M/DBP Stage 2 Federal Advisory Committee (FACA2) Health Effects Data Update and Discussion of Problems/Solutions for Stage 2

Meeting Summary - January 2000

Meeting #8

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ATTACHMENTS

I.a Meeting Participants - M/DBP FACA, January 12-13, 2000

I.b Meeting Agenda - MDBP FACA, January 12-13, 2000

I.c TWG Guiding Principles - *draft* from January 10 TWG meeting notes

II.a *draft* Problems/Solutions List - December M/DBP FACA meeting

II.b *draft* Caucus Lists of Problems and Solutions

II.c *draft* Joint-Plenary Problem Statements List - January M/DBP FACA meeting

II.d *draft* Consolidated List of Solutions/Question for the TWG

III.a Reproductive and Developmental Effects of Exposure to DBPs: John S. Reif, Department of Environmental Health - Colorado State University, January 13, 2000

III.b Reproductive and Developmental Toxicity Assessment of Drinking Water Contaminants: Stage 2 DBPs: R.W.Tyl, Research Triangle Institute, January 13, 2000

Introduction

On January 12-13, 2000, EPA held the eighth meeting of the Stage 2 Disinfection Byproducts and Long-Term 2 Enhanced Surface Water Treatment Rules (MDBP) Federal Advisory Committee (FACA). The purpose of this meeting was to refine the problems/solutions document developed in at the December FACA meeting and thereby provide direction to the TWG. Health effects experts John Reif and Rochelle Tyl presented an update on epidemiological and toxicological DBP data. This was an unprecedented meeting for the FACA because there was no presentation from the TWG. See Attachment I.a for a list of meeting participants and Attachment I.b for the draft meeting agenda.

Arnold reminded participants that a public comment period is included each meeting day for non-FACA members to present or comment on data, or voice their views and opinions.

Arnold reported that the TWG held a two-day meeting earlier in the week on January 10-11. Prior to the TWG meeting, FACA members and interested parties received the draft TWG agenda and draft TWG groundrules. The TWG decided that instead of adopting the draft groundrules they would clarify the informal guiding principles that TWG members have developed over time, and which have been successful in the past. Notes from the discussion of the TWG's guiding principals are included as Attachment I.c. All TWG work and products are available to the FACA.[(1)] In response to the large workload and additional FACA meetings, the TWG added a few meeting dates. The current TWG schedule is:

- January 25-26 - SWAT meeting, Denver, CO
- January 31-1 Feb. - Microbial occurrence, Washington, DC (RESOLVE)
- March 7-8 - (RESOLVE)
- April 17-18 - (RESOLVE)
- May 16-17 - (RESOLVE)
- June 26 - (RESOLVE)

The FACA adopted the proposed revisions to the FACA groundrules extending the schedule for Stage 2 negotiations until July 31, 2000. This meeting report summarizes the presentations and plenary discussions, and proposed next steps from this meeting.

II Discuss and Revise List of Problems/Solutions for Stage 2

FACA members reviewed the draft Problems/Solutions List from the December FACA meeting [Attachment II.a.]

After a full discussion, the FACA agreed to meet in interest group caucuses to discuss and bring back to the FACA Plenary group the problems and solutions that FACA members think will best move the group forward. FACA members broke into four interest group caucuses (utility, government, health/environment, and equipment manufactures) and began their deliberations.

II.1. FACA Plenary Discussion of Caucus Lists of Problems and Solutions

Following the caucus discussions the FACA reconvened in Plenary to present and discuss the flipchart notes produced in the caucuses. The transcribed notes from the utility, government, and health/environment caucuses were distributed to meeting participants [Attachment II.b.] The FACA plenary reviewed the notes from each caucus. A FACA member noted that the amount of consistency between the caucuses is remarkable, others around the table agreed.

At the suggestion of a FACA member, the Plenary agreed that the way to proceed was to continue in Plenary session and to consolidate the caucuses' problem statements into a single Joint-Plenary Problems Statement list [Attachment II.c.] The FACA members agreed on four groundrules for this discussion:

a. The joint-problem statements reflects a first cut or "straw" draft at identifying those problems FACA members agree the FACA ought to address.

b. It does not preclude any discussion of additional problems, questions, or information from occurring.

c. The list is not comprehensive or complete, in other words there are other problems respective caucus members may want the FACA to address.

d. The list does not represent a consensus by the FACA.

The following points were made during the discussion of a Joint-Problems Statement:

- FACA members expressed concern that there is great uncertainty surrounding mixtures of DBP, or the DBP "soup." A FACA member noted that the FACA may not be looking at the correct or most sensitive endpoints. Uncertainty regarding the correct endpoints to focus on is a direct result of the uncertainty surrounding the DBP soups. Toxicological data focuses on specific DBPs and specific endpoints. There are limited epidemiological studies. A FACA member suggested that one approach would be to looker more broadly by lumping cancer and reproductive and developmental effects to identify overall risk.
- Unknown/unidentified DBPs may be important in producing health effects. Surrogates should be identified and utilized.
- Elevated DBP exposure may be primarily the result of variability. Variable spatial and temporal exposure may need to be addressed.
- FACA members from the utilities caucus discussed their view that cancer data is not compelling enough to warrant a major shift in technology. However, there is enough data to justify efforts to tweak systems and technology to reduce variability.
- A FACA member expressed concern that some members may feel that the lack of new health effects data means that the FACA should not act and that the lack of new data does indicate that there is no problem or no risk.
- Cancer endpoints as well as all other potential health effect of DBPs need to be addressed by the FACA. The data base on DBP cancer effects was robust when the Stage 1 Rule was developed. There have not been many new cancer studies since then (though a few have been published since the 80/60 Rule). However, there has been incrementally growing data base on reproductive and development effects that are cumulatively important.

Day one, January 12, of the FACA meeting adjourned following this discussion.

II.2. Interest Group Caucuses Identification of Problems/Solutions & Consolidation of These Lists into the Consolidated List of Solutions/Questions for the TWG

On day two, January 13, FACA members agreed to meet by interest area caucuses and, using the Joint Problem Statements as a guide, come up with a list of items or topics that they would like the TWG to analyze. One use of these lists would be to provide the TWG with direction for what data and analysis to prioritize in the coming months. Caucuses were asked to raise or phrase questions so that they can be answered, e.g., "what would happen if...."

Technical consultants McGuire and Summers, along with McLain and Regli of EPA, used the flipchart notes taken from the FACA caucuses to compile a draft Consolidated List of Solutions/Questions for the TWG. The consultants worked quickly during the Reif and Tyl DBP health effects data presentations. This technical team was asked to combine solutions and questions identified by the respective caucuses whenever possible. When this list was presented some of the respective caucus participants raised concerns that the draft did not adequately reflect caucus discussions. FACA members agreed to review the list and return comments to RESOLVE for inclusion in the list by January 21, at 12 noon EST. RESOLVE will send out a revised list via e-mail by COB Jan. 21.[(2)] See attachment II.d for the revised Consolidated List.

The TWG will use the Consolidated List to prioritize their activities over the next few months. However, questions on the List are not a reflection of the FACA priorities. The TWG will sort out what it can answer quickly, and a schedule for all remaining questions.

FACA members made additions and modifications to the list during this discussion. These have been incorporated into the Consolidated list. The following are points made by FACA members during their discussion of the original draft Consolidated List:

- A FACA member began the discussion of the Consolidated List by acknowledging the good work of the Technical Consultants and other staff who worked to consolidate the information from the caucuses.
- The FACA needs information to identify the "knee of the curve", the point at which technology shifts become necessary or large costs are incurred.
- There are different levels of understanding around the room regarding different regulatory options. Some options, for instance, may be ineffective or too expensive, but they should still be considered. Information on effectiveness and cost should be shared at the table among FACA members.

III Overview of DBP Reproductive and Developmental Health Effects Data: Epidemiology and Toxicology

John Reif, Colorado State University, and Rochelle Tyl, Research Triangle Institute, were invited by the FACA to present overviews and updates of epidemiology and toxicology data on DBP reproductive and developmental health effects. Reif and Tyl presented DBP health effects data at the July FACA meeting.[(3)]

III.1. Reproductive and Developmental Effects of Exposure to DBPs: An overview of epidemiological data

John Reif, Department of Environmental Health - Colorado State University, presented an overview of epidemiological data [Attachment III.a] covering:

1) The results of recent epidemiological studies of reproductive and developmental outcomes and DBPs and re-analysis of earlier studies provided by several investigators.

2) The preliminary summary of the Colorado State University's report to Health Canada summarizing reproductive and developmental effects. The evidence for association with adverse

reproductive and developmental outcomes. And how epidemiological data can be used to establish concentrations of THMs which may be health hazards.

3) Summary of strength and weaknesses of the epidemiological data base, relationship to risk assessment.

This presentation is based on a presentation Reif made in November 1999 to Health Canada regarding balancing risks of microbial and DBP exposure. Reif also cited the notes from his presentation to the FACA in July 1999 as a source of additional information.

Reif concludes from epidemiology data on DBPs on female reproductive and developmental health outcomes:

- Reproductive and developmental health endpoints are sensitive to environmental toxicants.
- Small increases in risk are of public health significance due to ubiquity of exposure - outcomes are common so even a small change could have a large public health impact.
- Short interval between exposure and disease manifestation (latency) -unlike the situation in cancer, makes these endpoints much easier to study.

Reif reviewed the epidemiology data base for reproductive and developmental outcomes from disinfected water in general and specifically for THMs, and broke out existing studies by what endpoints were assessed, study type, and disinfection method studied.

Reif presented a summary of the studies that addressed the following outcomes and that incorporated estimates of exposures to TTHMs. These outcomes include low birth weight, small for gestational age, prematurity, congenital defects and spontaneous abortion/stillbirth. He showed a series of slides which plotted the exposure levels for TTHMs used in each of the studies for each outcome. He described in some detail two studies that were also discussed in July. The California Prospective Cohort study of spontaneous abortion had a population of about 5000 women who were followed through the course of their pregnancy. An association with spontaneous abortion and consumption of 5 or more glasses of water daily containing 75 ppb TTHM or more was found and was strongest for exposure to bromodichloromethane. This data has is being reanalyzed. The Nova Scotia Historical Cohort Study found a statistically significant incidence of stillbirth at TTHM levels greater than 100 parts per billion, but unlike most of the other studies, did not show associations with low birth weight, small for gestational age or congenital defects.

In response to a questions from a FACA member, Reif explained that the studies that only looked at crude indicators of DBPs such as water source or disinfection method are not very useful in identifying dose/response relationship or causality. They may still be useful however, since we do not know what the important component of the byproduct mixture actually is. One goal is to identify surrogates which will assist in identifying exposure levels in these studies.

Reif presented a slide comparing the findings of four studies for stillbirths and spontaneous abortions (SABs). SABs and stillbirths can be considered together from the standpoint that they are part of the same continuum of effects. This is not a meta-analysis, but a comparison of results of different studies. The graph indicates possible evidence of a dose-response relationship. Comparing point estimates to the zero effect estimate line (1.0) shows a slight increase with rising TTHM concentration. In response to a question regarding "threshold" for effects Reif explained that misclassification of exposure and variability between individuals in the middle of the range makes it very difficult to evaluate the potential existence of a threshold or to accurately describe a dose-response relationship if one exists.

Finding for low birth weight include one study with no effect, one study with significant but low effect, and two studies with significantly elevated effects. Reif also reviewed intrauterine growth retardation, pre-term delivery, and data on neural tube defects. In response to a question Reif noted that differences between

study populations due to ethnicity have been accounted for in the study design but the question of genetic differences between subjects has not been addressed to date.

Reif reviewed the risk assessment paradigm: hazard identification, exposure assessment, dose-response relationship, and risk characterization. Using this analogy, the reproductive data can contribute to the hazard identification and exposure assessment components, but are not yet adequate to fully describe dose-response relationships or to permit risk characterization for specific levels of DBPs. Reif believes that risk estimates tend to be low because of non-differential mis-classification of exposure data. There is not enough epidemiology data to answer the Risk Characterization question: which components of the DBP mixture must be reduced, and to what extent, to bring the risk to an "acceptable" level?

In the discussion following his presentation Reif and FACA members made the following points:

- Reif explained that in Stage 1 the FACA had to consider causality for cancer. With only five studies there was not enough data to make statements regarding causality, the risk was not very large, there was not adequate dose/response data, nor were there other large databases to contribute to the weight of evidence. This data, however, still suggests possibility of hazard.
- A FACA member noted that pharmaceuticals and other contaminants in source water could be indicators of very different types of pollution. There may be relationships between different types of water contaminants that are not currently understood.
- In response to a question Reif noted that social status has been considered in each of these studies. There has been no convincing demonstration that DBPs are higher in poorer communities. Studies have used indicators of socioeconomic status such as maternal or paternal education, or other surrogates for family income to control for social/economic status. He referred to the following table to show that these studies had taken socioeconomic status into account in multivariate analysis and therefore it was not likely to be an important source of confounding.

Reif: Studies included in presentation and risk factors included

Factor:	Age	Race	Education	Smoking	Prenatal care
Study					
Kramer	y		y	y	y
Bove	y	y	y		y
Savitz	y	y	y	y	
Gallagher	y	white	y	y	y
Klutz	y	y	y		y
Waller	y	y	y	y	
Dodds	y		family income	y	y

- A FACA member noted the number of children born with neural tube defects is quite large. Reif added that there is a body of toxicologic data that addresses this, and there may be data that suggests a mechanistic relationship.

III.2. Reproductive and Developmental Toxicity Assessment of Drinking Water Contaminants: Stage 2 DBPs

Rochelle Tyl, RTI, presented an overview of the reproductive and developmental toxicity data base for Stage 2 DBPs [Attachment III.b.] Tyl also reviewed what will be covered in her preliminary technical appraisal of the DBP toxicology database.

Tyl reviewed findings from the hazard characterization, and reviewed caveats regarding the analysis. Most DBPs in the analysis have been assessed in *in vitro* and/or *in vivo* screening studies. Many have "intrinsic capacity to do harm" to mammalian reproduction and/or development, especially brominated DBPs. She added that present studies may include inappropriate routes of exposure and only account for short-term exposure. Though male reproductive toxicity has been studied, there is a lack of data for female reproductive toxicity. Developmental toxicity has been the focus because a developing system is likely to be more vulnerable to adverse effects than an adult. Tyl reviewed the new ongoing initiatives to collect dose response data and a schedule for results from various studies on BDCM and DBA. EPA also has a collaborative research project with Colorado State University and EPA in-house studies.

RTI's review of the DBP toxicology data base will cover 33 DBPs, a table of endpoints, table of studies, weight-of-evidence, and information needed to fill data gaps. Weight-of-evidence is determined by combining the findings of smaller studies.

In response to question a question on thresholds for effects, Tyl explained that, in her experience, data suggests that there is a threshold for effects from DBPs. There is an assumption that developmental and reproductive effects, if they exist, manifest as a non-linear dose-response. The capacity to determine a threshold effect depends in part on which endpoints are being evaluated. For example, focusing on the effects to cells may miss damage on the molecular or DNA level since the cell may be able to repair. Large study populations in determining effects and threshold levels are important because of intra-species variation. Existing studies test for exposures much greater (by a factor of 100 to 10,000) than actual human exposures.

Studies look at more than one species because we do not know the relevance of effects across species. If an effect is seen in two different species (e.g. rats and rabbits) we assume that the toxin will effect humans. The default is to use the most sensitive effect. If we know the mechanism of the effect, then we can use that information to understand if the effect will be seen in other species.

IV Next Steps

FACA members discussed the following next steps:

1. Review the draft Consolidated List and returned additions and comments to RESOLVE for inclusion in a revised draft. The revised draft will be circulated to FACA members for review, then circulated to all interested parties.

2. Anticipated February FACA Agenda Items

- TWG Report: (1) Baseline, (2) If possible, answers to some of the questions on the Consolidated List (3) Schedule for answers to the balance of questions on Consolidated List
- Caucus Time

V Public Comment

No speakers asked to address the FACA.

Adjourn

Footnotes

1. Contact Eddie Scher, RESOLVE, if you would like more information on any TWG activities or would like to join the TWG e-mail list-serve.

2. Submissions were incorporated and the revised List was distributed by e-mail to FACA members for review on January 21, 2000. After this review the Consolidated List will be distributed to all M/DBP FACA interested parties.

3. Presentation materials and meeting summary from the July FACA meeting are available by contacting Eddie Scher, RESOLVE, at escher@resolv.org or by phone at 202-965-6203.