M/DBP Stage 2 Federal Advisory Committee (FACA 2) DBP Reproductive and Developmental Health Effects

MEETING SUMMARY

Meeting #3

July 21-22, 1999
Washington, DC

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I. Introduction

On July 21-22, 1999 EPA held the third meeting of the Stage 2 Disinfection Byproducts and Long-Term 2 Enhanced Surface Water Treatment Rules (MDBP) Federal Advisory Committee (FACA). This meeting focuses on reproductive and developmental health effects of disinfection byproducts (DBPs). [See Attachment I.a for a list of meeting participants.] The purpose of this meeting is to help FACA members understand the scientific (raw collection and analysis) and policy (risk assessment tools) context for Stage 2 MDBP rule development.

After introductions mediator Abby Arnold, RESOLVE, reviewed the objectives of this meeting:

1. Provide and discuss a framework to evaluate the reproductive and developmental health effects data in a regulatory context.

2. Provide an overview of current and ongoing epidemiological and toxicological data on developmental and reproductive health effects of DBPs.

The FACA approved the proposed agenda [See Attachment I. b.] This meeting report summarizes the discussions and next steps from this meeting.

Please note: during the course of this meeting the FACA decided to change the date for the March 2000 meeting to March 28-29 [the former dates were March 15-16].

II. Overview of the Regulatory Context for the Meeting

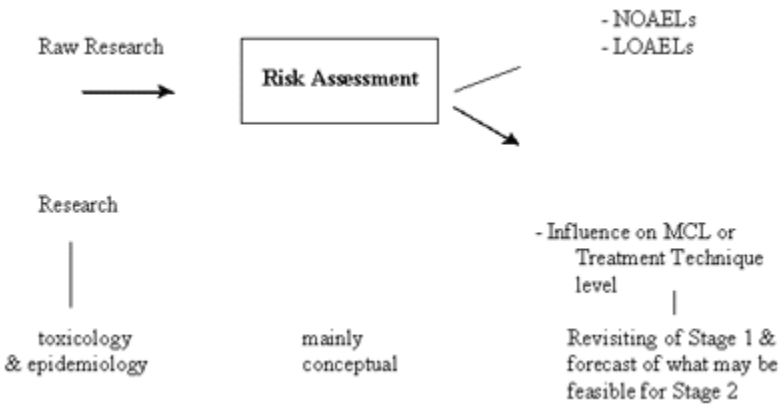
Stig Regli, EPA, provided an overview of (1) the types of information EPA uses in the development of drinking water regulations, and (2) how health effects information is used by the Agency in the development of these regulations. [See Attachment II.]

Regulations are based on four "types" of information:

- Health Effects Assessment *(covered in July FACA meeting)*:
- NOAEL: no observed effect level
- LOAEL: lowest observed effect level
- MCLG: maximum contaminant level goal
- Epidemiology
- Analytical Methods *(will be covered in future meeting)*:
- MCL/Treatment Technique
- Compliance Monitoring
- Occurrence/Exposure *(will be covered in future meeting)*
- Treatment Technology *(will be covered in future meeting)*:
- MCLs/Treatment Techniques

The second, third, and fourth meeting of MDBP FACA, including this meeting on reproductive and developmental health effects, are focused on *health effects and assessment*. The FACA schedule covers DBP cancer effects (May 20-21, 1999), DBP reproductive and developmental effects (July 21-22, 1999), and microbial risk occurrence (September 8-9, 1999). [See Attachment I.C for list of meeting dates and proposed topics.]

Regli reviewed how EPA applies health effects research to rule development [see Figure 2.] The Safe Drinking Water Act (SDWA) requires that EPA publish maximum contaminant level goals (MCLGs) and either maximum contaminant levels (MCLs) or treatment technique requirements, which are the standards for regulatory action. The MCLG is based either on the NOAEL (no observed adverse effect level) or lowest observed adverse effect level (LOAEL) which is divided by an uncertainty factor that is determined through toxicology research. EPA uses the most sensitive endpoint as the basis for the MCLG and RfD. When cancer is the endpoint, the MCLG/RfD is set at zero.



Regli presented a list of health effects related issues that EPA must consider in making regulatory decisions:

1. Is there a sufficient basis for setting new MCLGs based on developmental & reproductive effects?

2. If toxicology data is insufficient to support NOAEL or LOAEL, to what extent, if any, does it contribute to weight of evidence?

3. To what extent does epidemiology data (in total), contribute to weight of evidence?

Following Regli's presentation FACA members discussed the following points:

--Regulatory action for a contaminant can be based on weight of evidence, toxicology and/or epidemiology data without a NOAEL or LOAEL.

--In response to a question regarding how EPA weighs regulatory decisions in the context of the current national water system infrastructure, EPA explained that risk assessment and risk management are different processes. EPA is asking the FACA to help determine the level of uncertainty and make judgements on what regulatory actions are supported by existing data.

--A FACA member remarked that EPA needs to provide the FACA with information on health effects, occurrence/exposure, analytical methods, and treatment technologies (see Figure 1). FACA members will assess possible risk assessment approaches, the quality of the science, and possible risk management options. EPA responded that the risk assessment will be in development as the FACA is working (through Fall 99 and Winter 00). The FACA will have opportunities to review and give feedback on the risk assessment as it is developed by EPA.

III. Overview of Risk Assessment

Rita Schoeny, EPA Office of Water, and Eric Clegg, EPA Office of Research and Development, presented an overview of the process EPA used to develop risk assessments for reproductive and developmental endpoints. [See Attachment III].

Schoeny began by discussing principals common to assessment of all types of human health risk. She noted that for EPA's risk assessment processes:

- Risk assessment is one of three linked, yet distinct endeavors in developing regulations: 1) collecting data through research; 2) assessing risk; and 3) making risk management decisions. Risk assessment can inform researchers as to data needed and is used in conjunction with information on control technology as well as analyses of costs, benefits and social impacts, to determine a risk management approach.

  U.S. EPA uses the four-step risk assessment process defined by the U.S. National Academy of Sciences in 1983.

- *Hazard Identification* uses toxicological and epidemiological, data to determine a) whether the agent is hazardous to humans and b) the types of effects it is likely to cause.
- The *Dose Response Assessment* answers the question of how much of the agent produces what degree of effect. In other words, this is an analysis of the potency of the agent as a toxicant.

In this assessment it is necessary to have some information (or a plausible hypothesis) of the mode of action -- how the agent produces its toxic effect. For those toxicants which are thought to have a practical threshold for effect, EPA calculates a Reference dose (RfD). The risk assessor examines the available data to determine a critical effect. She then decides what dose represents a no adverse effect level (NOAEL); if there is no experimental level in the data set with no adverse effects, the lowest observed adverse effect level (LOAEL) is used. Alternatively, one can estimate a NOAEL by using a benchmark dose approach. The RfD is determined by dividing the NOAEL by uncertainty factors. Uncertainty factors (up to a factor of 10 each) are used to adjust the NOAEL for intra- species variability, inferences between species to species, for use of data from short term assays and for use of a LOAEL in the absence of a NOAEL. The magnitude of the uncertainty factor may be determined empirically but is most often a matter of scientific judgement.

- The *Exposure Assessment* estimates how much of the agent is delivered to the population and by what routes (inhalation, ingestion, dermally). Exposure assessment also deals with pharmacokinetics, estimating the dose to the target organ or tissue,
- *Risk Characterization* estimates the risk from a specific exposure scenario (e.g. a spill) or for a specific population (e.g., children exposed to an agent in a community water supply). In this step, the risk assessor spells out the defaults, uncertainties and assumptions used in determining the extent of the risk.

Eric Clegg explained that EPA has developed Risk Assessment Guidelines which are available on the world wide web.[(1)] These guidelines are primarily focused on endpoints.

Adverse health endpoints on reproductive systems that may result from exposure to environmental agents include:

- prenatal or postnatal death of offspring;
- structural abnormalities;
- altered growth, and;
- functionality deficits.

Additionally,

- reproductive effects may appear at any time in an offspring's life,
- statistically significant change in an endpoint in comparison to controls (such as organ weight) is considered an adverse effect.

Exposure at different points in the development of a fetus (including development that occurs after birth) can produce different effects that can be correlated with the critical periods for the development of different organ systems. These critical periods vary by species.

In the absence of contrary health effects information, EPA uses the following default assumptions in its risk assessments:

- Human data are the best source, however, most often EPA extrapolates from an animal test species. EPA assumes that effects in animal models will be similar to those in humans.
- The most sensitive animal is the best model for humans.
- If an effect is observed in a male it will occur in a female also. This is known as gender equivalence.
- The application of a threshold/nonlinear low dose exposure is appropriate, i.e. there is a level of exposure below which there is no effect.

Clegg remarked that there are significant limitations on the usefulness of using short-term/high-level exposure tests to estimate the effects of long-term/low-dose exposures. Short-term tests cannot adequately measure developmental effects that would not be observed until later in life. However, positive effects in short-term tests should be used to indicate the need for further study. Additional concerns with existing studies include:

- studies may not indicate developmental toxicity occurring in the absence of maternal toxicological effects.
- estrogen cycle normality effects have not been investigated for DBPs.

Clegg presented a series of slides outlining different toxicity testing protocols. He explained that detailed understanding of testing protocols is important for FACA members to evaluate the strengths and weaknesses of the toxicology database, and the conclusions that can be drawn from it. Clegg reviewed the following types of studies:

- multi-generational reproductive studies
- continuous breeding (RACB) studies, and
- short-term tests (SIDS, NTP, ICH, dominant lethal, subchronic toxicity).

Schoeny ended the presentation by reviewing EPA's hazard characterization approach. In hazard characterization one arrays assessments of a number of potential toxic effects of an agent and makes decisions as to what constitutes the sentinel toxicity; in other words what is the "real problem" with the agent for human health. She presented the characterization of methyl mercury as an example.

IV. Primer on Reproductive and Developmental Endpoints

At the request of the FACA committee, Maureen Hatch, Mt. Sinai School of Medicine, presented a primer covering the importance of reproductive and developmental health endpoints, the general rate of reproductive/developmental problems in the population, and the significance of adverse reproductive/developmental health effects. [See Attachment IV.]

Hatch provided an overview of identified reproductive/developmental endpoints, including the known risk factors of various health endpoints. Identifying the endpoint of concern from an exposure is difficult because reproductive/developmental effects occur in very complex multi-organ systems with many feedback loops. There are various steps in the reproductive and developmental cycle where endpoints surface; fertility, conception, unrecognized fetal loss, recognized pregnancy, miscarriage or late fetal death, and live births. At each point along the way small (often nondetectable) health effects could have a large impact on reproduction.

Studies have shown that over the generations studied, there is not a change in the rates of infertility, however there probably is a change in the rate of fecundity, due perhaps to delay in attempting conception B fecundity is reduced with the age of the couple.

Fetal loss is estimated at greater than 31%; 20% of this is unrecognized fetal loss*. [see below for references.]* Little is known about the causes of fetal loss. We do know that loss is associated with chromosome anomalies and with increasing maternal age. We also know that humans have a higher level of loss than animals, such as those used in the toxicological studies. However, the reasons for these high rates of loss in humans as compared with other species have not been identified. It is very difficult to study early fetal loss in animals because of their very low loss rate.

The US rate of preterm live births is very high relative to other countries. The rate ranges from 5 to 8% among whites, and the non-white rate of preterm live births is close to triple, at 15-18%. Few risk factors have been identified and those that have explain little of the variation among subgroups. A FACA member stated that some of these losses in preterm births may be due to chromosomal abnormality or correspond to the transition, in embryo development, of females to males.

Low birthweight is difficult to study because low birthweight babies are not classified either as premature or full term delivery on birth certificates.

There are few detailed databases of birth outcomes, including birth defects, being collected. The Centers for Disease Control does maintain a national registry (on a voluntary basis) and keeps more detailed information for four regions of the US.

The health impact associated with exposure to a contaminant may not be consistent. For example, the effect and severity may depend on when the exposure occurs within the menstrual cycle or at what time during pregnancy. Time of exposure can be traced from the organ affected; for example neural tube defects are most likely to occur in the first three weeks of development. Health impacts from contaminants may depend more on timing and peak exposures than averages. Hatch acknowledged in response to a FACA member that reproductive/developmental effects from exposure may occur postnatally because brain development in humans continues for one year or more after birth.

Evaluation of reproductive/developmental effects must continue much later into the life of a subject to identify effects such as behavioral dysfunction. In response to a question, Hatch explained that it is unclear where the greatest areas of uncertainty surrounding endpoint identification are. Hatch also pointed out that endpoints of concern may be unrecognized. For example, fetal loss may occur in an unrecognized pregnancy or changes in menstrual hormones may not alter length of the cycle.

FACA members discussed the following reproductive/developmental issues which remain controversial in the field:

- There is debate about whether sperm counts have changed over time. There are large geographical differences around the world in sperm counts that have not been explained.
- One meeting participant explained that a possible decline in fertility could be due to present exposure, but is more likely related to exposure during the parent's development, 20-30 years prior.
- One participant calculated that if there are approximately 2 million births per year in the US, and 3 million conceptions (given 1/3 pregnancy loss) then, if any effect caused a 1% increase in miscarriages, it would result in 30,000 additional miscarriages. What may be considered a small increase could lead to a large public health impact across the US population. However, a 1% change of occurrence in the endpoint might not be detectable.
- In response to a question on the current level of understanding of mechanisms of action in reproductive/developmental effects, Hatch explained that smoking is one of the few which is

known (hypoxia). Most DBP studies are occupational, including chemical sprayers, industrial plants, and accidental releases.

- A FACA member asked if the level of uncertainty in comparing mouse and rat data had been evaluated as an indicator of the level of uncertainty in using animal models to assess human impacts. In response, John Reif, a technical consultant to the Committee from Colorado State University, explained that this type of comparison would be useful only in comparing the same effect in both animals (e.g. spontaneous abortion). Shelly Tyl, another technical consultant to the Committee from RTI, added that animals used as models have been inbred to allow for the identification of cause and effect relationships. This makes animals studies easier both to perform and identify effects, but it is more difficult to extrapolate to the considerably more genetically diverse human population.

Dr. Hatch provided the following references:

1. Hertig AT. The overall problem in man. In: Benirschke K, ed. *Comparative aspects of reproductive failure.* New York: Springer-Verlag; 1967:11-41.

2. Wilcox AJ, Weinberg CR, O'Connor JF, et al. Incidence of early loss of pregnancy. *N Engl J Med* 1988; 319:189-194.

V. Overview of Reproductive and Developmental Assessments

Ambika Bathija, EPA Office of Science and Technology, presented an overview of the risk assessments performed by EPA to develop Stage 1 MCLGs and MRDLGs [See Attachment V.]

Risk assessments are based on *toxicology* studies (i.e. developmental and reproductive, carcinogenicity, and other systemic toxicity) and *epidemiology* studies (for carcinogenicity, and developmental and reproductive effects). MCLGs for DBPs are set either at zero if studies show potential human carcinogenicity, or at a "threshold" level if they are based on reproductive/developmental or other noncancer effects.

EPA sets Maximum Residual Disinfectant Level Goals (MRDLGs) for disinfectant concentrations in drinking water distribution systems. They are different than MCLGs because they take into account the benefits of disinfection of water.

MRDLG for chlorine dioxide, and MCLGs for chlorite, and trichloroacetic acid (TCA) are based on developmental toxicity data. The MCLG for chlorite and MRDLG for chlorine dioxide are based on neurodevelopmental effects seen in pups in a 2 generation reproductive study in which rats were given chlorite in drinking water. The MCLG for TCA, is based developmental effects seen in a study in rats treated with various levels of TCA in drinking water during gestation day 6 - 15.

Dr. Bathija also reviewed how EPA developed MCLGs for chloroform, bromodichloromethane, bromoform, dichloroacetic acid and bromate based on carcinogenic effects, and for dibromochloromethane, chloramine and chlorine based on systematic, noncancer effects. For chloromine the NOAEL/LOAEL for systematic noncancer effects was used because these levels were lower than the NOAEL/LOAEL for developmental effects.

There is some epidemiology evidence of a link between DBPs in drinking water and reproductive/developmental risks. However, a causal relationship to consumption of chlorinated drinking water is not established. Based on the available data, the Agency considers MCLGs for Stage 1 "protectivez" for reproductive/developmental health effects.

Following Dr. Bathija's presentation, the following discussion points were raised by FACA members:

- In response to a question regarding how EPA approaches the endpoints it looks for when developing a NOAEL/LOAEL, Bathija explained that studies (especially the "critical" study which is used to develop the NOAEL/LOAEL) are reviewed by an expert panel to determine how effective they are at detecting an effect. Following the general toxicology practice, EPA assumes that there is no threshold level for potential human carcinogens.
- For risk assessment calculations, the Agency uses an uncertainty factor (UF) of 10 to account for intra-species variability, and another UF of 10 for the use of a Low Adverse Effect Level (LOAEL). In the case of reproductive/developmental effects, EPA uses developmental studies which include *in utero* studies and studies of the offsprings of exposed parents. A FACA member questioned whether 10 fold UF is adequate because of the large difference in body weight between adults and children.
- EPA Pesticides Program is currently examining the use of an additional safety factor of 10 for children for pesticides. The Office of Water is not using this additional safety factor at this time, and will follow the decision of the Pesticide Office as to whether to use it in the future.
- The RfD and MCLG are based on dose-response information from toxicology studies, not on environmental exposure.

VI. Reproductive and Developmental Effects of Exposure to DBPs - An Overview of the Epidemiological Data

Following the general overviews of reproductive/developmental endpoints and how EPA performs reproductive/developmental health assessments, John Reif, Colorado State University, and Rebecca Calderon, EPA, gave presentations focused on the epidemiology database for reproductive/developmental effects of DBPs.

John Reif began by presenting an overview of 11 existing DBP epidemiology studies [See Attachment VI.a.][(2)] Epidemiology studies for reproductive/developmental effects and cancer effects differ by the shorter intervals between exposure and effect permitting relatively accurate recall of exposure, better estimation of exposure during critical periods of development, and use of prospective cohort studies or follow-up design.

The available literature of reproductive/developmental epidemiology studies on DBPs is sparse. Currently the only reproductive/developmental outcomes assessed are those found on birth certificates. Only four of the eleven published DBP studies contain data on the water disinfection method used or water source. Seven of the studies address THMs specifically; Reif reviewed each of these studies and the study type.[(3)] Reif reviewed the reproductive outcomes assessed in the seven studies of THMs.

Reif reviewed one of these studies, a 1999 cohort study in Nova Scotia -- which has relatively high THM levels, in detail because it was published after the February 1999 Health Effects Workshop. This study found a statistically significant increase in stillbirths at THM levels greater than 100 ppb. Virtually all the risk from spontaneous abortion and exposure to THMs is attributed to one DBP species, bromodichloromethane. In response to a question from a FACA member on how to interpret the results of this study, Reif explained that in his professional judgement it is best to focus on the overall picture, not individual values, because this study does not provide confidence intervals or sample size.

Data gaps remain on endpoints of concern, including lack of male reproductive data, menstrual changes, and time to conceiving. The major remaining questions surrounding DBP epidemiology data are the same as for cancer health effects:

- Are the reported associations between DBPs and fetal growth or developmental anomalies causal? -If no, are they due to bias? confounding? chance?
- If yes, do the epidemiologic data provide an adequate basis for determining the concentrations of THMs or other DBPs where an adverse effect is likely to occur?

Critical to resolving uncertainty in epidemiology studies of DBPs is determining the extent that differences in the distribution of DBPs could be responsible for inconsistencies in epidemiologic data. The mix of DBPs in drinking water, including brominated verses chlorinated waters, may be an important factor. Reif reviewed some of the difficulties in performing exposure assessments in DBP studies.

Another challenge is the misclassifcation of exposure and effects:

Differential Misclassification:

- If exposure is overestimated for persons with the disease vs. those without the disease, then the risk will be overestimated.
- If exposure is underestimated for persons with the disease vs. those without the disease, then the risk will be underestimated.

Non-Differential Misclassification:

- If exposure is equally over- or underestimated for persons with the disease vs. those without the disease, then the risk will be underestimated (bias towards the null).

Reif explained that although he does not expect that there may be non-differential misclassification between geographic regions, it is possible. It is more likely that regional differences are correlated with some other factor, such as differences in bromine levels in source waters. A more realistic example of non-differential misclassification is recall by normal-birth mothers (who may not remember details) versus defect-birth mothers (who may remember much more). In general, all studies will include some non-differential misclassification because we expect to do an equally bad job on all samples - which would not favor one group over another. A FACA member added that when comparing different studies of different designs, variation is most likely to obscure and lower the estimated effect.

Rebecca Calderon continued by reviewing issues in epidemiologic studies of reproductive/developmental effect [See Attachment VI.b]. EPA has produced two reports reviewing the DBP database. These reports contained the following recommendations:

1993 ILSI/EPA Report

- Improve exposure assessment
- Standardize exposure assessment
- Identify health endpoints
- Refine studies using existing databases

1997 EPA Panel Report

- Replicate California study
- Study other endpoints - male, birth defects
- Workshop on exposure for epidemiology
- Workshop on biomarkers of exposure
- Validate exposure assessments

The routes of exposure studied for DBPs in water are inhalation, dermal, and ingestion. DBP compounds and groups studied include:

- Total trihalomethanes (THMs): mainly epidemiology data

- Haleoacetic Acids (HAAs): mainly toxicological data
- Individual compounds: includes brominated vs. chlorinated comparisons
- DBP mixtures: there are over 186 DBP compounds, hard for epidemiology studies to distinguish effects.

Calderon reviewed summary points regarding the measurement of DBP exposure and

presented the components or points at which exposure can be measured, and the issues surrounding their use, and suggested that all need to be considered in epidemiology studies.

Based on her review of the data base Calderon presented the following conclusions:

- Evaluate the body of literature - not single studies
- Associations when found are small because of bias, confounding, and effect modification (interaction between risk factors such as possible interaction between nutritional status and DBP exposure).
- Sparse data set - consistency, geographically makes comparisons between studies difficult
- There is a lack of exposure (dose) data - response data (standardized questionnaires are needed, this is being worked out for future)
- Standardize exposure assessments B studies each do assessment differently and there is no consensus in field on appropriate approach

Next steps for epidemiologists are to:

- Produce a body of literature, see next presentation
- Work in interdisciplinary teams to get new perspectives on data and to include utility participation in studies. Epidemiologist will need help from other communities to resolve problems with measuring exposure.
- A major initiative is needed to improve exposure assessments, more funding is needed though it is not currently a high priority.
- Intervention studies to see if Stage 1 and other interventions have worked.

Calderon also presented a list of ongoing and planned epidemiology studies that will address DBP exposure.

Following Reif and Caldron's presentations FACA members and meeting participants raised the following points:

- One population-based study (Aschengrau) found higher risks in chlorinated than in chloraminated systems. Reif suggested that existing studies are useful for qualitative evaluation -- not quantitatively B because THM and other water quality data is missing from this study. Also, there is overlap in the data between chlorinated vs. chlorinated systems.
- Inhalation exposure is being studied, past efforts have mainly looked at chloroform. EPA is extending results from chloroform to other DBPs which are not as volatile. THMs may be a marker and not the "bad actor" in inhalation exposure. Reif added that the Waller study collected data on showering and swimming (i.e. inhalation and dermal exposure), though not dose information. This study is *in press* and will be available in November or December.
- A FACA member requested that the Technical Workgroup provide data on distribution systems, including temporal and spatial variations in DBP concentrations. One option might be to base regulations on the unique characteristics of each distribution system. This data might also be used to help utilities isolate and address problems.

VII. Reproductive and Developmental Effects of Exposure to DBPs: An Overview of Toxicological Data

Rochelle Tyl, Research Triangle Institute, presented the FACA with an overview and assessment of the DBP toxicological database [See Attachment VII.]

Tyl provided the following executive summary of her presentation:

- Most of the animal studies on DBPs are screening assays, with high doses and short duration of dosing. This is one of the major shortcomings of the DBP toxicological database.
- Neither metabolism nor mechanism of action is known for any of the DBPs.
- In general (in high dose/short term studies):
    - Trihalomethanes (THMs) cause reduced fetal/pup viability and body weights (developmental toxicity), no teratogenicty (malformations), and no reproductive toxicity.
    - Haloacetic Acids (HAAs) cause reduced fetal/pup viability and body weights, malformations, and effects on sperm.
    - Halogenated Acetonitriles cause reduced fetal/pup survival and body weights.

The current animal data set is useful for:

- identification of most toxic (potent) DBPs
- identification of endpoints of concern
- providing information for subsequent studies
- weight of evidence considerations

The current animal data set is *not* useful for:

- establishment of relevant NOAELs
- quantitative risk assessment

Remaining data gaps:

- Long-term, low-dose reproductive toxicity studies
- Toxicokinetics and metabolism (ADME)
- Mechanistic studies

Tyl reviewed seven toxicity study designs, including discussion of their strengths and weaknesses. Four of these (WEC, NTP 35 day, CKA, and CKA++) are considered screening studies which are used to identify which compounds present a significant risk. The Seg II study design is useful for producing dose-response information. The male reproductive study design is used as a screen or hazard identification test. These tests are all short-term high-dose tests. The exception is the Multi-GEN study design. which is a 3 generation rat study. Multi-GEN studies are expensive and not feasible for every compound.[(4)]

Tyl presented the following overview of the DBP toxicological database:

- Many DBPs have *not* be evaluated for reproductive/developmental effects.
- Doses used in studies are very high.
- The primary and secondary disinfectants appear relatively innocuous
- Some DBPs caused reduced fetal/pup variability, whole litter losses, reduced fetal/pup body weights, and malformations (birth defects; terata).
- Some DBPs cause reproductive effects, mostly on end-stage sperm (dependent on endpoints examined).

- Since doses are high, NOAELs/LOAELs are high. Are they relevant to long-term, low-dose exposures?

Tyl provided tables showing findings of reproductive and developmental toxicology studies for various DBPs. There are significant gaps in the database with no data for many DBPs.

The Margin of Exposure (MOE) is the ratio of the NOAEL from the most sensitive (or most appropriate) species compared to the estimated human exposure level from *all* potential sources. The MOE is an indicator of the level of concern. A *low MOE indicates a high level of concern.* A *high MOE indicates a LOW level of concern* (the amount consumed is much lower than the RfD). The MOE can also be calculated from the LOAEL, if the NOAEL is not available, by applying an uncertainty factor. The MOE is used in risk characterization. Tyl added the following observations concerning the use of MOEs:

1. NOAELs are actual doses employed. Current studies are based on short-term and high dose designs. There is no information at low doses (i.e. ambient levels).

2. There is a risk that NOAELs are inappropriately high, so MOEs may be inappropriately high.

The MOE assumes a 60 kg person consuming two liters of water per day, however, children drink more water as a ratio of their body weight. Animal models may be helpful in determining whether this assumption is appropriate. The EPA Office of Research and Development has ongoing studies to review the use of alternative exposure. EPA has water consumption data by age category, sex, race and other variables.

The Linder et al. study looked at 4 days versus 14 days of exposure and found that the LOAEL was lower for the longer exposure. Tyl predicts that low-dose/long-term studies will tend to lower the NOAELs and LOAELs. It is possible that low-dose long-term effects may be entirely different then those observed in high-dose short-term studies.

Data gaps in exposure assessment include:

- DBP mixtures including; cumulative exposure and changes in mixtures through time/season. Toxicology data gaps for mixtures includes metabolites that may be more or less toxic.
- Alternative routes of DBP exposure are difficult to control in drinking water studies.

Tyl provided a summary of DBP reproductive/developmental toxicity in animal models which includes, for each compound (by class): doses studied, reproductive effect, NOAEL, and reference to the critical study. Tyl also presented EPA's guidelines for determining what data is needed to classify a reproductive/developmental toxicant.

Tyl reviewed mechanisms used for translating toxicological data into regulatory action.

No Observed Adverse Effect Level (NOAEL) is the highest dose level measured from the data base (critical study) at which no effect from a chemical was observed. The Lowest Observed Adverse Effect Level (LOAEL) is the lowest level measured at which an effect was observed.

Weight of Evidence is a risk determination, based on a qualitative "best judgement" on the database for a compound.

Maximum Contaminant Level Goals (MCLGs) for noncarcinogens are the unenforceable regulatory goals set by EPA.

Tolerable Daily Intake (TDI), as defined by the World Health Organization, is the concentration of a constituent that does not result in any significant risk to the health of the consumer over a life time of consumption.

Because of the data gap for dose response information between the levels found in drinking water and the NOAEL/LOAEL for most chemicals, there is great uncertainty over the shape of the dose-response curve at low doses. The NOAEL will depend on study design (including doses tested and sample size) and is typically set at a level several orders of magnitude higher than exposure levels.

Tyl outlined her criteria for determining the biological plausibility of a link between exposure and effect, and her assessment of DBPs based on these criteria:

- Do the exposures occur when the process is occurring (e.g., spermatogenesis) or when the organ(s) is (are) forming (e.g., heart)? - *Yes in the animal models and likely in the epidemiology studies.*
- Are the effects reproducible (in same or similar study designs)? - *Yes in animal studies, no in epidemiology studies.*
- Are the effects consistent across species? B *Maybe, resorptions and heart and great vessel defects in animal models at high doses (increased risk for spontaneous abortions/miscarriages and/or heart defects in epidemiological studies not consistent study to study.)*
- Do we understand the dose-response pattern? - *No, not in the environmentally relevant range of doses.*
- Do we understand toxicokinetics and metabolism? - *No, for most DBPs, but EPA is looking (critical for species to species, route to route, and high to low dose extrapolations.)*
- Do we understand the mode (one or more necessary steps) or mechanism (sequence from exposure to effect) of action of any of the DBPs for the reproductive and/or developmental effects? B *No but current mechanistic studies in the works.*

Tyl closed her presentation with a list of **Tyl's bottom lines** based on her review of the DBP developmental/reproductive database:

1. What is known?

- *At high doses (relative to ambient), some of the DBPs (especially the brominated species) are reproductively and/or developmentally toxic in animal models in mostly short-term, high-dose designs.*
- *Epidemiological studies are not consistent; some show increased risks for spontaneous abortions and/or birth defects.*

2. What is not known?

- *What are the consequences of low-dose, long-term exposure (by a relevant route of administration) for reproductive and/or developmental effects (dose range down to environmental levels)?*
- *What is the mode or mechanism in animal models?*
- *What is the extrapolation to humans (very low doses, metabolism, endpoints, mechanisms).*

3. The existing DBP data set in animal models is useful to:

- *identify the most toxic DBPs*
- *identify endpoints of concern*
- *provide information for subsequent studies*
- *weight-of-evidence*

4. The existing DBP data set in animal models is not useful for:

- *Establishing relevant NOAELs (under human exposure scenarios)*
- *Risk assessment*
    - *data base not adequate for quantitative risk assessment*
    - *little or no information is available on ADME (absorption, distribution, metabolism, excretion), including transplacental and/or translactational exposures*
    - *currently, low confidence in NOAELs and therefore RfDs*

5. What needs to be done:

- *Long-term studies evaluating reproduction and development (pre- and postnatal), with relevant route administration and dose range down to environmentally relevant levels; in proposal and/or planning stages*
- *Toxicokinetics and metabolism (ADME) in animal models; in progress*
- *Mechanistic studies (to identify bad actors), in progress*

The following are additional discussion points raised by individual FACA members:

- In response to a question from a FACA member, Tyl explained that EPA tested the hypothesis that increasing sample size would lead to more sensitive results. The "mega-mouse" study found little effect of larger sample size.
- EPA assumes a threshold for noncancer effects. One explanation for the use of a threshold is that, though the molecular effect may be linear, the body can overcome (either through repair or compensation) for certain levels of exposure before there is a biological effect. Very subtle reproductive effects can be identified (e.g., embryo loss of just a few cells) however, there is some observed effect in control.
- Uncertainty factors (UF) depend on the quality of data, the greater the confidence in the NOAEL, the lower the UF used. The UF usually includes a factor of 10 for interspecies variation (animal to human) and 10 for intraspecies variation (variation among humans). Human variability, especially variability linked to age, is little understood.
- More information is needed about the differences and similarities between humans and animal models. Mechanism studies are needed, however, much useful data exists.

VIII. Current DBP Reproductive Effects Toxicology Research

Fred Hauchman, EPA, presented the DBP reproductive effects studies currently underway [See Attachment VIII.].

Hazard Identification studies are screening assays that provide information on which DBPs should be further studied. Evaluation of postnatal developmental effects for DCA, DBA, DCA, BDCM, and bromoform are underway with results expected in FY 2000. Preliminary results from this study will be available in the next six months and will be presented to the FACA. Two studies on haloacid mixtures studies will be available in FY 2000.

Ongoing *Dose-Response* studies consider DBA, BCA, DCA, and BDCM. Results from the first of two DBA developmental effect studies (on rodents) are expected in November and will be presented to the FACA. A second DBA study on rabbits will allow for an examination of consistency between studies. The results will be available in FY 2001.

Mode of Action studies are focused on haloacids. Preliminary results from studies on embryo development and the correlation of changes in fertility with a sperm protein which is potentially a sensitive biomarker may be available in time for FACA consideration.

Near-term research priorities for DBPs include: THM pregnancy outcome studies as well as HAA developmental reproductive effects studies in both male and females. Multigenerational and dose-response studies are ongoing with results planned for release in 2001-2003. These studies are expected to assist in developing higher confidence NOAELs/LOAELs and RfDs.

In response to a question, Hauchman explained that EPA focuses on chemicals that yield effects in screening studies. Noncancer effects are more difficult to detect in screens than are cancer or gene toxicity effects. Screens may miss some effects, especially those associated with low-dose long-term exposure. However, EPA has reasonable confidence that chemicals that are negative in the screens are of lower concern. It is prohibitively expensive to perform a multigenerational study on all compounds. Use of structural alerts and other flags based on structure of the compound are presently limited, but are currently being developed by EPA.

EPA does not have toxicokinetic information, though there is some data on metabolism. However, this information was not used in prioritization of chemicals for further study. Dosimetry data on DBA is now beginning to become available. Department of Defense frog embryo (FETAX) studies are being evaluated; a fairly complete pharmokinetic database is beginning to be developed.

In response to a question on whether the research to be conducted over the next 12 - 36 months may provide surprises or dramatic changes from ongoing or future studies, EPA staff responded that evidence that links epidemiology and toxicology findings, including across species (e.g., animal/animal and animal/human), is a major data gap.

EPA will develop the risk assessment for DBPs concurrently with the FACA deliberations. The final risk assessment is expected to be complete in spring or early summer 2000. However, EPA will share its approach and initial findings with the FACA as they are developed (beginning in October). The risk assessment may depend heavily on weight of evidence judgements. Health effects data for alternative disinfectants is an important data gap. Gathering this type of data is cost intensive and EPA may depend on "landscape perspective" of risks. EPA may fund additional studies if a subgroup of the FACA defines parameters and endpoints needed to understand general "topography" of alternative disinfectants.

IX. Report from Technical Workgroup

Michael McGuire, McGuire Environmental Consultant, Inc., presented an overview of the progress of the Technical Workgroup (TWG) since the previous update at the May FACA meeting [see Attachment IX.a.] McGuire reviewed TWG activities that are underway, but would not be covered in this presentation. He also presented an overview of the organization of the TWG. There are now 17 TWG subgroups [Attachment IX.b.]. The TWG is tasked with assisting the FACA to wade through the enormous amount of data involved in Stage 2 decisionmaking. To make informed decisions, FACA members will have to digest a large amount of complex data, very quickly. McGuire suggested that FACA members rely on their own staffs as well as the TWG for technical support. McGuire requested, on behalf of the TWG, direction from the FACA in choosing priorities for TWG efforts.

McGuire reported that the first 6 months of ICR data is currently available. The TWG will present this data at the September 22-23 FACA meeting. The TWG expects to develop the ICR baseline at its October 25-26 meeting and develop the Stage 1 baseline at its December 6-7 meeting.

Two possible priority activities for the TWG suggested by individual FACA members were:

1. Developing the ICR and Stage 1 baselines.

2. Vertical analysis (i.e., between water plants) of chloramine versus chlorine plants.

McGuire reviewed the Auxiliary Database Relationships flowchart and gave an overview of the ICR data analysis web site which contains the analysis of the first 6 months of data. The web site is available to FACA members and participants -- and is designed for technically inclined.[5] Questions should be directed to the TWG through RESOLVE [aarnold@resolv.org] or McGuire [mikemec@gte.net] and cannot be sent directly through the web site. A public web site is being developed which will provide key data that will not be detailed enough for FACA needs. McGuire reviewed each of the formats used for data presentation on the web site.

The TWG has structured its data analysis approach around a list of questions developed at a public stakeholder meeting, in February 1998 that anticipated questions that the Stage 2 FACA would consider in its deliberations. McGuire provided examples of this list of questions and made available the full list of questions.[6] It is important for the FACA members to understand the TWG data analysis strategy. The TWG is looking to the FACA members to provide direction, as priorities change, on the approach that the TWG is taking to ensure that the FACA is given the necessary analysis. A FACA member added that the FACA will depend on the expertise of the TWG for help identifying what data will be most helpful.

McGuire covered limitations on ICR data:

- ICR data cannot answer some questions on water quality or treatment performance capabilities including; filter performance, national trends in particle removal by particle count, impact of ozone on biological stability of treated water, and secondary impacts of anticipated changes in treatment.
- ICR data cannot address some distribution system water quality issues and evaluation of where in the distribution system maximum exposures are occurring. For example, ICR data samples water in four locations in each treatment plant quarterly; there is limited data on the temporal or geographic variation of concentration within a distribution system. Utilities have estimated travel times in distribution systems by chlorine decay, floride tracking, and "best guesses".

The following are additional discussion points raised by individual FACA members:

- Prioritization of questions may depend on: (1) Identifying the rule options that the FACA will consider (as the FACA identifies possible options, the important questions may become clearer.) and (2) Developing the risk analysis, ICR baseline, and Stage 1 baseline.
- Determining baseline may not be as important as identifying health risks of concern. Knowing the baseline will not help answer the health risk questions, it will, however, help determine the impact of further regulation.
- A member requested a primer on treatment technologies. Treatment technique used is related to the characteristics of raw waters. The TWG should be able to provide estimates that the risk reduction from best available technology (BAT). The current FACA meeting schedule is an attempt to address the necessary topics (including; health effects and occurrence) in coordination with the schedule for availability of ICR data.
- McGuire pointed out that the TWG has many ongoing activities which are related to developing and testing models and methods for evaluating data other than ICR data (including treatment studies), including delphi (professional judgement) approach.
- An important remaining issue is how to include data from small water systems.

Followup Activities

1. EPA will provide FACA members with information on the risk assessment as it becomes available.

2. The TWG will develop the ICR and Stage 1 baselines and present them to the FACA.

3. The FACA will be given the present list of questions, with priority questions marked, used by TWG in developing the data analysis strategy. The FACA was asked to provide comments on the questions list by August 5, 1999.

X. Public Comment

Two speakers addressed the FACA during the public comment period on July 21: Frank Maitski, Santa Clara Valley Water District and Stewart Krasner, Metropolitan Water District Southern California. See Attachment X.a. and X.b. for the full text of these comments.

Frank Maitski, Santa Clara Valley Water District

The Santa Clara Valley Water District in San Jose, California is struggling with choosing the appropriate water treatment technology to improve water quality and meet new drinking water regulations and has committed to making major changes at their water treatment plants. Their struggle is with what to build, given the sensitivity to reproductive health effects and wish to reduce disinfection by-product concentrations in our treated water.

Mr. Maitski asked that the FACA first determine which treatment technologies are viable (especially for large Systems), and the total public health benefits each can provide, before establishing the package of Stage 2 regulations.

Stuart W. Krasner, Metropolitan Water District Southern California

Krasner asked that the FACA examine issues surrounding the mix of DBPs (THMs versus HAAs, chlorinated versus brominated species) to fully understand the implications of these epidemiology studies. Krasner also explained that the FACA needs to consider how boiling water (e.g., in the preparation of coffee or tea) effects DBP concentrations.

Adjourn

Attachments

I.a List of Meeting Participants

I.b Meeting Agenda

I.c List of meeting dates and proposed topics

II. Overview of Regulatory Context for Meeting - Stig Regli, EPA

III. Risk Assessment - Rita Schoney

IV. A Primer of Reproductive/Developmental Effects - Maureen Hatch, Mount Sinai School of Medicine

V. Stage 1 DBP Rule: Assessment and Conclusions - Ambika Bathija, EPA

VI.a Reproductive And Developmental Effects Of Exposure To DBPs: An Overview Of The Epidemiologic Data - John Reif, University of Colorado

VI.b Issues in Epidemiologic Studies of Reproductive and Disinfection By-Products - Rebecca Calderon, EPA

VII. Reproductive and Developmental Effects of Exposure to DBPs: An Overview of Toxicological Data - Rochelle Tyl, RTI

VIII. Current DBP Reproductive Effects Toxicology Research - Fred Hauchman, EPA

IX.a Technical Workgroup Presentation to FACA2 Committee - Michael McGuire, MEC

IX.b List of TWG Subgroups

X.a Public Comment: Statement of Frank Maitski, Santa Clara Water District

X.b Public Comment: Stuart W. Krasner - Public Comment to Stage 2 FACA Presentation 7/21/99

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[1]These guidelines are available on the web at: [http://www.epa.gov/ncea/raf/rafguid.htm].

[2]Reif also suggested that participants refer to the meeting summary from the February 10-12 Health Effect Workshop for additional information. This summary is available through RESOLVE by contacting Eddie Scher at [escher@resolv.org].

[3]see Attachment V.a for details

[4]See Attachment VII for description of each of these study designs.

[5]The web site address is [http://www.ecradlab.com/twg]. To enter the site will ask for *User ID* type [*guest*] and *Password*, type [*username*].

[6]The full set of questions was distributed to FACA members and interested parties following the FACA meeting. To receive a copy contact Detra Stoddard by email at [dstoddard@resolv.org].