

**Brief Report**

# Summation from a Regulatory Perspective

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There is an urgent need to discuss the Office of Drinking Water's standard-setting or rulemaking process since most of the researchers whose papers are presented here directly or indirectly play a crucial role in this complex undertaking. Therefore, this paper will address the research data required to support policymaking and regulatory decisions pertaining to health effects of disinfectants and disinfection by-products.

## Statutory Requirements and Regulatory Plan

The Office of Drinking Water (ODW) is currently engaged in the most detailed and comprehensive assessment of drinking water quality specifications ever attempted. The Safe Drinking Water Act (SDWA) of 1974 requires the U.S. Environmental Protection Agency (EPA) to establish primary drinking water regulations that apply to public water systems; specify contaminants that, in the judgment of the Administrator, may have an adverse effect on human health; and specify for each contaminant either a Maximum Contaminant Level (MCL) or treatment techniques.

The SDWA includes provisions for interim and revised regulations. Interim regulations were to be established within 180 days of enactment of the SDWA. Revised regulations are to be developed in two steps: the Environmental Protection Agency is to establish Recommended Maximum Contaminant Levels (RMCLs) and then is to establish MCLs as close to the RMCLs as feasible. MCLs are to be proposed at the time of promulgation of the RMCLs.

RMCLs are nonenforceable health goals and are to be set at a level at which, in the EPA Administrator's judgment, "no known or anticipated adverse effects on the health of persons occur and which allows an adequate margin of safety." The House Report on the 1974 legislation provides congressional guidance on developing RMCLs: "... the recommended maximum level must be set to prevent the occurrence of any known or anticipated adverse effect. It must include an adequate

margin of safety, unless there is no safe threshold for a contaminant. In such a case, the recommended maximum contaminant level should be set at zero level."

MCLs are the enforceable standards and must be set as close to RMCLs as feasible. Feasible means "with the use of the best technology, treatment techniques and other means, which the Administrator finds are generally available (taking costs into consideration)."

The National Revised Primary Drinking Water Regulations will span all classes of drinking water contaminants including biological contaminants, organic and inorganic chemicals, and radionuclides. The complete process will require four years of formal regulatory action, but it has been preceded by several years of detailed assessments. For each substance being examined, supporting assessments are produced, including environmental occurrence, human exposure, toxicology, analytical methods, treatment technology, unit costs, implementation forecasts, costs to communities and consumers, and the national economic impact assessments, along with several other analyses required by Executive Orders and/or statutory imperatives.

Management of this immense and continuing task requires separation of the mass of candidate contaminants for regulation into four phases.

- Phase I: Volatile synthetic organic chemicals
- Phase II: Synthetic organic chemicals, inorganic chemicals, and microbiological contaminants
- Phase III: Radionuclides
- Phase IV: Disinfectants and disinfection by-products including trihalomethanes

In general, the approach for all four phases will be similar. Initially, an Advance Notice of Proposed Rule Making (ANPRM) will be published, followed by a comment

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period and a public meeting. Public technical workshops will also be held. The workshops provide an opportunity for EPA to present the issues that must be addressed in the development of regulations and to receive information on scientific and technical matters as well as to receive comments on regulatory approaches. RMCLs will then be proposed followed by a public comment period and a public hearing(s).

RMCLs will then be promulgated and proposals published for MCLs, monitoring and reporting, and other requirements followed by a public comment period and a public hearing(s). Technologies that were used as the basis for determining the MCLs will be identified; in addition, generally available treatment technologies (GAT) will be identified for use in issuing variances. The MCLs, monitoring and reporting, and other requirements including GAT will then be promulgated.

Our regulatory activities concerning Phase IV of the revised regulations dealing with disinfectants and disinfection by-products should be of major interest to this audience.

## Disinfectants/By-Products

Drinking water standards for trihalomethanes (THMs) were promulgated by EPA in 1979, since these contaminants were determined to be common in chlorinated drinking water. Among the reasons given at the time: THMs were the principal identified by-products of chlorination; very large populations were exposed to relatively high concentrations of THMs compared to other synthetic organic drinking water contaminants that had been detected; and perhaps, most importantly, THMs are indicative of the presence of other yet-to-be-identified chlorination by-products that are much more difficult to analyze and potentially of greater health concern.

Water disinfection is clearly the major source of synthetic organic chemicals as well as a source of contamination by the disinfection agents and their decomposition products in public drinking water supplies. Phase IV of the revised regulations is intended to take a major step toward examining most of the principal chemical contaminants in drinking water resulting from the disinfection process, including a reassessment of THMs.

In October 1984, the Office of Drinking Water (ODW) initiated the development of drinking water criteria documents on: chlorine/by-products; chloramines and ammonia; chlorophenols; chlorine dioxide/by-products; trihalomethanes; chlorinated acids, haloalcohols, and haloaldehydes; acetonitriles; and iodine/by-products, bromine/by-products, ozone, potassium permanganate, high pH, ionizing radiation, silver, ultraviolet light, and ferrate.

## Documentation and Quantification of Toxicological Effects of Disinfectants/By-Products

The objectives of criteria documents include: establishing core information based on health effects of chem-

icals in drinking water; compiling and evaluating data for providing the qualitative and quantitative health effects basis for RMCLs; and providing the health effects basis for Health Advisories. Each criteria document consists of nine chapters as follows: (1) Summary; (2) Physical and Chemical Properties; (3) Toxicokinetics; (4) Human Exposure; (5) Health Effects in Animals; (6) Health Effects in Humans; (7) Mechanism of Toxicity; (8) Quantification of Toxicological Effects; (9) References.

Chapter 8 is the most important chapter in the whole criteria document. The quantification of toxicological effects of a chemical consists of an assessment of the non-carcinogenic and carcinogenic effects. In the quantification of noncarcinogenic effects, an Acceptable Daily Intake (ADI) is calculated. An Adjusted Acceptable Daily Intake (AADI) and Health Advisory (HA) values for the chemical are then calculated to define the appropriate drinking water concentrations to limit human exposure. For ingestion data, this approach is illustrated as follows:

$$\begin{aligned} \text{ADI} &= \frac{\text{NOAEL or LOAEL (in mg/kg/day)}(\text{body weight in kg})}{\text{Uncertainty/Safety factor}} \\ &= \text{mg/day} \\ \text{AADI} &= \frac{\text{ADI}}{\text{Drinking water volume in L/day}} \\ &= \text{mg/L} \end{aligned}$$

where NOAEL is the no-observed-adverse-effect level, LOAEL is the lowest-observed-adverse-effect level, body weight is taken as 70 kg for adults or 10 kg for children, and drinking water volume is taken as 2 L per day for adults or 1 L per day for children. The uncertainty/safety factor = 10, 100, or 1000.

When these equations are used, the following drinking water concentrations are developed for noncarcinogenic effects: 1-day HA for 10-kg child, 1-day HA for 70-kg adult, 10-day HA for 10-kg child, 10-day HA for 70-kg adult, and lifetime AADI for a 70-kg adult.

The distinctions made between the HA calculations are associated with the duration of anticipated exposure. The 1-day HAs assume a single acute exposure to the chemical. The 10-day HAs assume a limited period of exposure (possibly 1 to 2 weeks). The HA values will not be used in establishing a drinking water standard for the chemical. Rather, they will be used as informal scientific guidance to municipalities and other organizations when emergency spills or contamination situations occur. The AADI value is intended to provide the scientific basis for establishing a drinking water standard based on noncarcinogenic effects.

A NOAEL or LOAEL is determined from animal toxicity data or human effects data. For animal data, this level is divided by an uncertainty factor because this is the universally acceptable quantitative method to extrapolate from animals to humans. The possibility must be considered that humans are more sensitive to the toxic effects of chemicals than are animals. For human data, an uncertainty factor is also used to account

Table 1. Three-category approach for developing RMCLs.

| Evidence of carcinogenicity | Classification   | RMCL  |
|-----------------------------|--|---|
| Strong                      | EPA Group A or B <sup>a</sup><br>IARC Group 1, 2A or 2B <sup>b</sup> | RMCL is set at zero   |
| Equivocal                   | EPA Group C<br>IARC Group 3  | RMCL is derived by:<br>(a) ADI approach with additional safety factor, or<br>(b) Set $10^{-5}$ to $10^{-6}$ cancer risk range |
| Inadequate or lacking       | EPA Group D or E<br>IARC Group 3                                     | RMCL is derived by standard ADI approach:<br>RMCL = (AADI) (% of drinking water contribution)                                 |

<sup>a</sup> Consult Table 2 for detail.

<sup>b</sup> Consult Table 3 for detail.

for the heterogeneity of the human population, in which persons exhibit differing sensitivity to toxic chemicals. An ODW modification of the guidelines set forth by the National Academy of Sciences (NAS) is typically used in establishing uncertainty factors as follows. An uncertainty factor of 10 is used when good acute or chronic human exposure data are available and supported by acute or chronic toxicity data in other species. An uncertainty factor of 100 is used when good acute or chronic toxicity data identifying NOAEL are available for one or more species, but human data are not available. An uncertainty factor of 1000 is used when limited or incomplete acute or chronic toxicity data in all species are available or when the acute or chronic toxicity data identify a LOAEL (but not NOAEL) for one or more species, but human data are not available.

The uncertainty factor used for a specific risk assessment is judgmental. Factors that cannot be incorporated in the NAS/ODW guidelines for selection of an uncertainty factor, but must be considered include the quality of the toxicology data, the significance of the adverse effect, the existence of counterbalancing ben-

Table 2. EPA-proposed classification of carcinogens.

| Group | Evidence of carcinogenicity   |
|-------|---|
| A     | Human carcinogen (sufficient evidence from epidemiological studies)   |
| B     | Probable human carcinogen   |
| B1    | At least limited evidence of carcinogenicity to humans  |
| B2    | Usually a combination of sufficient evidence in animals and inadequate data in humans   |
| C     | Possible human carcinogens (limited evidence of carcinogenicity in animals in the absence of human data)  |
| D     | Not classified (inadequate animal evidence of carcinogenicity)  |
| E     | No evidence of carcinogenicity for humans (no evidence for carcinogenicity in at least two adequate animal species or in both epidemiological and animal studies) |

Table 3. IARC classification of carcinogens.

| Group | Evidence of carcinogenicity  |
|-------|--|
| 1     | Sufficient evidence of carcinogenicity to humans   |
| 2A    | Limited evidence of carcinogenicity to humans  |
| 2B    | Insufficient evidence of carcinogenicity to humans and sufficient evidence of carcinogenicity to animals |
| 3     | Available data cannot be classified as to its carcinogenicity to humans                                  |

eficial effects, the length of the study, and the route of exposure.

If toxicological evidence requires the chemical to be classified as a potential carcinogen, mathematical models are used to calculate the estimated excess cancer risks associated with the ingestion of the chemical via drinking water.

To predict the risk for humans, these data must be converted to an equivalent human dose. This conversion includes correction for noncontinuous animal feeding, non-lifetime studies, and for the difference in size. The factor that compensates for the size difference is the cube root of the ratio of the animal and human body weights. It is assumed that the average human body weight is 70 kg and that the average human consumes 2 L of water per day. The multistage model is often used by EPA's Carcinogen Assessment Group to attempt to project the risk at low doses. The upper 95% confidence limit of this estimate is used as an upper boundary of the risk. The lower boundary would be zero if the nonthreshold assumption of the model were not valid. Excess cancer risks ( $10^{-4}$ ,  $10^{-5}$ , or  $10^{-6}$ ) can also be estimated by using other models such as the one-hit model, the Weibull model, the logit model, and the probit model. A risk of  $10^{-4}$ , for example, indicates a probability of one additional case of cancer for every 10,000 people exposed; a risk of  $10^{-5}$  indicates one additional case of cancer for every 100,000 people exposed; and so forth. There is no basis in the current understanding of the biological mechanisms involved in cancer to choose among these models. The estimates of low risk associated with doses can differ by several orders of magnitude across these models.

The scientific database used to calculate and support the setting of risk rate levels has an inherent uncertainty. This uncertainty arises because the tools of scientific measurement, by their very nature, involve both systemic and random error. In most cases, only studies using experimental animals have been performed. Thus, uncertainty exists when the data are extrapolated to humans. When developing risk rate levels, several other areas of uncertainty exists, such as incomplete knowledge concerning the health effects of contaminants in drinking water, the impact of test animal age, sex, and species and the nature of target organ systems examined on the toxicity study results, and the actual rate of exposure of internal targets in test animals or humans. Dose-response data are usually only available for high levels of exposure, not for the lower levels of exposure for which a standard is being set. When there

is exposure to more than one contaminant, additional uncertainty results from a lack of information about possible synergistic or antagonistic effects.

The ODW's three-category approach for developing RMCLs for drinking water contaminants is shown in Tables 1-3. It should be obvious that the research data presented in this volume will have a significant impact on the development of RMCLs for drinking water disinfectants and disinfection by-products.

## Conclusion

Research data presented in this volume provide us with ample evidence that chlorination produces a complex mixture of chemicals that have toxic properties, but quantitative information on the noncarcinogenic and carcinogenic effects of most of these chemicals is not available to be incorporated in our criteria documents. Of particular concern is the evaluation of the carcinogenic potential of the numerous disinfection by-products, since a finding of carcinogenicity (no safe threshold) leads to the conclusion that the RMCL for that particular chemical be set at zero.

The primary focus of future experimental, clinical, and epidemiological research undertaken for a regulatory agency such as EPA must be to provide the essential to support policymaking and regulatory decisions. Thus, research efforts must be directed toward answering specific questions, such as:

- Which of the many by-products formed during the disinfection of drinking water are of sufficient health concern that further toxicological testing is justified?
- For each of the specific by-products that are of significant health concern, what are the NOAEL/LOAEL for short-term and chronic exposure via drinking water?
- For which chemicals is there significant carcinogenic potential following oral exposure?
- What changes in disinfection technology can be made to reduce the risk of toxic effects from by-products, without sacrificing protection against waterborne disease?

In summary, the state of drinking water research and regulatory activities in the environmental impact and health effects of disinfection has been an active field for several years and will continue to be so. A great understanding of the technology and toxicology of disinfection processes has been gained, but much more work needs to be done and significant deadlines are approaching. Our greatest needs are in the identification of the significant toxic endpoints and in the quantitation of the dose-response relationship.

I would like to conclude this paper with the following quotation from Robert Frost:

"We danced round in a ring and suppose

But the secret sits in the middle and knows."

In our case, the secrets are the NOAELs/LOAELs for disinfectants and disinfection by-products.