

May 20-22, 1999, M/DBP Stage 2 Federal Advisory Committee (FACA2) DBP Cancer Health Effects

MEETING SUMMARY

Meeting #2
May 20-21, 1999
Washington, DC

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I. Introduction

On May 20-21, 1999 EPA held the second meeting of the Stage 2 Disinfection Byproducts (DBP) and Long-Term 2 Enhanced Surface Water Treatment rules Federal Advisory Committee (Stage 2 FACA) on DBP cancer health effects. After introductions A. Arnold, mediator, RESOLVE, reviewed the objectives of this meeting ⁽¹⁾

- Discuss how to characterize cancer risk from DBPs.
- Review elements of cancer health effect risk assessment.
- Review ongoing studies related to DBP cancer health effects.

¹ See Attachment I.a. for a list of meeting participants.
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The FACA then approved the agenda [Attachment I. b.]. The FACA, by consensus, also agreed to adopt the groundrules circulated prior to this meeting [see Attachment I.c]. This meeting report summarizes the discussions and next steps from this meeting.

II. Report from Technical Workgroup

Mike McGuire, McGuire Environmental Consultant, Inc., provided the FACA with an overview of the membership and activities of the Technical Workgroup (TWG), and a review of the tasks identified by TWG for the future [see Attachment II.a for McGuire's presentation materials]. The TWG is made up of volunteers, with some consultants, who work on non health-effects related questions/issues posed by the FACA. The TWG's expertise extends across many kinds of issues. At this time there are 13 subgroups working on various questions/tasks. The TWG welcomes anyone with expertise who wishes to participate in meetings and conference calls. [See Attachment II.b for list of subgroups]. To get more information on a particular subgroup, contact the lead.

ICR Data Analysis Plan

In anticipation of the Stage 2 FACA negotiations, in 1997 an informal group of technical experts began to prepare an ICR Data Analysis Plan. They started with a list of hundreds of questions that they anticipated the FACA would ask of the ICR data. The formal FACA TWG is continuing with development a plan to extract data sets from ICR FED (the comprehensive database of all ICR data) into 8 easier to handle auxiliary data bases. These auxiliary data bases are designed to allow analysis of the ICR data on desktop or laptop computers. The TWG anticipates much of the data analysis will consist of descriptive statistical and graphical measures.

The FACA members agreed to have a TWG presentation at the July meeting exploring how the data should be presented, the kinds of graphs, at what detail, and over what period. The FACA expressed a desire to see data expressed:

- across distribution systems and for individual distribution systems
- for peak as well as average estimates (maximum's and averages), and
- contaminant by contaminant.

Non-ICR Data Analysis

The TWG anticipates using other sources of data in addition to the ICR. These other sources of data are:

- ICR Supplemental Survey
- Ground Water Supply Survey (GWSS)
- Community Water Systems Survey (CWSS)
- Disinfection Survey
- Water Industry Data Base (Water/Stats)
- Bromide Survey (AWWARF)
- Unregulated Contaminant Information Systems (URCIS)

Treatment Studies

As part of the ICR, utilities collected data that will provide additional treatment data. The steps for gathering additional treatment data include:

- Gathering data on the ability of granular activated carbon and membranes to
- control DBPs;
- Estimate the costs of implementing these technologies on a national level;
- Use this information to support Stage 2 DBP rule development; and,
- Accelerate local feasibility studies to prepare utilities for compliance with the

- Stage 2 MCLs.

Compliance Forecasting with ICR Data

The TWG is developing the following three tools that will assist the FACA in understanding the effects rule options will have on utilities:

- Compliance assessments use ICR data and other data to determine the population of those systems expected to violate a rule option scenario;
- Compliance forecasts using Water Treatment Plant model and other tools to estimate the treatment technologies used by water systems to achieve compliance with a rule option scenario; and,
- The Water Treatment Plant Simulation Model predicts improvements in water quality with the use of certain technologies - based on industry averages. Since the FACA TWG members are developing the model, the FACA will have direct access to individuals who understand the assumptions and equations behind the model.

TWG Next Steps

The TWG has developed its schedule of milestones and meetings to respond to the FACA meeting schedule. In late spring and summer 1999 the TWG will begin to analyze ICR data in preparation of the September FACA meeting where some of the data will be presented.

- July 19-20: TWG meeting, subgroups will report their progress to the full TWG.
- August 17-18: TWG will review the first 6 months of ICR data.
- September 10: receive feedback following the September 8-9 FACA and prepare for the presentation of ICR data analysis to the FACA at the September 20-21 meeting.
- October 25-26: ICR baseline
- December 6-7: Stage 1 baseline
- January 10-11: Evaluate Stage 2 rule options
- Feb-April, 2000: Evaluate Stage 2 rule options - Regulatory Impact Analysis

UV disinfection

McGuire summarized the report heard by the TWG on UV disinfection technology. McGuire stated that this is a potential new alternative treatment technology. It can inactivate *Crypto* and can be less expensive than other disinfection alternatives. A number of symposia have been held and are planned addressing UV issues. This Fall the TWG will be prepared to provide the FACA with more information on UV, if desired.

Summary and Conclusions

- The TWG is formally established and is preparing to meet the FACA schedule.
- A thorough ICR data analysis plan is in place and is operational.
- Auxiliary databases will be critical to successful ICR data analysis - development of these 8 "aux" data bases is on schedule.
- Non-ICR data will be used for predicting small systems compliance.
- GAC and membrane treatment studies will provide crucial data for compliance impact analyses.
- The WTP Simulation Program is the key to forecasting compliance of regulatory alternatives.
- The schedule for completion of the many analytical tools is on track, but it will take time to create the complex tool set.

Following are the points raised by individual FACA members after McGuire's presentation:

- In response to a question, McGuire explained that upon preliminary review of the initial data the TWG believes that the ICR data is excellent and the quality assurance/quality control has been very good.
- There are completed pilot and bench scale studies. The TWG intends to use algorithms for GAC and activated carbon, run the Surface Water Analytical Tool (SWAT), predict what plants will use activated carbon and membranes, and then make comparisons.
- It appears that many utilities are complying with Stage 1 earlier than required by the Stage 1 Rule, because they are piggybacking treatment improvements on expansion plans or other improvements in anticipation of compliance.
- Modeling will help determine what the Stage 1 baseline really is. The Stage 1 baseline prediction may be a minimum; if utilities are going beyond Stage 1 requirements then it may be lower. Estimates of the Stage 1 baseline are based on what is going on at the time data is collected.
- Confidence intervals around all estimates are very important. We should make clear what this range of error is in all presentations of data, including ICR data and models.
- The TWG's main concern for small systems data is collecting information on treatment - it is not known how small systems treat water. Many small systems use groundwater, so profiles of the small systems can be developed using source water quality data, and some of the supplemental surveys that collect small system data.

III. Overview of Safe Drinking Water Act

Ephraim King, Office of Water, EPA, presented an overview of the legal requirements the agency must meet to publish a drinking water regulation, specific MDBP statutory requirements, and questions to be addressed by the Stage 2 FACA related to DBP cancer related health effects. [See King's presentation materials, Attachment III.a.]

EPA is required to publish drinking water regulations for a contaminant under the Safe Drinking Water Act, as amended, if the contaminant meets three requirements:

1. Adverse effect on the health of persons;
2. Substantial likelihood that it will occur in public water systems with a frequency and at level of public concern; and
3. Regulation presents a meaningful opportunity for risk reduction.

Maximum Contaminant Level Goal (MCLG) is the unenforceable goal level at which no health effects occur - allowing for an adequate margin of safety. The Maximum Contaminant Level (MCL) is the enforceable standard based on the MCLG. The MCL must be as close to the MCLG as "*feasible*" given technological and economic constraints. The MCLG and MCL must be published simultaneously. The SDWA requires that the Agency look at costs and benefits, both quantifiable and non-quantifiable, as a balancing factor, not a driving factor.

If the criteria list above are met for proposing a regulation, but not those for developing an MCL then EPA must promulgate a treatment technique requirement (TTR). This occurs in situations where methods to measure (monitor) contaminants do not exist, or are not economically or technically feasible. In these cases EPA will identify technologies that reduce the contaminant of concern and measure the performance of the technology as a surrogate for measuring the contaminant levels. The TTR is based on the "best available technology" (BAT), a technology that is demonstrated to work in the field - not just a model - and has real life demonstration of effectiveness. The TTR also considers the cost of technology. An example of a TTR is the use of enhanced coagulation in the Stage 1 rule.

The SDWA also requires that a Health Risk Reduction and Cost Analysis (HRRCA) be performed on the contaminant. The HRRCA is an economic assessment tool and a part of the regulatory impact

assessment, used after development of the MCLG to help determine costs and benefits associated with different regulatory options (either MCL or treatment technology.)

King then highlighted the major regulatory questions for the Stage 2 DBP Rule:

- What is the magnitude of risk in chlorinated drinking waters for different endpoints?
- What is the risk in brominated versus non-brominated DBPs?
- What is the relative risk from waters disinfected with chlorine versus alternative disinfectants?
- Which individual DBPs pose the highest risk?
- How much does exposure to DBP risks vary within distribution systems and what are health effects of DBPs?
- Which DBPs occur most often and which DBPs are the public being exposed to?

The following discussion points were made following King's presentation:

- The SDWA names granular activated carbon (GAC) as a BAT for certain "synthetic organic chemicals." GAC has a wide range of applications (expensive and inexpensive). What is being treated has implications for how the GAC system is set up (e.g. bed depth and contact time). The FACA acknowledged that a review of all technology options will be discussed the Fall or early 2000.
- A key element of the HRRCA is transparency about confidence in data.

IV. EPA Analysis of Toxicology Data - Methodology & Reasoning

Jim Cogliano, EPA, presented an overview of EPA's risk assessment paradigm for cancer health risks. [See Attachment Inv.] EPA assesses cancer health risks based on:

- Hazard Assessment: *Is the agent carcinogenic to humans? What circumstances favor carcinogenicity?*
- Dose-Response Assessment: *What is the relationship of dose to response considering animal-to-human, high-to-low, route-to-route differences?*
- Exposure Assessment: *How do people come in contact with the agent? How much are they exposed to? What are pathways and levels of exposure?*
- Risk Characterization: *Integrates Hazard Assessment, Dose Response, Exposure Assessment - describes assessment's strengths and limitations (including sensitive sub-populations, strengths and weaknesses of understanding).*

Hazard Assessments consider many kinds of information. Principal sources of information are human and animal studies. In the past, human studies were the focus, epidemiological studies are mostly occupational exposures, there are only 20 chemicals with this type of data. Toxicological and animal studies are conducted mainly on rats and mice or both. Toxicology and lab studies are used to understand how contaminants cause cancer in animals and predict if they pose risk to humans. EPA is developing a framework to further understand how contaminants cause cancer in animals.

- Cancer is studied in animals using high doses. Many agents will be hazardous at high levels, fewer will be hazardous at low concentrations and only some will be carcinogenic.
- Guidelines for assessing carcinogenicity are always evolving and must include preexisting conditions, co-exposures, routes, and other factors that may influence the level of risk.

Dose Response Assessment Cogliano continued with an explanation of dose response assessment. Data observed in studies is extrapolated to the exposure levels that are expected in the environment; high doses to low doses; animal studies to humans; and inhalation route versus oral exposure. Multiple models exist for how to do this extrapolation. The choice of the mathematical model used to fit a dose-response model to the animal data and to extrapolate to human exposure at low doses will have a major effect on our estimates of risk.

The various models generally can yield results that differ by several orders of magnitude. The EPA uses a linear model to generate a dose response curve with an upper confidence limit at lower doses. The results are consistent with what we observe in a bioassay, but it is an upper bound estimate. It will be difficult to sufficiently validate a model to everyone's satisfaction. Selecting a good data set is difficult and is the source of much of the uncertainty with respect to the prediction of dose-response curves.

The following points were raised by individual FACA members following Cogliano's presentation:

- EPA considers the use of the upper 95 percentile as a conservative estimate. However, the conservatism of the dose-response curve depends on the model used.
- EPA believes that the use of a linear model is conservative. That is, it predicts a level of risk at low exposures, whereas most of the alternative models do not and are, therefore, more protective. We do not have data at the low exposures, but believe that the linear model yields a plausible upper bound for risk at low exposure.
- The EPA dose response model estimates that only zero exposure yields zero risk. The shape of the dose-response curve will depend on cancer initiation and confounders that contribute to cancer.
- EPA does not report the maximum dose response estimate (an alternative approach to estimating risk at low exposures) because these estimates are imprecise. The maximum dose response estimate depends on the species and number of animals used in the studies. The upper bound is not as sensitive to small changes in data and which animals are included. The upper bound and maximum dose estimate is usually within two orders of magnitude.

V. EPA Perspective on Toxicology Data & DBP Cancer Health Risk - Stage 1 DBPR RIA Cost/Benefit Analysis

Stig Regli, EPA, presented how EPA estimated DBP cancer risks from drinking water based on **toxicology data** for Stage 1, the basis for cancer risk and risk reduction estimates in Stage 1, and the benefits and costs for avoiding risks under Stage 1. [See Attachment V.a.]

For the Stage 1 Rule EPA estimated DBP cancer risk based on the estimated number of "cancer cases per year" nationally. This estimate is derived from (a) population exposed to DBPs, (b) DBP concentration exposure, and (c) the annual drinking water risk factor. The annual drinking water risk factor is derived from the Maximum Likelihood Estimate (MLE) or 95% confidence interval and a conversion factor (human body weight, daily water intake, lifetime expectancy). The Stage 1 cancer risk estimates assumed the following:

- The population exposed to DBPs was estimated at 239,137,010.
- The pre-Stage 1 national DBP occurrence mean was estimated (based on TTHM only) for all systems at 44 µg/l.
- Distribution of specific THMs was estimated based on EPA field studies.
- Annual risk factors of each THM were applied to give total estimated cancer cases.

Risk reduction by Stage 1 DBP Rule was estimated by the following steps:

- Developing a compliance decision-tree based on treatment effectiveness and cost.
- Estimating change in TTHM baseline (estimated mean used is 24% reduction in all TTHMs for all systems).
- Assuming that risk is lowered in proportion to reduction in TTHM exposure (0.2 to 24 cancer cases per year depending on whether the MLE or upper 95% confidence interval is used).

Benefit of cancer cases avoided in the Stage 1 DBP Rule were estimated assuming that the type of cancer cases avoided is bladder cancer. EPA estimates that Stage 1 DBPR may led to **\$45 million in avoided costs per year** (based on the upper 95% confidence interval estimate and willingness to pay assumption). This estimate is based on toxicological data only, TTHMs only, and has not accounted for the effect of bromate reduction or formation. This EPA estimate assumes a mean cost of \$5.6 million for each fatal case of bladder cancer. The cost of non-fatal cases, 77% of all cases, are estimated using cost of illness measurement (\$121,000) or willingness to pay measurement (\$587,500) as the mean.

EPA estimates the costs of Stage 1 DBPR at \$701 million total (based on monitoring, treatment, and annual state costs). Costs per household break down into three categories:

- 95% of households will incur \$0-12/yr.
- 4% of households will incur \$12-40/yr.
- 1% of households will incur \$120-400/yr. (mostly due to membrane technology in groundwater systems -approximately 900,000 households.)

These estimates are based on toxicology data. However, EPA evaluated Stage 1 DBPR based on collective weight of evidence of toxicology *and* epidemiology risk estimates. For example; toxicology studies estimate risks of 1 to 100 cases while epidemiology studies estimate national risk at 100 to 10,000 cases. On the second day of this meeting the FACA discussed how the epidemiology risk estimates assumptions fit into the Stage 1 Rule analysis.

Following Regli's presentation individual FACA members raised the following points. There was not an attempt to reach any conclusion or consensus, so these points reflect individual member's observations.

- Economic benefits of avoiding cancer are estimated using EPA Office of Air calculations of the economic value of saving a generic statistical life. \$5.6 million estimate is the mean of a range of values, and is the same for all types of cancer.
- Estimates do not include mixtures of DBPs.
- EPA considered a spectrum of risk, and simplified calculations by estimating risks based on bladder cancer. The calculation of benefits presented here is based on toxicology data only.
- EPA estimates for systems not meeting the Stage 1 80/60 standard includes estimates of large systems with TTHM levels of 60 to 100 and small systems, some of which are in the 100 to 1000 range, that will be coming into compliance as Stage 1 is implemented.
- Regarding where risk reduction takes place, there might be a small population with huge risk and large systems with small risk. The systems facing very expensive changes may be those going from very high levels to very low levels. There is proportionality between costs incurred and level of risk reduction.
- Though EPA is estimating risk reduction based only on TTHMs, technology changes will reduce other DBPs.
- Estimates for willingness to pay are based on Office of Air calculations for bronchitis. OGWDW does not have any willingness to pay data for cancer endpoints.
- The Stage 1 baseline estimate is 24% below where the baseline was anticipated to be during the Stage 1 FACA negotiations. The Stage 1 FACA negotiations anticipated the baseline on TTHMs not HAAs. However, HAAs may be the driver of the risk calculations.
- In response to a question, Regli explained that it is reasonable to conduct a cumulative statement of total benefits, including toxicology and epidemiology. EPA can provide more information on what is involved in calculating the value of life - monetizing.

- Occurrence data for small systems is estimated using 1980 source water TOC data. EPA applied a source water distribution model for predicting THMs and assumed that all small systems were chlorinating. EPA looked at source water estimates, assumed treatment practices, and then estimated occurrence for distribution systems.

VI. Ongoing DBP Cancer Studies

Gary Boorman, NIEHS, presented an overview of DBP toxicology cancer studies, what conclusions can be drawn based on preliminary analysis, and future research. [See Attachment VI.a.]

NIEHS is currently supporting six types of toxicology research on DBP cancer health effects, see attached presentation slides for compounds, completion schedule, and initial findings:

- Reproductive toxicology
- Immunotoxicology
- Neurotoxicology
- Transgenic mouse assays
- Medaka fish assays
- Toxicology/carcinogenicity studies

Open toxicological questions on mechanisms for carcinogenesis include:

- Same mechanisms in rodents and humans?
- Same mechanisms at low concentrations? Are cells resilient, do they respond to toxins and at what levels
- Role of DNA repair enzymes -can cells repair an "Adict" (chemical disruption of DNA replication)?

Studying drinking water from the toxicological perspective is very complex. The contaminants being studied are at extraordinarily low levels in the water. Understanding the effects of these compounds on cancer is at the cutting edge of toxicology research- there is lots of new information available now and in the near future.

The following points were raised by individual FACA members following Boorman's presentation:

- Each study costs approximately \$1 1/2 million.
- Rodents are useful for identifying what chemicals are at potential risk, not at getting dose response curves, this will take new procedures that are now being developed.
- Mixtures are derived either by (1) finding mixtures or (2) creating mixtures by adding chemicals, this approach is reproducible. Mixture data usually includes a combination of chemicals and we do not have data on the makeup of the mixture. One solution may be to work with chemists and water utilities to identify mixtures to study.
- Mixture research requires Transgenic mouse or fish models. Carcinogenicity studies require studying individual chemicals.
- Researchers are using corn oil gavage techniques in some studies so we can relate the data back to earlier studies conducted with the same technique.

VII. Characterization of Risk From Unidentified/Untested DBPs

Jennifer McLain, EPA, presented EPA's approach for characterizing the risk from unidentified and untested DBPs. [See Attachment VII.a.] There is currently an extensive DBP research program focused on the highest occurring known DBPs. However, a significant fraction of DBPs are unknown. Prioritization approach is based on Structure Activity Relationship (SAR) for cancer and developmental effects.

EPA uses SAR to classify DBPs by degree of concern (1, lowest, to 6, high). SAR is determined based on literature search for DBPs and experience of experts analyzing chemical structure for bioactivity features. TOPKAT analysis using QSTR software package is also used which yields a quantitative prediction if a chemical will be found to be carcinogenic. Criteria for classification are:

- Available literature
- Structural similarity to chemicals with toxicity data
- Structural features associated with activity
- Structural features suggestive of low cancer risk
- Consideration of bioavailability

Preliminary conclusions of SAR analysis are that there are only a handful of chemicals with moderate or higher levels of concern. These are not sufficient to explain the level of risk suggested by epidemiology, however, we know that some high concern chemicals are still in the unidentified category. EPA will focus on moderate to high concern level DBPs for possible future testing.

Following McLain's presentation individual FACA members raised the following points:

- SAR Classifications describe and estimate level of concern for research prioritization. These priorities are not quantitative, but are made using professional judgement.
- The computerized QSTR model will be available in July or August, 1999 and results will be available to the FACA.
- Stability of compounds across a wide range of pH levels has not been looked at.

VIII. Other Perspectives on Toxicology Data & DBP Cancer Health Risk

Panelists Melvin Anderson, Colorado State University and Ronald Melnick, NIEHS, were asked to comment on the two questions noted below.

- *What is the magnitude of cancer risk from the toxicology data?*
- *How far does the Stage 1 DBPR go towards addressing this risk?*

Each panelist provided a short presentation and participated in a discussion of these questions. [See Attachment VIII.a for Andersen's presentation materials, and Attachment VIII.b for Melnick's presentation materials.] The following summary includes the points made by Andersen and Melnick:

Based on the current toxicology data base, what is your perception of cancer risk from DBPs in drinking water?

Melvin Andersen: Based on the toxicology work with these compounds, the cancer risk from DBPs in humans at prevailing concentrations appear to be very small.

- Conservative bounding techniques are used to infer human cancer risks from the animal carcinogenicity data base.

- The risk assessment methods used to date have assumed that DBPs act like strong mutagens or radiation and have linear dose-response curves. These techniques provide a range of risks. With the exception of a few compounds, such as MX, most DBPs are not strong mutagens.

Ronald Melnick: Based on convergence of animal and human data, there is a significant health risk from DBPs in drinking water.

- The carcinogenicity of several DBPs has been demonstrated in experimental animals, including the induction of tumors of the liver, kidney, and lower GI tract.
- Human data on DBPs, particularly the trihalomethanes (THMs), indicate increased cancer risk for the bladder and lower GI tract.
- The magnitude of risk is difficult to estimate because of limited toxicological and exposure data, inadequate information on possible interactions, effects of unknown DBPs, and limited information on the impact of susceptibility factors on inter-individual variability.

How do risks from brominated DBPs compare with chlorinated DBPs?

Andersen: The risks of brominated analogs are expected to be higher than chlorinated analogs of the DBPs.

- Some brominated DBPs have been associated with intestinal cancer in rats; a finding shared with several other brominated compounds, including some fire retardants.
- Brominated compounds are generally more reactive toward displacement reactions than are corresponding chlorinated compounds.
- In rats and humans, brominated THMs react at a higher rate with a co-factor, glutathione, compared to chloroform.
- In studies with certain bacterial mutation models evaluating the biological properties of these glutathione reactions, brominated THMs were found to be mutagenic and chloroform was not.
- Even though these brominated DBPs are expected to be more toxic and more mutagenic, the carcinogenic risks to humans may still be extremely small at exposure levels found in drinking water supplies in the US.

Melnick: Within a particular family of chemicals, the risk from brominated DBPs may be higher than chlorinated DBPs.

- Bromine is a better leaving group than chlorine, therefore we might expect more rapid metabolism of Br-DBPs than Cl-DBPs within a particular family of chemicals.
- Brominated DBPs are more lipophilic, may partition in tissues greater than chlorinated DBPs. Within a particular family of chemicals, the risk from brominated DBPs may be higher than chlorinated DBPs.

How do risks from alternative disinfectants compare with chlorine disinfection?

Anderson: There is currently very little information on which to formulate a solid opinion. The chlorine DBPs are more thoroughly characterized and some do show toxic and carcinogenic properties.

Melnick: More data is needed: exposure/toxicology/epidemiology. A reasonable strategy for cancer risk reduction is to filter to reduce organic precursors before adding disinfectant.

How can possible risk from unidentified DBPs in drinking water be characterized?

Anderson: This question is an oxymoron for the toxicologist. If DBPs are unidentified, we cannot very easily test them. Large data gap exists with respect to the toxicity of some of the compounds that have

already been identified. For instance, what are the effects of the chlorinated haloacetonitrile? Does bromination alter the toxicity/mutagenicity of these compounds as it does with THMs? The studies outlined by Dr. Boorman at the NTP should help to resolve some of these questions.

Melnick: DBPs must be characterized from different sources and disinfection processes. Relative activities within families should be studied (dosimetry, effects of Br vs. Cl & numbers of halogens, tissue responses, and effects in *in vitro/in vivo* models.) With this information it may be possible to make reasonable estimates of risk for future identified DBPs which lack adequate toxicity/carcinogenicity data.

How can data on individual DBPs be used to characterize cancer risks posed by chemical mixtures?

Andersen: Several strategies are possible. In general, they involve reconstituting a representative mixture, as found in drinking water supplies, and evaluating critical responses of animal model systems to the mixture. For example, these studies could:

- Evaluate the toxicity/mutagenicity of representative mixtures of DBPs at moderate dose levels and evaluate their effects on the target tissues identified in animal studies and those identified in epidemiological evaluations of human populations.
- Conduct *in vitro* assays for mutagenicity of the mixtures in comparison to individual compounds to assess any potentiating of responses.
- Consider developing animal models to evaluate the potential of these DBP mixtures to act as a tumor promoter in bladder (the proposed human cancer site) and in large intestine (a tumor site for brominated DBPs observed in rodents). The human epidemiological data indicate that bladder is an important site of DBP activity in humans. This tissue has not been carefully evaluated in toxicology studies of DBPs.

Melnick: Information on potential interactions may be obtainable from future extensions of studies on individual DBPs in:

1. Alternative animal models, e.g. Transgenic or knockout (e.g., APC +/-).
2. Validated biologically based dose-response models.

How can differences in estimated risk from exposure to DBPs based on toxicology data versus epidemiology data be reconciled?

Andersen: First, the question is whether there really are differences in the estimates. Both disciplines provide risk ranges that include very low estimates of risk. The low risk estimates may be correct. There continues to be debate about the role of lifestyle factors or confounders in the human studies. Nonetheless, the epidemiological data should not be simply ignored. The overall uncertainties in toxicology and in the magnitude of the upper bound human risks estimated from epidemiology indicate that some further evaluations and approaches are necessary. Not all compounds have been studied and mixture issues are unresolved (and perhaps unresolvable).

Melnick:

- Estimated risks of 1-100 cancer cases/year seem low based on potency estimates from animal studies, human exposure data, and number of people exposed.
- It may be that humans are more susceptible to bladder and colorectal cancer than lab animals; spontaneous rates of these cancers are low in animals, while the incidences are high in humans.
- Exposure circumstances are different in laboratory animals and human populations -interactive effects of mixed exposures may occur in humans at different stages of the carcinogenic process. Risks from mixed exposures may not be additive.

- Humans experience multiple routes of exposure: oral, dermal, inhalation; animal studies are generally limited to single routes of exposure.
- Different periods and duration of exposure and evaluation: e.g. neonatal human bladder may be more susceptible than the adult rodent bladder, animals may be killed before late developing tumors are detected.
- Cancer risks in highly susceptible sub-populations have not been addressed: humans differ with respect to genetics, levels of enzyme induction, age, other exposure experiences (some may be further along in the carcinogenic process.)
- If epidemiologist tell me there are good studies, more than one, showing a chemical to be a carcinogen, even in the absence of toxicology data or a mechanism, I would agree that it is a carcinogen.
- Epidemiology data have been obtained from different populations; you cannot expect perfect convergence between different populations. The mechanism data needs to be bolstered.
- Epidemiology studies may have limitations, but toxicology does not now cover mixtures or presence of other carcinogens that people are exposed to. Animal studies are done under very controlled conditions.

What are the largest remaining data gaps or uncertainties that need to be filled to better characterize risk from DBPs? Will current research substantially reduce these uncertainties?

Andersen: Our best hope in the mid-term is that research will help to more sharply focus the questions related to the human health consequences of DBPs. Primarily, we may be able to better evaluate whether the bladder is the site of primary concern. For instance, we can ask whether targeted animal studies might help to corroborate that the bladder is a target site action of DBPs or their metabolites. Secondly, specific studies of colorectal responses in animals should aid in determining if this tissue is a target for brominated DBPs in humans. On-going work needs to incorporate a more integrated vision of the role of both epidemiology and toxicology in defining and resolving specific questions. Looking to both disciplines, we can ask what major unresolved issues exist in each:

The most important unresolved toxicological questions include:

- Are there mutagenic interactions among DBPs with respect to in vitro or in vivo behaviors?
- Do specific DBPs or mixtures have promoting/enhancing activity in animal models for bladder or for colorectal cancer?
- What is the tissue distribution of metabolizing enzymes - cytochrome P450 2E1 and the glutathione-S-transferases - in animal and in human tissues. An important mechanistic data gap is whether or not there is an association between the localization of the enzymes and the sites of toxicity/carcinogenicity. If there were, it would strengthen the case for a causative role of metabolites in these effects and intensify mechanistic studies with particular metabolites. This point is illustrated by the studies correlating toxicity of chloroform with sites with high levels of the cytochrome P450 2E1 enzyme in rodent studies.
- The past few years have seen an expanding number of DBP compounds being studied. More will be scrutinized in the years to come. The studies probably will not resolve all the uncertainties, but should narrow the areas of concern. We have come to a point where we can ask better questions about the bladder and colorectal cancer sites and about the metabolism by different enzymes (especially the transferases) in animals and people. However, it is unlikely that some small set of magical studies will resolve all the issues immediately. Progress will be incremental in the toxicology/epidemiology areas and we all have to be careful to have reasonable expectations for this next round of studies.

The largest data gap in the epidemiology data base relates to whether the increases in bladder cancer rates with DBP exposures in human populations are causal or some other type of association. Some steps that would be useful in answering this question include:

- Improve dose reconstruction methodologies used in the human studies (what are the doses of the various DBPs in these studies? This reconstruction might be possible based on knowledge of the input concentrations of organic materials etc. and the nature of the disinfection procedures.)
- Examine cancer incidence/morbidity in selective populations with high brominated DBP exposure. Can we actually find specific evidence for increased cancer/disease burden in humans exposed to these DBPs that appear to be more toxic and more likely targeted to colorectal sites.
- Evaluate historical changes in bladder cancer incidence. Do the current population attributable risk estimates make sense in light of the historical use of disinfection in the US population?
- Consider other comparisons to assess possible confounding factors in the human populations.

Melnick:

- Need better exposure analysis to identify unknown DBPs
- Need epidemiology studies in regions with high bromide levels
- Need separate analysis for sensitive subpopulations: age, genetics, other exposures
- Need to characterize potential interactions from mixed exposure and the influence of susceptibility factors
- Need to expand toxicology database on DBPs, including characterization of gene alterations.

How far does Stage 1 go in addressing cancer risk?

Andersen: The possibility exists that risk is low regardless of which data base - toxicology or epidemiology - you use to draw conclusion. With that preamble, certain remarks can be made about the Stage 1 reductions.

- The Stage 1 reduction is comforting since it is hard to disagree with a reduction in exposure to potentially harmful contaminants in drinking water. However, the reduction may have little effect on altering cases of bladder cancer in human populations. The uncertainties around the estimates are just too large.
- Costs and uncertainties of other disinfection processes need to be better evaluated before proceeding.
- Risk reduction from Stage 1 DBP Rule is not likely to be proportional to reduction in exposure. This would only be expected if the dose response curve was linear at these low doses. Nonetheless, even if the reduction in cases is minimal and much less than linear, the continuing uncertainties indicate that reducing exposure should be a goal. Obviously, eliminating the toxic compounds would be desirable, but is not feasible or not likely to create an improvement in public health.

Melnick:

- Based on our current knowledge it is reasonable to assume risk reduction would be nearly proportional to reduction in exposure.
- For chlorination disinfection it is reasonable to assume that THMs can serve as a surrogate for other DBPs.
- Further research may allow modification of these two assumptions.

In the discussion that followed the presentation, the following points were raised:

Andersen:

- In the laboratory, it is possible to create test systems in bacteria or animal cells that demonstrate the mutagenicity of some DBPs. These results may not be easily extrapolated to suggest mutagenic potential in humans at relevant exposure levels.

- During his presentation, Dr. Andersen had stated that the site of increased incidence in humans has not been identified as a site of animal cancer in studies with DBPs. A question was posed as to whether one would expect concordance between sites of cancer in rodents versus sites of cancer in humans. Arsenic, for instance, is a human bladder carcinogen while it does not cause these tumors in rats. Andersen explained that concordance is expected when the mode of action is fairly certain and is shared by different species.

Melnick:

- Cancer is a multi-step process and the causes are multi-factorial. Cantor *et al.* study did show that effects of DBPs is much stronger in smokers than non-smokers, not all studies have found it.
- It may be that some of the cancer steps do not occur at low doses. You have to know processes at lowest dose. It is possible to think that a low dose linear relationship may exist. A linear low dose response curve is plausible.
- In response to a question, he explained that he would not require site to site concordance, depending on the observed tissue response because of differences in tissue dosimetry and tissue response in animal models versus humans. The first step is to identify hazard based on human/animal/mechanistic data. It is important to note that while kidney and GI tract tumors were induced by THMs in animals, epidemiology studies indicate an association between consumption of THMs and increased risk of risk of bladder and GI tract cancers.
- Bladder cancer has a very long latency, 35 years⁽²⁾. Bladder cancer is a disease of the elderly. Exposure levels for DBPs have changed drastically over the years, so to try and reconcile results, given long latency, is very difficult.
- A consideration for toxicology data is that animal studies do not routinely address perinatal exposure and how effects at this stage of development may influence cancer outcome. The utility of cancer studies of DBPs in Transgenic mice has not yet been demonstrated.

²Dominique S. Michaud, *et. al.* "Fluid Intake and the Risk of Bladder Cancer in Men" May 6, 1999 - Contact Eddie Scher [escher@resolv.org] for a copy of the article.

IX. EPA PAR Analysis of Epidemiology Data - Methodology and Reasoning

Mary Manibusan, EPA, presented an overview of the purpose, methods and conclusions of EPA's Population Attributable Risk (PAR) Analysis. [See Attachment IX.a.] The PAR is used by EPA to estimate the benefits derived from reducing exposure. Results from the PAR analysis were used to support the regulatory impact analysis for the Disinfectant/Disinfection Byproducts (D/DBP) Stage 1 Rule, which was promulgated in December of 1998. PAR is defined as "that fraction of the diseased population that would be eliminated if the exposure were absent." In this particular case, the association between bladder cancer and exposure to chlorinated surface water was evaluated and causality assumed for the purposes of this analysis. The PAR range of 2-17%, with the acknowledgment that the range may also include zero for lack of causation, was identified from the best available bladder cancer epidemiology studies on chlorinated surface water.

In using data from these five studies to estimate national risk EPA is making the following assumptions:

- The study population in these studies (13 states) is reflective of the nation.
- Levels of DBPs found in chlorinated surface water in studies is similar to that experienced by the population served by surface water. (Only 2 studies provided a measure of the geometric mean THM levels.)
- DBPs are a major bladder carcinogen present in chlorinated surface waters.

- The association between bladder cancer and exposure to chlorinated drinking water observed in these studies reflects a causal relationship.

EPA has acknowledged the difficulty in extrapolating any national assessment from study populations without sufficient data. However, the weak associations evidenced between bladder cancer and exposure to chlorinated byproducts warrant the pursuit of public health policy that sought to reduce the levels of DBPs in chlorinated drinking water. Based on the above-mentioned assumptions and odds ratios from each of the five studies, EPA estimated between 0-1,100 and 9,300 cases/year of bladder cancer (out of 54,500 total bladder cases per year nationally) may be attributable to exposure to chlorinated drinking water. The next step in the regulatory impact analysis is to estimate the reduction in exposure to DBPs from the implementation of the Stage 1 D/DBP rule and how this impacts the number of bladder cancer cases that could be avoided based on this reduced exposure. Finally, the number of cases avoided was monetized and compared to the costs of the Stage 1 D/DBP rule to determine whether the benefits exceed the cost.

Following Manibusan's presentation, the FACA discussed the following points:

- Non-differential exposure misclassification may bias these estimates downwards. It is possible that the attributable risk could be much higher than the PAR estimate.
- The PAR analysis has undergone internal (within EPA) and external review and EPA is confident in the 1,100 to 9,300 range, however it was noted that there may be insufficient data to quantify.
- The PAR analysis does not include dose/response or exposure data and does not address the issues of causality directly. The PAR is designed to look at a large population and quantify benefits of large scale public health decisions.
- In the PAR analysis, the assumed levels of DBPs are based on only 2 studies and do not include mixtures (e.g., THMs are presumed to be sole source for bladder cancer risk). These studies span 1997-1998 and, because of the long latency period of bladder cancer, exposures contributing to currently observed disease spanned 1950's and 1960's when drinking water contained other contaminants including DDT and other unidentified chemicals.
- The PAR Analysis was done to quantify benefits that EPA believes would occur if actions are taken to reduce risk. EPA used existing toxicology data and 30 DBP epidemiology studies to decide that there was enough evidence of an association between DBPs and health effects to justify regulatory action. The PAR analysis is an attempt to quantify this association. It does not use all the studies, but those that meet specific criteria. In the RIA EPA discusses all the data.
- There are additional studies on food and water intake and bladder cancer that do not look at DBPs and water source, but would be useful for the FACA to hear. A recent article in the New England Journal reported that water consumption decreased risk of bladder cancer.⁽³⁾ A participant pointed out that the reason may be due to the flow of fluid through the bladder. However, if it turns out that exposure to DBPs in water is attributable and drinking lots of water is good for you - these findings do not conflict.
- In estimating that 2-17% of bladder cancer is attributable to DBPs, EPA acknowledges that this is the most likely range, yet also includes 0. However, EPA has not provided an upper limit above the 17% based on the upper bound of each study to include in the PAR. Another option is to take the 95% upper confidence interval. If the estimated risk range is 2 to 17% and also includes a lower limit (0), it should also include the most conservative estimate - the upper limit on what the data will support.
- The long latency period of bladder cancer (approximately 35 years), and weaknesses in the PAR report put obvious difficulties in results. Studies with high end risk estimates may have the greatest inconsistency. For instance, there was not enough consistency in the data for EPA to do a PAR analysis on rectal and colon cancer.
- EPA is required to try and quantify benefits. The PAR analysis is EPA's best attempt to take scientific data and quantify benefits. The PAR analysis is tied to the previous judgement that toxicology data (even with inconsistencies) shows enough evidence of risk to support moving forward with regulatory action. There is toxicological evidence DBPs can cause cancer in lab

animals, the difficulty is estimating what that means for human health. The question that the PAR analysis is addressing is how to balance risk and relative risk.

- Existing uncertainties are more likely to raise risks than reduce them. Deciding if there is a causal relation ship is very difficult. If you assume DBPs are causal, then you have underestimated risks.

³Dominique S. Michaud, et. al. "Fluid Intake and the Risk of Bladder Cancer in Men" May 6, 1999 - Contact Eddie Scher [esch@resolv.org] for a copy of the article.

X. EPA Perspective on Epidemiology Data & DBP Cancer Health Risk- Stage 1 RIA Cost/Benefit Analysis

Stig Regli, EPA, presented an overview of the basis for estimating national cancer risks from the PAR analysis (pre Stage 1 and pre Stage 2) and estimating the benefits and costs for avoiding risks under Stage 1 (Regulatory Impact Analysis perspective). [See Attachment X.a.]

The estimated range of pre-Stage 1 bladder cancer cases based on the PAR analysis is 1,100 to 9,300 per year (with the mean of each PAR assumed to represent possible risk range.) This estimate also includes zero risk. EPA predicts that Stage 1 implementation will lead to a 24 percent reduction in TTHMs. Therefore, 264 (1,100 x .24) to 2,232 (9,300 x .24) of all bladder cancer cases per year are avoided (including zero). EPA assumes that 23% of these cases would be fatal and 77% would be non-fatal.

The assumed benefit of cancer cases avoided by Stage 1 DBPR is:

- Fatal cancer case: \$5.6 million mean/case
- Non fatal case: \$121,000 mean/case (determine by cost of illness calculation) -or- \$587,000 mean/case (determined by willingness to pay calculation).

EPA is faced with a wide range of possible benefits with no clear indication of a central tendency. There is a wide range of potential cost, technology changes, and risk trade-off implications depending on the level of control set for DBPs.

The Regulatory Impact Assessment performed within EPA considered a number of approaches:

- Overlap technique - comparing the range of benefits to the range of costs.
- Break even analysis - determine what level of risk would have to be present to break even (for benefits to balance costs).
- Central tendency approach - bases assumptions on probability distributions for uncertainties, computes expected costs and benefits (costs, exposure reductions, risks)
- Minimize maximum regret - minimizes downside risks in total social cost calculation.

Based on the findings of these assessments EPA has concluded:

- Monetized benefits are likely to exceed costs. The potential downside for taking no action is too great.
- Taking practical steps to reduce exposure is better than taking no action.
- Expected benefits exceed expected costs.
- Some benefits were not included (e.g., taste and odor improvement) and so these analysis have understated the benefit. And,

- A staged solution was considered the best option.

In a discussion of the Stage 1 DBPR Minimizing Maximum Loss Analysis chart presented [Attachment X.b.], FACA members discussed the following points:

- EPA has tried to look at different types of analyses of rule benefits and costs. This analysis will allow users to pick a risk scenario, and then follow the chart vertically to see the relative difference between the cost of the selected decision and the cost of the decision that would have been optimal under the risk scenario.
- The chart presented was developed during Stage 1 using 1997/8 data. EPA has developed additional cost information since this one that will be shared with FACA members.
- EPA has not performed a separate analysis for small systems. For small systems EPA assumes higher DBP levels, so there are higher costs and also greater risk reduction.

XI. Ongoing DBP Cancer Epidemiology Studies

Fred Hauchman, EPA, presented a review of ongoing efforts to reanalyze cancer risk based on existing epidemiology studies using improved methods. Hauchman also requested suggestions for additional near-term epidemiology and toxicology research that would potentially contribute to Stage 2 decision making. [See Attachment XI.a.]

EPA/NCEA-Cincinnati is currently evaluating ways to improve the exposure component of cancer epidemiology studies (will be completed in FY 2000), and will be using these improved methods to reevaluate the estimates of cancer risk from studies that have already been conducted (to be completed in FY 2000 or 2001.)

A related project to improve the exposure assessment based on existing cancer epidemiology studies is being supported by the Microbial/Disinfection By-Product (M/DBP) Research Council, which is a partnership between the U.S. EPA and the American Water Works Association Research Foundation (AWWARF) that includes representatives from EPA, AWWARF and key stakeholder groups. This study will be completed in 2001.

Hauchman reminded the FACA that at the February Stakeholder Workshop on health effects he had solicited suggestions for additional near-term epidemiology and toxicology research. Hauchman requested that any ideas be forwarded to him. He has received responses from a small number of individual researchers/stakeholders.

- EPA has conducted internal deliberations and discussions with Chlorine Chemistry Council concerning toxicology studies.
- Types of recommendations he has heard to date include:
 - Epidemiology: accelerated analysis of exposure data
 - Toxicology: animal/human metabolism study, bladder cancer mechanisms, pre-cancerous lesions

XII. Other Perspectives on DBP Cancer Health Risk

Panelists Robert Morris, Tufts University and John Reif, Colorado State University, were asked to comment on the following questions:

- What is the magnitude of cancer risk from the epidemiology data?
- To what extent do the epidemiology studies in the PAR analysis reflect the range of potential risk?
- How does the exposure time frame of the epidemiology studies impact the perception of risk?
- How far does the Stage 1 DBPR go towards addressing this risk?

Each panelist provided a presentation and participated in a discussion of these questions. [See Attachment XII.a for Morris's presentation materials, and Attachment XII.b for Reif's presentation materials.]

Robert Morris

Dr. Morris presented the following overview of epidemiological perspectives on DBP cancer health risks:

There are four possible explanations for an observed association in epidemiological data:

- Chance- appears to be increasingly unlikely though it can never be completely excluded.
- Bias- errors in measuring the exposure, outcome or both that can increase or decrease observed effect relative to the actual effect.
- Confounding factors- other sources of risk that interfere with measurement of factor you are trying to measure.
- *if these are ruled then:*
- Causality

The PAR analysis is fundamentally a form of meta-analysis similar to those used in 1992 meta-analysis. The numerical results are reasonable, epidemiology data dose suggest a range similar to that of PAR analysis (1,000 to 10,000 cases/year). Potential problems with the PAR analysis include:

- Populations of individual studies may not be representative of national population.
- Exposures of individual studies might not be representative of current national exposures.
- Selection of a limited number of studies discards potentially useful information.
- Assumption that point estimates represent an upper limit of risk.
- Implicit assumption of zero risk for other types of cancer.

The toxicological data base may underestimate risk because it:

- Evaluates a limited number of DBPs.
- Does not assess the effects of mixtures of DBPs.
- Does not assess the interaction with non-drinking water related exposures.
- Biological model does not adequately represent effects in humans.
- Extrapolation to low doses may not be appropriate.

The epidemiological data base may overestimate risk because:

- Confounding factors (e.g., urban exposures, carcinogens in water supplies that require a high chlorine dose, preexisting carcinogens, or unknown sources).
- Bias (e.g., recall of water consumption may be different in people with bladder cancer).

Because of the long latency period of bladder cancer, epidemiological studies are based on historical exposures. DBPs levels have declined over time so epidemiology studies may not reflect current level of

risk. Only three epidemiology studies have quantified exposure. More data is needed on the historical levels of DBPs in drinking water.

On the other hand, the epidemiology database may underestimate risk because of:

- bias (random misclassification), and
- confounding factors (e.g., higher level of cancer risk than expected in "unexposed" group such as arsenic in ground water, or higher levels of a protective factor in areas served by water with high DBPs).

Epidemiology data supports the assumption that risk reduction is proportional to reduction in DBP exposure.

The FACA should discuss data gaps to identify priorities. These may include:

- Effect of DPB mixtures,
- Effect of Baseline Bromide levels, and
- Effect of alternative disinfectants (requires toxicology, not epidemiology data because of long latency periods).

Morris then discussed how to make the best use of available data:

- Evaluate differences in characteristics of DBP's among different studies (HAA/THM and Bromide levels)
- Improve exposure assessment (may help us generate dose response information)
- Evaluate interactions (e.g., increased risk among smokers or persons with high fat consumption)

John Reif

Dr. Reif presented an overview of epidemiological perspectives on risks on human bladder cancer associated with DBPs:

Human epidemiology is typically done in occupational (high exposure) and community (lower exposure) settings. Bladder cancer has a long latency period. At low dose exposure to a carcinogen, this period is likely to be longer than in occupational settings. The long latency period is likely to result in some misclassification across concentrations of DBPs due to temporal variability, and perhaps in exposure itself. In reviewing the epidemiology data, Reif focused on the same 5 studies used in the PAR analysis⁽⁴⁾.

⁴ See List of Attachments for a complete listing of these studies.

Bladder cancer is the most frequently studied cancer site for DPBs. Findings (regarding duration) in these studies is relatively consistent. All studies have adequate sample size and control for smoking. These studies show biological plausibility of a correlation between DBP exposure and bladder cancer. Only two of the studies present data which evaluate THM concentration.

Epidemiology data on bladder cancer and DBPs show:

- Most consistent finding is increased risk with long-term exposure to DBPs.
- All 6 studies show increase in risk associated with long duration of exposure to chlorinated water overall or in major subgroups.
- There is some inconsistency in risk by subgroup (gender, smoking). There is no obvious explanation for these inconsistencies.

- There is some evidence for a duration-response relationship in the data.

Reif concluded his presentation with the following points on data gaps and uncertainties:

- Use of TTHM in epidemiology studies represents a surrogate for multiple exposures from a complex chemical mixture.
- There is only a small amount of epidemiological data available to estimate risk for concentrations of TTHM.
- Identification of specific chemical carcinogens from Toxicology, mechanism of action, or human studies (biomarkers) is needed.
- Development of chemical-specific risk estimates in epidemiology studies, e.g., for BDCM is needed.
- One approach that Reif would like to see would be chemical specific risk estimates.

Additional points made by Reif:

- It is difficult to understand where concentrations are harmful, and where not harmful. This is a question of power - can you find an effect if one is really there? This is dependant on sample size. Bladder cancer seems to occur more often in men (3 to 1 of all cases are in men). Not all of the 5 studies are comparable because of the different approaches for dividing data.
- All of these studies show some association between DBP and bladder cancer. There is association - not causality - but enough to go forward with Stage 1. The Canada and Iowa studies are new since Stage 1 and contain a lot of good information.
- Differences in effect size due to the variability among studies with respect to the nature of the exposure and the population being studied. These should not mean ignoring the variability, we do not understand all variability, but it should not lead us to dismiss the data.
- Misclassification of the sample by shifting as little as 10% of the exposed group to unexposed group can have an enormous effect on the observed results.
- Regarding the fluid intake study question (New England Journal study) DBPs are at the low end in terms of the numbers of bladder cancer. Other studies have looked at the risk of bladder cancer from water consumption: five have found positive association, four no association and one, recent study that shows increasing negative association. These studies did not measure DBP exposure.
- Because of differentiation between colon and rectal cancer, Reif would go to bladder cancer to decide what the risk is and what level.

The following points were discussed by FACA members following the presentations by Morris and Reif:

- In response to a question on the level of confidence epidemiologist put in data in the 1 to 2 odds ratio range, Reif explained that odds ratios are the way that we measure relative risk, we do not measure incidence directly, we do not follow people - instead we use odds ratio to estimate occurrence rate. The odds ratio is a good surrogate for relative risk. If relative risk is 2 it means that inferences that incidence is 2 times as high in people with exposure compared with people without exposure. For example, with secondhand smoke the first analysis of first 13 studies put risk estimate at 1.3, however, it is now considered a human carcinogen. We must also identify what confounders are driving that risk up. In better studies most of the recognized risk factor for bladder cancer have been taken account (diet, coffee, fluid intake, etc). For the most part, these studies have collected information about recognized confounders. If there are things out there that have not been identified (and it meets both criteria - risk factor for cancer of interest, and exposure for exposure of interest) it could take an odds ratio of 1.5 and move it to 1. Caveat is we cannot control for unrecognized confounders - the higher the risk estimate, the higher the confidence in the number.
- If you assume that there is an association between bladder cancer and chlorinated drinking water, the 1.2 means that you increased your risk of getting bladder cancer by 20%, then the

question of what that means comes back to a risk management question. 2.0 would be a doubling of risk. The stronger the association the less likely it is that some unidentified factor (that is something other than causality) could be responsible. For many of the issues we deal with in environmental epidemiology the associations are not very strong.

- The idea that you can not distinguish risk below 2.0 is no longer valid, thinking on this has changed within the field. It is very common to see relative risks of 1.2 to 1.6 that are considered important. One clue in cancer studies is that very high exposure groups see risks higher than 2.0. This makes bias a less important factor in what you are seeing. In making a case for causality it makes other explanations less likely.
- The meaning of the percentage increase in risk depends on the numbers you are talking about, doubling of risk is different depending on if you go from 1 case to 2 or 1,000 to 2,000. This is a risk management question.
- Out 15 studies, 13 had confidence interval below 1 (meaning no meaningful association). How you interpret the data base is partly a statistical power and partly judgement question. The precision of the point estimate is not that great, but epidemiologists have gotten away from thinking about only studies without 1 in interval. It is more useful to look at an entire body of information. This does not rule out a negative study. A complication is whether it is a 1 or 2 tail test. If you are thinking about DBPs, and you think they can only exert negative effect it is 1 tail. If you think it is could possibly exert a positive effect (decrease risk) then a 2 tail test is appropriate. (One suggestion from the audience was to get a biostatistician who is used to looking at epidemiology data.)
- An important question is whether you have the replication/power/numbers to be sure of point estimate.
- In response to a question from a FACA member on the usefulness of the PAR, Reif explained that the PAR is a math process for after you have done the epidemiology and produced an odds ratio. It is useful to give bounds on how many cases we are talking about nationally, to give relative impact. EPA took on PAR because they can estimate how many cases of cancer can be attributed to the risk factor.
- No repooling of the data from new studies has been done. To do so properly would require that researchers sit down with investigators of those studies, get data, improve exposure assessment. It is possible that we could get additional data out of those studies, little new information could be generated in the time we have. There may be ways to look at existing studies in new way to get new/useful/helpful information.
- A cohort study is generally considered the ideal study design in epidemiology. In a cohort study, we measure exposure in a group of people and follow them over time to see if they get a particular disease. However, this would require following thousands of people for 30 or 40 years. Instead, you do a case-control study where you find people who have cancer and go back and estimate dose. The rarer the disease the more case-control required.
- *How could FACA determine the adequacy of Stage 1, and how should we estimate, and prove, a reduction of risk from Stage 1?*

Morris: We could revisit epidemiology studies to look at different exposures to understand dose response relationship - we are currently assuming linear relationship. This is a first case assumption that appears to be reasonable, but it would be better to have additional research.

Reif: If you know what the dose response curve looks like then you can estimate changing risk based on changing exposure. The better we know the curve the better we can estimate the results of any corrective action in Stage 2.

- In response to a question on the linearity of the dose/response curve for DBPs, Morris responded that the studies in the PAR analysis show an increase in risk from increasing exposure. Morris has not evaluated to see if it is perfectly linear, but it is a reasonable first approximation.
- One approach for isolating confounding effects of different chemicals in drinking water is to identify what other water chemicals would cause bladder cancer. Solvents maybe would cause cancer. Reif would expect to see solvent caused bladder cancer levels in New Jersey, but not

in Arizona (with less industry). However, existing studies include a broad geographical area and do not show this to be a factor.

- We should try and get a measure of what improvements have been made in water treatment plants in the past 45 years. It gets to dose response curves, we are in a far better place now, and better place after Stage 1 is enacted. Most of the exposures in the published epidemiological studies that reported specific DBP levels were below the current standards.

XIII. Closing Remarks, Next Steps and Public Comment

Following the FACA's discussion of epidemiology, FACA members discussed more broadly their thoughts on possible Stage 2 regulation.

- If it turns out that the FACA determines that DBPs are a real risk that needs to be reduced, a correlated issue will be the impact on industry; this may be a breaking point for shifts in technology.
- The FACA will need to give people the tools and necessary information to sell what is recommended.
- It would be nice to look at all the pieces of the puzzle by having a rule structure that the FACA can work from as a straw framework.
- A few FACA members expressed concern about applying the PAR analysis built on lots of assumption and are uncomfortable with the ICR large system focus (94% of all systems in US are under 10,000).
- A remaining question is the cancer health effects from alternate technology, such as chlorine dioxide and ozone.
- A number of FACA members indicated a desire to discuss the health risks reproductive, developmental, and microbial risks before making any conclusions.

Additional Health Effect Expertise

A sub-group of FACA members met during lunch on May 21 to discuss approaches for getting additional health effects expertise support for the FACA and decided that it was premature to organize a working group at this time, but that it may be appropriate to convene a group of experts in the future.

Public Comment

At the end of May 20 and May 21 time was set aside for public comment. No parties requested to address the FACA.

Adjourn

ATTACHMENTS

- I.a Meeting Participant List
- I.b Meeting Agenda
- I.c MDBP Stage 2 FACA -Adopted Groundrules
- II.a Technical Workgroup Presentation to FACA2 Committee -Michael McGuire, MEC
- II.b TWG Subgroups List
- III.a SDWA Overview, May 20, 1999 -Ephraim King, EPA
- IV.a Cancer Risk Assessment at the US EPA, May 20, 1999 -Jim Coglian, EPA

- V.a EPA Perspective on Toxicology Data & DBP Cancer Health Risk - Stage 1 DBPR RIA Cost/Benefit Analysis, May 20, 1999 -Stig Regli, EPA
- VI.a Disinfectant By-product Research -Gary Boorman, NIEHS/NTP
- VII.a DBP Research Prioritization, May 20, 1999 -Jennifer McLain, EPA
- VIII.a Expert Panelist Presentation: Toxicology - Melvin Andersen, Colorado State Univ.
- VIII.b Expert Panelist Presentation Toxicology - Ronald Melnick, NIEHS
- IX.a Quantification of Bladder Cancer Risk from Exposure to Chlorinated Surface Water, Population Attributable Risk (PAR) Analysis -Mary Manibusan, EPA
- X.a EPA Perspective on Epidemiology Data & DBP Cancer Health Risk - Stage 1 RIA Cost/Benefit Analysis -Stig Regli, EPA
- X.b Stage 1 DBPR Minimizing Maximum Loss Analysis chart -Stig Regli, EPA
- XI.a Ongoing Cancer Epidemiology Studies -Fred Hauchman, EPA
- XII.a Expert Panelist Presentation: Epidemiology -Robert Morris, Tufts University
- XII.b Expert Panelist Presentation: Epidemiologic Perspectives on Risks of Human Bladder Cancer Associated with Chlorination By-Products -John Reif, Colorado State University
- XIII.a DBP Cancer Toxicology: Risk Assessment and Risk Management Issues -Fred Hauchman, EPA

Additional Bladder Cancer Studies

Bladder Cancer, Drinking Water Source, and Tap Water Consumption: A Case-Control Study. Kenneth P. Cantor, *et. al.* JNCI, Vol. 79, No. 6, December 1987.

Bladder cancer and drinking water: a population-based case-control study in Washington County, Maryland (United States). D. Michael Freedman, *et. al.* *Cancer Causes and Control*, 1997, 8, pp. 738-744.

Case-control study of bladder cancer and chlorination by-products in treated water (Ontario, Canada). Will D. King and Loraine D. Marrett. *Cancer Causes and Control*. 1996, 7, pp. 596-604.

Case-Control Study of Bladder Cancer and Water Disinfection Methods in Colorado. Michael A. McGeehin, *et. al.* *American Journal of Epidemiology*, Vol. 138, No. 7. 1993.

Drinking Water Source and Chlorination Byproducts I. Risk of Bladder Cancer. Kenneth P. Cantor, Charles F. Lynch, Mariana E. Hildesheim, Mustafa Dosemeci, *et. al.* *Epidemiology*. January 1998, Volume 9 Number 1.