy decision by Congress, rather than an explicit determination that a certain level of risk is "unreasonable." For arsenic, Congress dictated that public water systems could spend 5 years with a 40 ppb exceedance of the new MCL (old MCL = 50 ppb, new MCL = 10) before being required to come in to compliance. EPA interpreted this statement as meaning that, in allowing this exceedance, Congress decided that exposure to 40 ppb for 5 years is not an "unreasonable risk to human health." For non-threshold carcinogens, cancer risk is directly related to both the concentration of the carcinogen in water and the amount of time that a person is exposed to the carcinogen. This value is essentially estimated by multiplying the water concentration in excess of the MCL by the number of years not in compliance with the MCL, resulting in the cumulative exposure. Thus, Congress decided that a cumulative arsenic exposure of 5 years x 40 ppb = 200 ppb-years did not constitute an unreasonable risk. EPA then stated that other combinations of different time periods and concentrations exceeding the MCL were not URTH as long as the cumulative exposure was for 200 ppb-years or less. For example, exposure to 20 ppb over the MCL for 10 years would not be URTH.

While this is, theoretically, an approach that could be applied to all non-threshold carcinogens, there is currently no accepted method for determining what cumulative exposure above the MCL is not URTH. The approach of allowing 5 years exposure to arsenic in excess of the new MCL is

based solely on Congressional policy. While similar extrapolations from Congressional policy could be conducted for other carcinogens, such extrapolations are unlikely to result in consistent levels of health protection. Therefore, we recommend that this approach not be generally applied for non-threshold carcinogens. A more consistent approach would use cumulative exposures based on acceptable levels of risk developed by risk managers, and using the principles described in Tiers 1-3, as described below.

Methods for Improving the Evaluation of URTH

U.S. EPA's approach to determining URTH is a well-reasoned and simple method that incorporates data on the toxicity of drinking water contaminants. However, the method proposed by EPA is, in reality, just a screening analysis – a method that incorporates numerous conservative default assumptions designed to be applicable nationwide. Both Congress (U.S. EPA, 1991) and EPA (U.S. EPA, 1990) recognized that States may need to adjust URTH values above the range recommended by EPA, based on site-specific considerations. Therefore, the remainder of this paper presents our suggestions for methods that States may use to incorporate more data to assess URTH on a site-specific basis. The methods are presented as a series of tiers that require an increasing amount of specialized expertise. These tiers and the issues addressed in each tier are illustrated in Figure 1.

For the purposes of this white paper, Tier 1 methods are approaches that can be applied easily based on readily available information, and require little or no specialized knowledge. Tier 2 methods require additional input from an experienced toxicologist/risk assessor, but can be completed without substantial mathematical or other specialized expertise. Tier 3 methods require expert analysis, and may be time-intensive, but have the advantage that results of the analysis can be incorporated into cost-benefit analyses.

Tier 1

In Tier 1, three approaches are examined to characterize URTH. The first is to look at EPA methods for URTH, the second is to look for recent toxicity/risk assessments on the specific contaminant, the third is to investigate the degree of imprecision in the contaminant's underlying risk value.

Look at EPA URTH Guidance. The first step in Tier 1 is to examine the existing EPA guidance for URTH as described earlier. If an adequate exemption to an exceedance can be granted using current EPA methods, one does not need to further pursue any other steps in Tiers 1, 2 or 3.

Review Literature for New Information. The second step in Tier 1 is based on the fact that in its 1990 draft guidance on URTH, EPA presented the URTH values for all contaminants that had MCLs at the time the guidance was written. However, that guidance is now 13 years old, and new science is available for many of the contaminants. Therefore, the second step in Tier 1 is to look at recent evaluations of the contaminant, and to determine whether the existing drinking water guidelines are based on current science. Sources for more current assessments includes IRIS (the Integrated Risk Information System) or the Office of Pesticides Programs (OPP). For example, a recent re-evaluation of atrazine has determined that the mode of action for

carcinogenicity is not relevant to humans (U.S. EPA, 2002c); this re-evaluation is currently being incorporated into updated evaluations from EPA's Office of Water. If new science is available for a compound, then follow EPA's decision rules, described above, to estimate a new URTH value based on new science.[7] Based on the updated RfD or cancer assessment obtained from more recent sources, health advisory values, as well as the DWEL, can be derived using the simple conversions described above. These drinking water concentrations can then be used to develop an URTH value according to EPA's current guidance.

Examine Risk Value Imprecision. If the contaminant concentration in drinking water is above the URTH value derived using EPA's methods and updated toxicity data, and if no new scientific assessments are available for the compound in question, then the third step in Tier 1 is to consider the uncertainty or imprecision in the RfD. For example, if the RfD that is the foundation for the MCL value is developed using an uncertainty factor of more than 100, then the URTH value could be up to 3-fold higher than the value proposed in EPA guidance. This 3-fold excess is based on the fact that most risk assessors consider the RfD as really only an estimate, and that the "true" RfD is within a 10-fold range around this estimate. Although interpretation of this statement varies, most scientists consider this to mean that the "true" RfD may be 3-fold above or below the estimated RfD (Felter and Dourson, 1998). That is to say that risk assessors generally cannot distinguish between an RfD and a value that is 3-fold higher or lower than the RfD because of this imprecision. However, the actual imprecision of the RfD depends on the amount of data available for that contaminant and the resulting size of the composite uncertainty factor. The imprecision is much higher for chemicals with large uncertainty factors than for chemicals with small uncertainty factors (Felter and Dourson, 1998). For example, when the RfD is developed from a complete database that identifies a NOAEL in a chronic study, the standard uncertainty factor is 100 or less. For such RfDs, the imprecision in the RfD is smaller, because the assessor is more certain about the critical effect, in comparison with RfDs for contaminants with uncertainty factors greater than 100.[8] Since the MCL is based in part on the RfD, this smaller imprecision for chemicals with uncertainty factors of 100 or less would suggest that any exceedance of the MCL is an URTH. In contrast, for contaminants with a composite uncertainty factor of greater than 100, there is less certainty that the RfD is near the threshold of human toxicity. In fact, because of the generally conservative nature of uncertainty factors, the RfD is likely to be lower than the actual threshold. In such cases, a three-fold exceedance seems less likely to be an URTH.[9]

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[7] This is a tier 1 exercise, requiring minimal to no toxicology expertise, if updated risk values exist. If new science exists, but the risk values have not been updated, this step would ~~fall into tier 2,~~ require ~~ing~~ toxicology and risk assessment expertise to implement.

[8] If, however, the RfD was developed before the database uncertainty factor was incorporated into the RfD methods, in approximately 1988, then an updated estimate of the RfD might be lower than the current RfD. This means that, for chemicals for which the RfD was developed prior to 1988, further investigation of the quality of the supporting database would be needed prior to considering a 3-fold exceedance acceptable, even for chemicals with uncertainty factors greater than 100.

[9] Evaluating the imprecision for RfDs based on acute toxicity should be approached carefully, particularly if the uncertainty factor in excess of 100 is based on lack of database or lack of NOAEL. Because we generally accept that toxicity increases with exposure duration, the principal underlying the concept of URTH is that short-term exceedances would not cause health effects when the MCL is based on a chronic effect. However, when the MCL is based on an acute effect this rule does not apply and one would need to conduct a more in-depth evaluation of the impact of the imprecision in the MCL.

Tier 2

In evaluating URTH for Tier 2, a risk assessor is asked to consider three types of contaminant-specific or site-specific data, rather than the default assumptions used by EPA to develop DWELs and longer-term health advisories. General toxicology and/or risk assessment expertise is needed to apply these approaches, but sophisticated mathematical knowledge is not needed. It is expected that in all cases, application of these three approaches requires data about the contaminant and/or the population served by the water system, so that one can move beyond Tier 1 defaults.

Evaluate Relative Source Contribution (RSC). As noted above, the RSC is the fraction of the total exposure to the contaminant that results from drinking water. This RSC is multiplied by the RfD in establishing the MCL.[10] Evaluating whether the RSC is based on data or is the default value of 20% can provide insight into URTH. For example, when the RSC for a chemical is small, let us say 20%, then a relatively small amount of the total exposure to that chemical comes from drinking water, while the remaining 80% of exposure comes from other sources. When possible, EPA uses data from nation-wide surveys to estimate the RSC. But if no data are available at the time of the MCL development, EPA will assume a default RSC of 20%. Therefore, if new exposure data are available since the time of the MCL development, or if data specific to the water system are available, it is not only possible, but recommended, to use these data to develop a RSC.

How does this data-derived RSC affect how one approaches URTH? It does so in two ways, first by changing the underlying basis of the MCL, and second, by allowing consideration of imprecision as discussed in Tier 1. As an example of the first way, consider the situation where sufficient exposure data were available to determine an RSC of 80%, rather than the default of 20%. This would mean that a drinking water concentration that protects the general population and sensitive populations is really 4-fold higher than the MCL. Such a situation could arise either due to new data that replaces the default RSC on a nationwide data (as described in the Chemical A example based on preliminary data, below), or due to site-specific information. This concentration 4-fold above the MCL is therefore not an URTH for the population of interest. Thus, investigating the value of RSC based on site-specific data directly affects the value of the MCL and the resulting analysis of URTH, and for a specific community, might be a worthwhile exercise.

The second way that RSC affects the URTH is by allowing consideration of the underlying imprecision of the MCL. For the majority of chemicals where a default RSC of 20% is used in the development of an MCL, a 3-fold exceedance of the MCL places the total exposure at 140% of the RfD. (This calculation is illustrated by the following example. Imagine a chemical for which the RfD is 10 mg/kg-day, and the RSC is 20%. This means that people eat or drink 8 mg/kg-day from sources other than drinking water (e.g., from food or bottled beverages), and they can consume up to 2 mg/kg-day from drinking water. The MCL would be based on the

[10] The RSC is actually used to derive the MCLG, and the MCL is then set as close to the MCLG as possible, taking cost and feasibility into account. To simplify the following discussion, we are assuming that the MCL and MCLG for the contaminant of interest are the same number.

value of 2 mg/kg-day, as described above. A 3-fold exceedance of the MCL means that these people would consume 6 mg/kg-day from drinking water. Adding in the 8 mg/kg-day received from other sources, the total dose is 14 mg/kg-day, or 140% of the RfD.) This is well within the precision of many RfDs and may not be of concern, depending on issues associated with imprecision as discussed above.

Examine Exposure Parameters. Under EPA's current guidance, drinking water guidelines and URTH values are developed using standard, default values that estimate how much tap water people drink or consume as part of food used in cooking. For example, it is assumed that adults drink 2 liters of water (a little less than half a gallon) every day for an entire 70-year lifetime and that 100% of that water comes from the water system in question. These exposure parameters are health-protective and are appropriate to use when developing guidelines at a nationwide level. However, if a small water system exceeds an MCL that was developed using these default assumptions, it is reasonable to assess whether the default exposure parameters are appropriate for the population that will actually be exposed. With a small water system, it would be feasible to gather data that describes how the population is exposed to the water. The basic question to answer is "how much of the water from the water system are people actually drinking each day?" If most of the people served by the system don't like the taste of the water and drink bottled water, then the exceedance of the MCL might not be an URTH.

Investigate Sensitive Populations. The RfD is a value that is designed to protect the entire population, including sensitive individuals, by incorporating health protective assumptions and using uncertainty factors to account for sensitive individuals. This suggests that if all of the people exposed at a particular water system are "average" rather than "sensitive," then it would be reasonable for the MCL to be higher than if the exposed population contained sensitive individuals. For example, consider a water system that only serves a factory and that only adults are exposed to the water. This information can be used in two ways. First, EPA's guidance says that URTH equals the longer-term HA for children. Therefore, in a situation where only adults are exposed, the longer-term HA for an adult can be used as the URTH, rather than the HA for a child. Also, for some chemicals, children constitute the sensitive population. Therefore, exposure of adults can be higher than the MCL without increasing risk to the exposed population. This might apply, for example, to a chemical like nitrate, to which young children have a much higher sensitivity than adults. (See the example, below.) Due to this difference in sensitivity, the URTH level for nitrate in a public water system that only serves a factory could be higher than the URTH for a public water system serving a school. Identifying how high the URTH level could be would require looking at the underlying epidemiology and toxicology data, and then deriving an RfD and DWEL for the less sensitive population, taking into account the variability in the exposed population. This consideration is applicable primarily for non-community water systems, and would be applied based on knowledge of both the specific chemical and characteristics of the exposed population.

Tier 3

Tier 3 describes methods that can be used to estimate the risk posed by exposures at higher concentrations than the RfD, or the MCL. These methods can help answer the question of how far the MCL can be exceeded without causing unreasonable risk to health. These methods do not

necessarily result in "an URTH value," however, as the Tier 1 and 2 methods do. Rather, they describe the probability that certain health effects will occur as the water concentration increases above the MCL. Specialized knowledge of both mathematical modeling procedures and toxicity of chemicals is needed to conduct a Tier 3 analysis. Once this type of analysis has been conducted, a risk manager has the tools to determine what level of risk is acceptable as well as compare the costs of achieving a certain water concentration with the health benefits of doing so.

For contaminants that cause cancer, methods that calculate the probability of response already exist for risk managers to consider in the determination of URTH. For noncancer risk assessment, however, the traditional focus is on identifying a "safe" dose, such as an RfD, as described above. The RfD method does not predict the risk at doses that are above the RfD. This means that risk managers have not been able to readily estimate the risk to the population of interest related to noncancer effects resulting from exceeding the MCL. However, the issue of how to evaluate risk above the RfD is an active area of research within EPA and elsewhere. It has been discussed in an EPA workshop and in several publications (e.g., Evans et al., 2001; Teuschler et al., 1997, 2001; Price et al., 1997; Dourson et al., 1997). Note that EPA has not developed formal guidance on how to evaluate risk above the RfD, and has not used any of these methods for regulatory purposes.

This section briefly introduces three general approaches for calculating the risk at low doses (termed "risk above the RfD"). These are categorical regression, probabilistic methods, and mechanistic understanding.[11]

Categorical Regression. Categorical regression is a tool that can be used to estimate the probability of an adverse effect at various doses above the RfD. This method fits a mathematical curve based on severity categories of overall toxicity, and can incorporate data on different endpoints, rather than focusing on just the critical effect. Categorical regression incorporates information on how both the likelihood and the severity of response increase with dose. Each response is placed into a category based on severity, or strength, of response. For example, responses may be classified as Severity 1: No Observed Adverse Effect Levels (NOAELs), Severity 2: adverse effect levels, and Severity 3: frank effect levels. Note that the numbering of the severity categories is strictly for placing the different responses in order of increasing severity. There is no quantitative interpretation to this numbering. For example, responses of severity 2 are not necessarily twice as bad as responses of severity 1.

Categorical regression can quantitatively include data that cannot be included in other modeling approaches. For example, qualitative information on the severity of effects observed at specified dose levels can be included in categorical regression, but cannot be included in other dose-response modeling approaches. Despite this advantage, the quality of each study and response from that study must be evaluated before a response is added to the categories. Depending on how the categories are defined for a given analysis, placing the responses into categories may require considerable toxicological evaluation and judgment. Another disadvantage is that

[11] All of these approaches can provide reasonable estimates in the absence of a better approach, but all also have hidden uncertainties. Uncertainties in these approaches are of particular concern if one is extrapolating from animal data, and does not know that the chemical acts the same in way humans and in the animal species of interest.

categorical regression requires mathematical expertise and sophisticated software to perform the modeling.

Categorical regression is most accurate when the RfD is based on human data, because in this case the degree of extrapolation is small and the end point of concern is known. For example, Dourson et al. (1997) applied categorical regression to data from human exposures to aldicarb and calculated risk at doses above the RfD. (See the example, below.) Teuschler et al. (1999) evaluated other chemicals of interest to EPA as well. Confidence in this approach was enhanced by the close proximity of the data to the RfD. (In this case, the RfD was only 1/10 the lowest dose for which data were available, so a dose 10 times the RfD was in the range of the data.) Greater caution would be needed in the estimation of risks further from doses at which data exist.

Categorical regression can result in a statement such as: "We estimate that there is a 10% probability that a dose of 0.5 mg/kg-day would be considered an adverse response or lower in the general population (if we had the human data)." Note that categorical regression does not always predict a population response (e.g., a response in 10% of the population) or the specific endpoint. While the fact that categorical regression does not predict probability of response can be a hindrance for some applications, it has been suggested that categorical regression can be used to consider relative risk from different chemicals (Teuschler et al., 1999). While URTH itself is considered on a chemical-by-chemical basis, such risk comparisons could be useful in comparing treatment technologies. For example, different disinfection methods result in different disinfection byproducts. Categorical regression may be useful in comparing the risks from different treatment methods, and choosing the best overall method.

Probabilistic Methods. Probabilistic methods note that the RfD is an *estimate* of the threshold for sensitive individuals, and provide information on the likelihood (probability) of response at various doses. One way to do such calculations focuses on the uncertainty factors that are used to develop the RfD. Traditionally, default uncertainty factors are designed to provide adequate protection for most chemicals. However, probabilistic methods take into account that the "true" uncertainty factor for each different chemical lies somewhere along a range of values (called a distribution). Probabilistic methods use the "distributions" for the uncertainty factors to estimate an overall distribution of the composite uncertainty factor, and therefore the distribution for the RfD. For example, the "true value" for animal to human extrapolation (UF_A) is estimated to be 10 or less for 95% of the chemicals in the world. However, it is unlikely that any individual chemical will be in the 5% of the chemicals for which the "true value" is 10 or higher for each of the five areas of uncertainty. Therefore, the information on the probability of the "true value" for each of the uncertainty factors is combined to develop a "probabilistic" estimate of the composite uncertainty factor. This probabilistic estimate is then used to estimate the RfD, rather than the default value. The distribution can also be used to estimate risks at doses above the RfD. Other probabilistic approaches estimate the risk based on general mathematical properties of distributions. A risk manager can evaluate these estimates of risk at specified doses, and make a judgement regarding whether the risks are "unreasonable." Estimates of risk at doses above the RfD are not possible using the traditional RfD method.

Mechanistic Understanding. If a contaminant has sufficient data on its mode of toxic action, this information can be combined with existing experimental animal toxicity data or epidemiology

data in humans. Calculations can then be conducted using information on basic physiology and on how the chemical interacts with the body, to estimate the threshold for an effect or to estimate the degree of response at specified exposure levels. A simplified example of this sort of calculation is provided for nitrate, below.

Examples of How the Various Tiers Might Work

Nitrate

Nitrate is found naturally throughout the environment as a result of human and animal waste and nitrogen-containing fertilizers used for agriculture. It can enter the water supply and can be found in drinking water, particularly wells in rural areas. When someone drinks water that contains nitrate, the nitrate is converted to nitrite by bacteria in the gut. Nitrite is then absorbed into the bloodstream, where it changes hemoglobin (the oxygen-carrying component of blood) into methemoglobin. Methemoglobin cannot bind oxygen and transport it to the tissues. Therefore, consuming enough nitrate can decrease the ability of the blood to carry oxygen. Normally, about 1% of the hemoglobin in the body is present as methemoglobin, and perhaps as much as 3%. A concentration of 10% or higher is associated with symptoms. People with 10% or higher methemoglobin in their blood, known as methemoglobinemia, have bluish skin and lips, because their tissues are lacking in oxygen. Infants are a sensitive population and are more susceptible to the effects of nitrate because they have high levels of the bacteria that convert nitrate to nitrite. Infants also have less acidic conditions in their stomachs, which makes it easier for these bacteria to grow. Bacterial contamination of water also increases the risk of methemoglobinemia, because it increases the amount of nitrate-converting bacteria in the gut. Adults with conditions that make their stomach less acidic also have increased risk. Vitamin C deficiencies have been shown to increase an individual's risk as well, since vitamin C reduces the amount of methemoglobin. Finally, diarrhea increases the risk from nitrate, because it makes the stomach less acidic and because people increase their water intake to compensate for fluid loss. Therefore, adults with less acidic stomachs, vitamin C deficiency, or diarrhea would all also be considered to be sensitive subpopulations

EPA derived an RfD of 1.6 nitrate-nitrogen/kg-day based on a NOAEL of 1.6 nitrate-nitrogen/kg-day in a sensitive population (infants ages 0-3 months), with a composite uncertainty factor of 1. This reference dose was based on looking at the relationship between reported cases of methemoglobinemia, and the concentration of nitrate-nitrogen in the water. Because this RfD is unusual in that the dose in mg/kg-day was calculated from the drinking water concentration, we have a good estimate of the drinking water concentration relevant to the target population. However, the authors of the key study noted that methemoglobinemia is not a reportable disease, so neither the number of infants exposed to nitrate in water nor the true number of methemoglobinemia cases is known. The study authors suggested that the number of methemoglobinemia cases reported their study is probably a poor indication of the true incidence. Thus, information is not available on the true percentage of the infants with methemoglobinemia at various concentrations of nitrate in drinking water. In addition, the study authors noted that clinical data were often insufficient for definite diagnosis, and the water samples were often collected months after the occurrence of the case, increasing the uncertainty in the exposure estimate.

Let us presume that a water system has a persistent concentration of nitrate of 15 mg/liter. The MCL for nitrate is 10 mg/liter. Can an exemption be granted for this exceedance based on one of these suggested tiers? Tier 1 suggests first looking at EPA's URTH guidance to determine whether a water concentration of 15 mg/liter (mg/L) is above the value EPA has determined to

be URTH. In the case of nitrate, the MCL is based on an acute effect, methemoglobinemia, in newborn infants, the sensitive subpopulation. Recall that EPA's URTH guidance states that the MCL equals URTH when the MCL is based on an acute health effect. Therefore, a water concentration of 15 mg/L would not qualify for an exemption because it exceeds EPA's URTH value of 10 mg/L

The next part of Tier 1 would be to seek new risk information that became available after the time of the MCL development. In the case of nitrate, no new epidemiology information is available that would suggest a different conclusion than the work of Walton (1951) and others that was used as the basis for the RfD and MCL. Thus, even though the risk information used as the basis of the MCL was developed many years ago, it still appears to be valid, and an exemption cannot be granted on this basis.

Finally, one investigates the underlying imprecision in the RfD supporting the MCL. In the case of nitrate, the underlying imprecision is quite small. For example, none of the cases reported by Walton (1951) were in infants drinking water containing 0-10 mg/L (the NOAEL used as the basis of the RfD), while only a small number of reported cases at concentrations of 11 to 20 mg/L (the LOAEL), were associated with this effect, and the affected infants might have also had bacterial infections at the same time. This suggests that the threshold for this effect is fairly well pinpointed. The authors noted, however, that methemoglobinemia is not a reportable disease, and the reported cases in their study are a poor indication of the true incidence. Since the authors based their evaluation only on reported cases, and did not conduct a statistically valid scientific sample, it is possible, therefore, that there were some cases of methemoglobinemia at concentrations at or near the NOAEL. Furthermore, the concentration in this example, 15 mg/L, falls into the concentration range associated with the LOAEL, indicating that methemoglobinemia may occur in sensitive infants at this water concentration. Thus, based on Tier 1, an exemption cannot be granted for 15 mg/L because one cannot conclude that this level would not be associated with an URTH.

One then turns to Tier 2.

Tier 2 suggests first investigating the basis of the Relative Source Contribution (RSC) used as the basis of the MCL to determine whether a value of 15 mg/L is associated with an URTH. In the case of nitrate, a relative source contribution of 100% was used to develop the nitrate MCLG. This is because newborn infants, the sensitive population, are presumed to be 100% bottle-fed, with nitrate coming from no other source. Not only is this presumption reasonable, but any value less than 100% would only serve to lower, not raise, the MCL, making the value of 15 mg/L more of an exceedance and more likely to be associated with an URTH. An exemption cannot be granted on this basis.

Next, exposure assumptions are investigated. In the case of nitrate, the RfD was developed assuming that 4 kg infants drink 0.64 liters of formula per day (and therefore 0.64 liters of water). Different exposure assumptions could have been used. However, the NOAEL used as

the basis of the RfD was actually measured in mg/L.[12] Therefore, even though different exposure assumptions could have been used to estimate the RfD, the underlying NOAEL of 10 mg/L would not change. Thus, an exemption cannot be granted on this basis. An additional exposure assumption is that newborn infants are bottle-fed. If babies receive all or part of their nutrition from breast-feeding rather than bottle feeding, it is likely that this would reduce the dose of nitrate that the infants receive. Information on the amount of nitrate excretion in breast milk, if any, would be needed in order to determine how much the dose is reduced. This would allow exceedance of the MCL for bottle-fed babies, but these higher drinking water levels would require that bottled water be used to prepare formula for bottle-fed babies, to prevent these babies from being put at risk.

Finally, the sensitive population could be investigated. In the case of nitrate, newborn infants are the primary sensitive population. In water systems where such individuals are not likely to be found, for example, a factory with its own water system or a military complex without children, granting an exemption seems reasonable. The approach in this case would be to look at the underlying epidemiology and toxicology data, and derive an RfD for the less sensitive population. In such a case, the derived general population RfD would need to take into account other sensitive populations mentioned in the first paragraph of this section (e.g., people with vitamin C deficiency or high stomach pH). This "general population" RfD would be higher than the existing value and could form the basis of the exemption.

One then turns to Tier 3.

Tier 3 suggests investigating categorical regression, which would involve looking at the entire database considered in the evaluation of the MCL to determine whether a value of 15 mg/L is associated with an URTH. In the case of nitrate, *TERA* conducted some preliminary categorical regression modeling in unpublished work for EPA several years ago. Based on this preliminary categorical regression analysis, we estimated that there is some degree of non-clinically significant methemoglobinemia (methemoglobin concentration in the range of 3-9%) in infants at water concentrations of 10 mg/L (the RfD), but that less that 1 in 1000 infants would respond (methemoglobin >10%) when water concentrations range from 11 to 20 mg/L (the LOAEL in the study used to derive the RfD). However, there is low confidence in this estimate because the incidence of methemoglobinemia was likely under-reported and there are no data that describe whether there are more cases of methemoglobinemia as the nitrate concentration increases, or whether the cases become more severe with increasing concentration. This also means that more precise estimates of risk are not possible with the available data. The animal data on nitrate are not appropriate to use for estimating the risk above the RfD because human infants are so biologically different from both adults and experimental animals. This information could be used by a risk manager to determine whether specific concentrations of nitrate in drinking water represent an unreasonable risk to human health.

We determined that probabilistic methods are not applicable for evaluating nitrate because of the data insufficiencies discussed above.

[12] This is the opposite of what usually occurs, where the mg/kg-day NOAEL is divided by uncertainty factors to develop the mg/kg-day RfD, and then the RfD is used with exposure assumptions, such as 2 L/day for a 70 kg adult to calculate the MCL measured in mg/L.

Next, mechanistic information could be used to evaluate the MCL to determine whether a value of 15 mg/L is associated with an URTH. While this sort of analysis does not estimate the risk above the RfD, it can confirm (or refute) the supposition that the risk at the RfD is zero, even in sensitive populations. In the case of nitrate, good mechanistic information exists in order to investigate this issue. For example, literature values of body weight and total hemoglobin are available for infants. Typical values for newborns are 3 kg and 48 g, respectively (Shabib, undated). The amount of nitrate that it takes to oxidize hemoglobin to a 10% level of methemoglobin in infant blood is estimated at 0.0046 g.[13] If we use a literature value for formula consumption by newborns of 0.16 L/kg/day (Davidson et al., 1975), then it follows that 3 kg infants consume 0.48 L of formula/day. We also assumed that the methemoglobin formed from a daily dose of nitrate remains in the blood as methemoglobin for a full day before being converted back to "normal" hemoglobin. Based on these assumptions, it follows that the amount of nitrate in water needed to cause a 10% methemoglobin concentration is 0.01 g/L, or 10 mg/L. This is the same as the value of 10 mg/L used as the basis of the RfD. Although this assessment could be refined if data were used to replace some of the assumptions,[14] this analysis suggests that an exemption could not be granted for nitrate on a mechanistic basis. However, in light of the assumption that all of the nitrate is ingested at once and is converted to nitrite, this approach does support the supposition that the risk at the RfD is zero, or very near zero.

Chemical A

This hypothetical drinking water contaminant is a pesticide, and is found contaminating both groundwater and surface water. The primary routes of human exposure are from contaminated drinking water, or eating food containing residues of Chemical A. Chemical A acts by interfering with the regulation of the nervous system. In the presence of Chemical A, certain types of cells are over-stimulated by the nervous system. This is a short-term effect that happens quickly after exposure to Chemical A. Symptoms of exposure in humans are seen mostly on the nervous system, including dizziness, skeletal muscle weakness, stomach cramps and pain, diarrhea, excessive sweating, blurred vision, breathing difficulty, and muscle convulsions.

[13] This value is derived in the following manner:

- it is known that 48 g of hemoglobin (literature value for newborns) x 1 mol/64,000g (molecular weight of hemoglobin) = 0.00075 moles;
- it is known that 0.00075 moles of nitrate x 62 g/mol (molecular weight of nitrate) = 0.046 g nitrate;
- if we assume that 1 mole of nitrate is needed to oxidize 1 mole of hemoglobin, it then follows that 0.0046 g nitrate is needed for 10% oxidation of hemoglobin to methemoglobin.

[14] For example, methemoglobin is always present in small amounts in the blood, and the body is able to convert methemoglobin to "normal" hemoglobin. Assuming that the methemoglobin formed is in the blood for a full day is likely to be incorrect. Conversely, these calculations assumed that infants not exposed to nitrate have 0% methemoglobin. While the concentration of methemoglobin in infants was not identified in this exercise, the concentration in adults is 1-3%. This means that a nitrate dose that converts only 7-9% of the hemoglobin to methemoglobin is sufficient to result in a methemoglobin concentration of 10%. Although these two considerations work in opposite directions, the first consideration is likely to have a larger impact. Therefore, this overall calculation is a conservative one, and it is possible that the nitrate concentration needed to result in 10% methemoglobin is higher than the concentration estimated here.

In this example, the RfD for Chemical A is 0.001 mg/kg-day, based on a NOAEL of 0.01 mg/kg-day in a clinical study in human volunteers. Because the NOAEL was identified in the general human population, an uncertainty factor (UF) of 10 was used in determining the RfD, to account for human variability and sensitivity.

EPA does not currently have an MCL for Chemical A. However, using standard methods, we will assume that the MCL for Chemical A is 0.007 mg/L, the same as would be the derived MCLG.[15] If a water system has a persistent concentration of Chemical A of 0.02 mg/L, can an exemption be granted for this exceedance based on one of these suggested tiers?

Tier 1 suggests first looking at the EPA guidance to determine whether a water concentration of 0.02 mg/L is above the value EPA has determined to be URTH. In the case of Chemical A, the EPA guidance would not support an exemption at 0.02 mg/L because the underlying risk information is based on an acute to short term effect in humans.

The next part of Tier 1 would be to seek new risk information since the time of the MCL development. In the case of Chemical A, a new and controversial evaluation is available from EPA's Office of Pesticide Programs that would suggest a lower MCL than that derived from the existing information on EPA IRIS. However, even though the risk information used as the basis of the assumed MCL of 0.007 mg/L is older, it may still be valid pending further review of EPA's newer evaluation and resolution of the controversy surrounding the use of human data as a basis of the RfD.[16] An exemption cannot be granted on this basis pending resolution of the current review and controversy.

Finally, one investigates the underlying imprecision in the RfD supporting the MCL. In the case of Chemical A, the underlying imprecision is small. Nervous system symptoms were not seen in any of the people exposed to 0.01 mg/kg-day, the NOAEL used as the basis of the RfD, but were seen in a small number of people exposed to a dose 2.5 times higher. The RfD is known fairly precisely in this case because it is based on human data, and as a result an uncertainty factor of only 10-fold is used to estimate the RfD. An exemption cannot be granted based on imprecision, because the total uncertainty factor is less than 100. Although a concentration slightly higher than 0.007 mg/L, such as 0.02 mg/L, might not be associated with symptoms in healthy adults, no data exist to ensure that sensitive groups would not develop symptoms. Thus, based on Tier 1, an exemption cannot be granted for 0.02 mg/L because one cannot conclude that this level would not be associated with an URTH.

One then turns to Tier 2.

Tier 2 suggests first investigating the basis of the Relative Source Contribution (RSC) used as the basis of the MCL to determine whether a value of 0.02 mg/L is associated with an URTH. In this example, we used a relative source contribution of 20%, because this is EPA's general

[15] This value is derived based on an RfD of 0.001 mg/kg-day (as above), a 70 kg body weight, 2 liters of water consumed per day and a RSC of 20% (i.e., 0.001 mg/kg-day x 70 kg ÷ 2 L/day x 0.2 = 0.007 mg/L).

[16] EPA's current assessment, found on IRIS, is based on human data. EPA's newer assessment, developed by OPP, is based on experimental animal data and is currently under active agency review, including a National Academy of Sciences review of the use of human data as the basis of risk values.

default value. For the purposes of illustration, imagine that a reevaluation of the RSC for Chemical A indicated that an appropriate RSC would be 80%. The resulting MCLG (and thus the MCL) could then be as high as 0.03 mg/L; on the basis of this new value an exemption of 0.02 mg/L could be granted.[17] In practice, however, a substantial database would be required before EPA would consider a RSC as high as 80% for a pesticide.

Another possible approach in Tier 2 would be to investigate exposure parameters used to develop the MCL. In the case of Chemical A, standard assumptions of 2 liters of water and 70 kg of body weight were used for lifetime consumption. Different exposure assumptions could be used if the population is different from what these assumptions might imply. For example, if the water system were in Alaska, and folks routinely drank less than 2 liters of water per day and weighed more than 70 kg, then an exemption might be granted pending the results of the calculation using the water consumption and body weight for the population of interest.

Finally, the sensitive population could be investigated to determine whether the water system of interest serves the sensitive population. However, in the case of Chemical A, the sensitive population is not known, and thus, an exemption based on this evaluation could not be granted.

One then turns to Tier 3.

Tier 3 suggests investigating categorical regression, which would necessitate looking at the entire database considered in the evaluation of the MCL to determine whether a value of 0.02 mg/L is associated with an URTH. While a categorical regression analysis does not exist for Chemical A, such an evaluation has been done by Dourson et al. (1997) for a related chemical, aldicarb. In the case of aldicarb, the underlying database is sufficiently strong in order to develop risk above the RfD, and therefore, risk above the MCL, with confidence. Dose-response data are available in humans, and minimal extrapolation is needed from the range of the data down to the RfD. Assuming that an average adult weighs 70 kg and drinks 2 L of water each day, and taking into account the default RSC of 20% (for illustrative purposes), an adult living where the water concentration of aldicarb is 0.02 mg/L would receive a daily aldicarb dose of 0.003 mg/kg. Dourson et al. (1997) estimated that at this dose there is the likelihood that between 1.5 and 7 people out of every 10,000 people would develop nervous system effects drinking this water. Risk managers would need to determine if this degree of risk is an URTH. If the risk is not considered unreasonable, an exemption could be granted.

Probabilistic methods or mechanistic information could also be attempted in the evaluation of the MCL to determine whether a value of 0.02 mg/L is associated with an URTH. However, such probabilistic or mechanistic information would have to be developed for Chemical A.

Bromate

[17] While this example is listed in tier 2 to illustrate the application of the RSC, in practice this updated value would be reflected simply in a revised MCL and MCLG. Replacing the RSC of 0.2 with 0.8 would result in a Lifetime Health Advisory of 0.03 mg/L, and hence an MCLG of 0.03 mg/L. In this case, 0.02 mg/L would not longer exceed the MCLG (and would certainly not exceed the MCL), and thus no exemption would be needed.

This contaminant can be formed as a byproduct in water when water containing the bromide ion is disinfected with ozone gas is used to kill harmful bacteria in the source water.

Bromate exposure can result in effects on the kidney. The most common, immediate signs of poisoning are severe irritation of the gut (vomiting, pain, diarrhea) and nervous system depression (lethargy, loss of reflexes). Bromate has also been found to cause cancer in rats, although studies in people are not available. Tumors were observed at multiple sites, including the kidney, the thyroid, and the peritoneum (a membrane in the stomach cavity). Bromate can cause damage to DNA directly by mutagenesis. It can also damage DNA by the production of reactive forms of oxygen (a condition known as "oxidative stress"), which then can result in damage to DNA. However, the exact mechanism by which bromate causes tumors is not known. Given the limited data on the possible mode of action for bromate, EPA assumed that the rat tumors are produced by a mode of action that is relevant to humans. Under EPA's rigorous standards, the data are not sufficient to conclude that bromate is causing tumors by a nongenotoxic mode of action. Based on these considerations, EPA used the linear no-threshold approach to estimate the cancer risk from bromate.

Because bromate is considered to be a carcinogen that interacts with DNA, the MCLG is 0. In the 2001 evaluation, EPA also calculated that a concentration of 0.005 mg/L corresponds to a 10^{-4} cancer risk. Expressed another way, the risk of cancer is 2 in a 100, or 0.02, for every mg/L of bromate in water. However, the current detection limit for bromate in water is 0.01 mg/L, which is twice the 10^{-4} cancer risk level. Therefore, EPA's current MCL, which was established prior to the 2001 evaluation, is set at the detection limit. As described in a recent Federal Register notice announcing the proposed Stage 2 Disinfectants and Disinfection Byproducts Rule, EPA intends to maintain the MCL at 0.01 mg/L, despite the revised estimate developed in 2001 of the 10^{-4} cancer risk (U.S. EPA, 2003c), because a more stringent bromate MCL could potentially decrease disinfectant use, resulting in less protection from bacterial contamination.

If a water system has a persistent concentration of bromate of 0.04 mg/L, can an exemption be granted for this exceedance based on one of these suggested tiers?

Tier 1 suggests first looking at the EPA's URTH guidance to determine whether a drinking water concentration of 0.04 mg/L exceeds the value that EPA has determined to be URTH. In the case of bromate, the EPA guidance would not support an exemption at 0.04 mg/L because the MCL exceeds a 1×10^{-4} risk level.

The next part of Tier 1 would be to seek new risk information since the time of the MCL development. In the case of bromate, the data presented above reflect a very recent EPA assessment, and new data that would change the assessment are not available. An exemption cannot be granted on this basis.

Finally, one investigates the underlying imprecision in the data supporting the MCL. In the case of bromate, the underlying imprecision is not determinable. This is because the dose response assessment for cancer endpoints does not generally consider imprecision issues, even though the underlying toxicity data used as the basis of the cancer evaluation is based on experimental

animals. Thus, based on Tier 1, an exemption cannot be granted for 0.04 mg/L because one cannot conclude that this level would not be associated with an URTH.

One then turns to Tier 2.

Tier 2 suggests first investigating the basis of the Relative Source Contribution (RSC) used as the basis of the MCL to determine whether a value of 0.04 mg/L is associated with an URTH. Since bromate was considered a likely human carcinogen and linear extrapolation was used to estimate cancer risk, EPA did not use a relative source contribution in the calculation of the MCL. Thus, an exemption could not be granted on this basis.

Another possible approach in Tier 2 would be to investigate exposure parameters used to develop the MCL. In the case of bromate, standard assumptions of 2 liters of water and 70 kg of body weight were used for lifetime consumption. Different exposure assumptions could be used if the population is different from what these assumptions might imply. As in the case of Chemical A, for example, if the water system were in Alaska, and folks routinely drank less than 2 liters of water per day and weighed more than 70 kg, then an exemption might be granted pending the results of the calculation.

Finally, the sensitive population could be investigated to determine whether the water system of interest serves the sensitive population. However, in the case of bromate, the sensitive population is not known, and thus, an exemption based on this evaluation could not be granted.

One then turns to Tier 3.

Categorical regression would not be an appropriate technique for a carcinogen when a low dose response assessment has already been accomplished. Thus, an exemption based on this method is not appropriate.

A form of probabilistic approach has already been conducted for the bromate MCL because the MCL is based on the probability of a cancer response. Risk managers would need to determine if the degree of risk associated with an exceedance of 0.04 mg/L, that is a risk of 8×10^{-4}, is an URTH (i.e., a concentration of 0.04 mg/L times a risk of 0.02 per mg/L = 8×10^{-4}). In this determination, it may be appropriate to consider the overall expected (or realized) length of excess exposure. For example, if the population is only expected to be exposed to this excess for about 10% of lifespan, then spreading this excess risk over the rest of the lifespan might be investigated. In this case the lifetime risk would be about 2×10^{-4} [i.e., $(8 \times 10^{-4} \times 10\%) + (1 \times 10^{-4} \times 90\%) = 1.7 \times 10^{-4}$]. If risk managers do not consider this risk to be unreasonable, then an exemption could be granted. Conducting a calculation of this form does not address the risk resulting from exposure prior to the promulgation of an MCL. However, this pre-existing risk would exist even if a system came into compliance with the MCL immediately after it were promulgated.

Finally, mechanistic information could also be attempted in the evaluation of the MCL to determine whether a value of 0.04 mg/L is associated with an URTH. A key issue for the bromate cancer assessment was determination of the mode of cancer action. While the data

supporting a nonlinear extrapolation were not sufficient to meet EPA's rigorous standards, some scientists have proposed that bromate should be treated as a nonlinear carcinogen (e.g., Chipman et al., 1998). Further consideration of mechanistic information could evaluate the degree of scientific consensus supporting a nonlinear mode of action. For example, if other federal agencies treat bromate as a chemical that damages DNA only via indirect mechanisms, it may be appropriate to use a nonlinear approach to evaluate URTH, even though the data are not strong enough to develop the MCL based on a nonlinear approach. In this case, one would follow standard EPA procedures to develop an RfD based on the cancer endpoint, and then evaluate URTH using the procedures described earlier. Further investigation of the approaches of other federal agencies would be needed to apply this approach. Thus, an exemption on this basis could not be granted at this time.

Summary

We have presented a tiered approach for considering enhancements to EPA's methods for unreasonable risk to health. Tier 1 includes straightforward applications of EPA guidance, literature review and examining risk value imprecision. Tier 2 includes the more complex methods of evaluating relative source contribution, examining exposure parameters, and investigating sensitive populations. Finally, Tier 3 includes more time-intensive methods such as categorical regression, probabilistic methods and mechanistic understanding. Every contaminant can be considered in at least one of these tiers. However, the ability to make sound decisions on unreasonable risk to health ultimately rests with the availability of information on a particular contaminant, or on our willingness to devote the necessary research dollars to find such information. Nor will these tiers abrogate the responsibility of risk managers to carefully weigh all information in their determination of unreasonable risk to health as they strive to protect the public's health through balanced appraisal of the risks, occasional benefits, and costs of removal of water contaminants.

Tier 1

1) Look at EPA guidance: Does EPA guidance allow the exemption to be granted?

2) Review literature for updated risk values: Do new risk values developed since the EPA guidance allow the exemption to be granted?

3) Examine risk value imprecision: Does a study of the precision in the underlying risk value allow the exemption to be granted?

Tier 2

1) Evaluate Relative Source Contribution (RSC): Can specific data change the basis of the RSC, allowing an exemption to be granted?

2) Examine exposure parameters: Can different exposure assumptions be used to estimate the MCL, allowing an exemption to be granted?

3) Investigate sensitive population: Does the population of interest contain the sensitive population that the underlying risk value is designed to protect? If not, can an exemption be granted based on a risk value derived to protect the population of interest?

Tier 3

1) Categorical regression: Can concentrations of a contaminant associated with probable health risk be developed with confidence in order to grant an exemption?

2) Probabilistic Methods: Can concentrations of a contaminant associated with probable health risk be developed with confidence in order to grant an exemption?

3) Mechanistic Understanding: Can the investigation of the mode of chemical action enable the development of a mechanistically-based safe dose, and grant an exemption?

Figure 1. Suggested Tiers for Assessing URTH. See text for discussion.

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