2004

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Linda K. Teuschler
*U.S. EPA*, teuschler.linda@epa.gov

Richard C. Hertzberg
*U.S. EPA*

Glenn E. Rice
*National Health and Environmental Effects Research Laboratory*

Jane Ellen Simmons
*National Health and Environmental Effects Research Laboratory*

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SCIENCE DIRECT®
Environmental Toxicology and Pharmacology 18 (2004) 193–199
ENVIRONMENTAL TOXICOLOGY AND PHARMACOLOGY ETAP
www.elsevier.com/locate/etap

# EPA project-level research strategies for chemical mixtures: targeted research for meaningful results

Linda K. Teuschler[a,*], Richard C. Hertzberg[a,b], Glenn E. Rice[c], Jane Ellen Simmons[c]

[a] *U.S. Environmental Protection Agency, Office of Research and Development (ORD), National Center for Environmental Assessment, 26 W. Martin Luther King Drive, Cincinnati, OH 45268, USA*
[b] *Homeland Security Research Center, U.S. EPA-Waste Management, 61 Forsyth St., Atlanta, GA 30303, USA*
[c] *National Health and Environmental Effects Research Laboratory, 109 T.W. Alexander Dr., MD-B143-05, Research Triangle Park, NC 27711, USA*

Received 3 March 2003; accepted 17 December 2003

**Abstract**

Project-level research strategies at the U.S. Environmental Protection Agency regarding chemical mixtures are impacted by administrative priorities, public interests, expert opinions, scientific advances, regulatory needs, and legislative actions, influencing the setting of priorities and goals. Perhaps, the most significant influence on conducting chemical mixtures research is the passage of laws requiring the EPA to investigate the potential toxicity of various mixtures, specifically the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, the Food Quality Protection Act of 1996, and the Safe Drinking Water Act Amendments of 1996. Scarce resources are allocated to broadly defined issues for consideration by teams of scientists, who design and implement specific projects. Because resources are limited, projects may have several goals, e.g., filling specific data gaps to support a regulation and, simultaneously, producing data to evaluate a risk assessment method. Research areas of emphasis are shaped by risk assessment needs, data gap uncertainties, and experimental design considerations. This paper discusses factors shaping EPA research strategies for chemical mixtures and presents an example of efficient research planning to investigate potential toxicity from exposure to drinking water disinfection by-products.
Published by Elsevier B.V.

*Keywords:* Chemical mixtures; Risk assessment; Research strategies; Disinfection by-products

## 1. Introduction

Project-level research strategies at the U.S. Environmental Protection Agency (EPA) regarding chemical mixtures are impacted by many factors. Administrative priorities, public interests, expert opinions, scientific advances, regulatory needs, and legislative actions all influence research prioritization and goal definition (Fig. 1). Financial and personnel resources are then allocated into broadly defined research areas (e.g., children's risk, endocrine disrupting chemicals, particulate matter) for consideration by multidisciplinary scientific teams, who design and implement specific projects to address targeted deficiencies in the science. Research areas of emphasis are driven by legislative and regulatory requirements, and shaped by risk assessment needs, data gap uncertainties, and experimental design considerations.

### *1.1. Impacts on research strategies for chemical mixtures*

Perhaps, the most significant influence on conducting chemical mixtures research is the passage of laws requiring the EPA to investigate the potential toxicity of various mixtures. Historically, the first law of major importance was the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), passed in 1980, which

* Corresponding author. Tel.: +1 513 569 7573; fax: +1 513 569 7916.
*E-mail address:* teuschler.linda@epa.gov (L.K. Teuschler).

1382-6689/$ – see front matter. Published by Elsevier B.V.
doi:10.1016/j.etap.2003.12.005

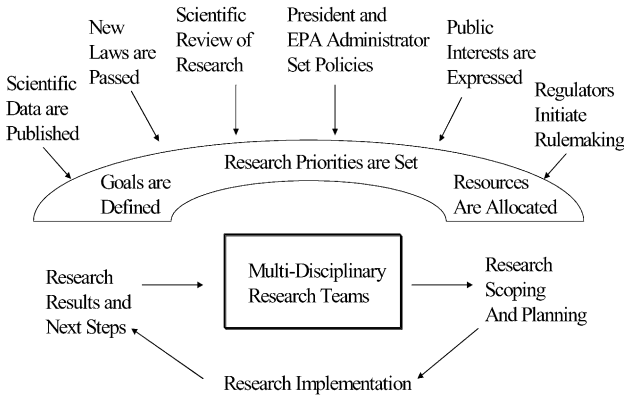


Fig. 1. Influences on research planning processes.

broadly defined environmental pollutants to include mixtures. Contaminants were to 'include, but not be limited to, any element, substance, compound, or mixture . . . which after release into the environment . . . may reasonably be anticipated to cause death, disease, behavioral abnormalities, cancer . . . in such organisms or their offspring' (U.S. EPA, 1980). The inclusion of contaminant mixtures within CERCLA had a significant impact on EPA risk assessment activities. Subsequent to CERCLA, EPA published the Guidelines for Health Risk Assessment of Chemical Mixtures (U.S. EPA, 1986), and the Risk Assessment Guidelines for Superfund (U.S. EPA, 1989); the purpose of these documents was to describe EPA's risk assessment procedures. These Guidelines defined and operationalized risk assessment methods, such as the hazard index (based on dose addition) and response addition method for assessing the impact of chemical mixtures on potential health risk.

More recently, the Food Quality Protection Act (FQPA) and Safe Drinking Water Act Amendments (SDWAA) of 1996 (U.S. EPA, 1996a, 1996b) increased awareness of chemical mixtures related health issues, prompting the authors of major EPA planning documents to include chemical mixtures research goals. FQPA is the most specific law on chemical mixtures, requiring the agency to consider potential human health risks from all pathways of dietary and non-dietary exposures to more than one pesticide or other substance within the mixture acting through a common mechanism of toxicity. EPA's Office of Pesticide Programs has responded to FQPA, producing guidance on determining criteria for deciding when a common mechanism of toxicity exists (U.S. EPA, 2002a) and conducting a risk assessment of 24 organophosphorus pesticides using a Relative Potency Factor approach to estimate mixtures risk across exposure pathways (U.S. EPA, 2001a). The SDWAA are less specific, directing the agency in a broad sense to 'develop new approaches to the study of complex mixtures, such as mixtures found in drinking water . . .' EPA has also responded to the SDWAA, producing documents on the risk assessment of drinking water disinfection by-products (DBP) mixtures (U.S. EPA, 1999, 2000a, 2002b) and developing a targeted research strategy, integrating toxicological and chemical evaluation of complex DBP mixtures produced by various water disinfection scenarios (Simmons et al., 2002).

Public input influences chemical mixtures research planning from a number of different directions including stakeholder meetings, industry initiatives, and public interest group inquiries. Expert panels are routinely convened to provide scientific reviews of the research planning process (e.g., National Research Council, EPA's Science Advisory Board, Federal State and Territorial Research Advisory Committees). In some instances, groups of scientists from outside the agency are asked to work as partners with EPA and draft recommendations for new research. One such effort pertaining to the toxicological evaluation of chemical mixtures has been sponsored by the Society of Toxicology (Teuschler et al., 2002). Another example is the National Drinking Water Advisory Council's (NDWAC) Working Group on Drinking Water Research, a collection of EPA, water industry and private sector scientists, and public interest group representatives, who have come together to advise EPA on its drinking water research plans as required by SDWAA (e.g., NDWAC, 2001).

Chemical mixtures research is incorporated into EPA planning documents to ensure the program is scientifically sound, coordinated across Office of Research and Development (ORD) research laboratories and centers, and responsive to the needs of EPA program and regional offices. Planning efforts are integrated and include many participants, agency wide, within ORD, and in the EPA's Program Offices and Regions. The development of multiple-year research plans are coordinated by the Office of Science Policy; these plans are authored, reviewed, and implemented by EPA's laboratories and centers. These plans set strategic goals in broad topic areas. Topic areas likely to include chemical mixture issues include contaminated sites, toxic air pollutants (e.g., metals, particulates, vapors), drinking water, water quality, and safe food. The plans identify goals for those areas and specify research and products to be generated. Progress is tracked and reported as required by the Government Performance Reporting Act. The Program Offices also develop research plans, where mixtures research may be identified. For example, EPA's Office of Water co-authored a document with ORD entitled, 'Research Plan for Microbial Pathogens and Disinfection By-Products (DBP) in Drinking Water' (U.S. EPA, 1997), which calls for the characterization of DBP mixtures risk. Chemical mixture research ideas can also be found within ORD planning documents, which are periodically updated. For example, two chemical mixtures research areas specified in the 2001 ORD Strategic Plan (U.S. EPA, 2001b) are to:

- identify the interactive effects from exposures to chemical mixtures with common or different modes of action; and

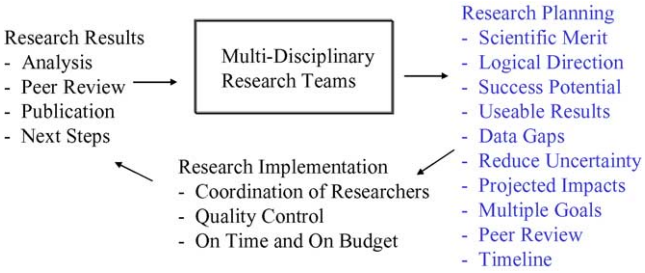


Fig. 2. Research team project planning for chemical mixtures.

- develop improved models and methodologies to better estimate human exposures, assess aggregate exposures to single stressors, and assess cumulative risks from exposures to multiple stressors.[1]

Thus, at the project-level, multi-disciplinary research teams plan and implement research beneath an umbrella of influential factors and priority setting activities (Fig. 2). Within this framework, teams consider the scientific merit and logic of projects. Because resources are limited, research may be structured to answer multiple questions and target several goals, such as filling specific data gaps for use in setting regulations and, at the same time, producing data suitable for evaluation of a particular chemical mixture risk assessment method. EPA scientific teams often operate under strict timelines, because of mandated deadlines for making regulatory determinations; thus, project planning includes a feasibility assessment regarding the potential for completion and success and the usability of results.

[1] The term 'stressors' in this case includes not only chemical mixtures but also non-chemical factors (e.g., excessive noise, microbial exposures, poor nutrition).


Fig. 4. Examples of research areas as defined by the risk assessment/risk management paradigm.

### *1.2. Research planning using the risk assessment paradigm*

Since the mid 1990s, ORD has been structured around the risk assessment/risk management paradigm (Fig. 3) into laboratories and centers, whose research focus is on health effects [National Health and Environmental Effects Laboratory (NHEERL)], exposure [National Exposure Research Laboratory (NERL)], risk assessment [National Center for Environmental Assessment (NCEA)], and risk management [National Risk Management Research Laboratory (NRMRL)]. ORD plans and implements research across the units of ORD and within the Grants program [National Center for Environmental Research (NCER)], targeting results for use in making risk assessment and risk management decisions. Within ORD, the Office of Science Policy (OSP) serves as the link between ORD's research laboratories and centers, and EPA's regulatory and program offices. Fig. 4 presents a sampling of research areas as they relate to the risk assessment/risk management paradigm.

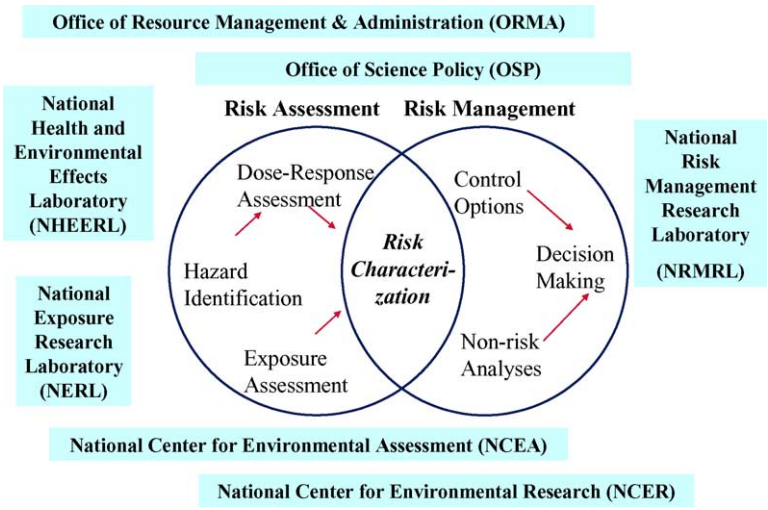


Fig. 3. Office of research and development structure.

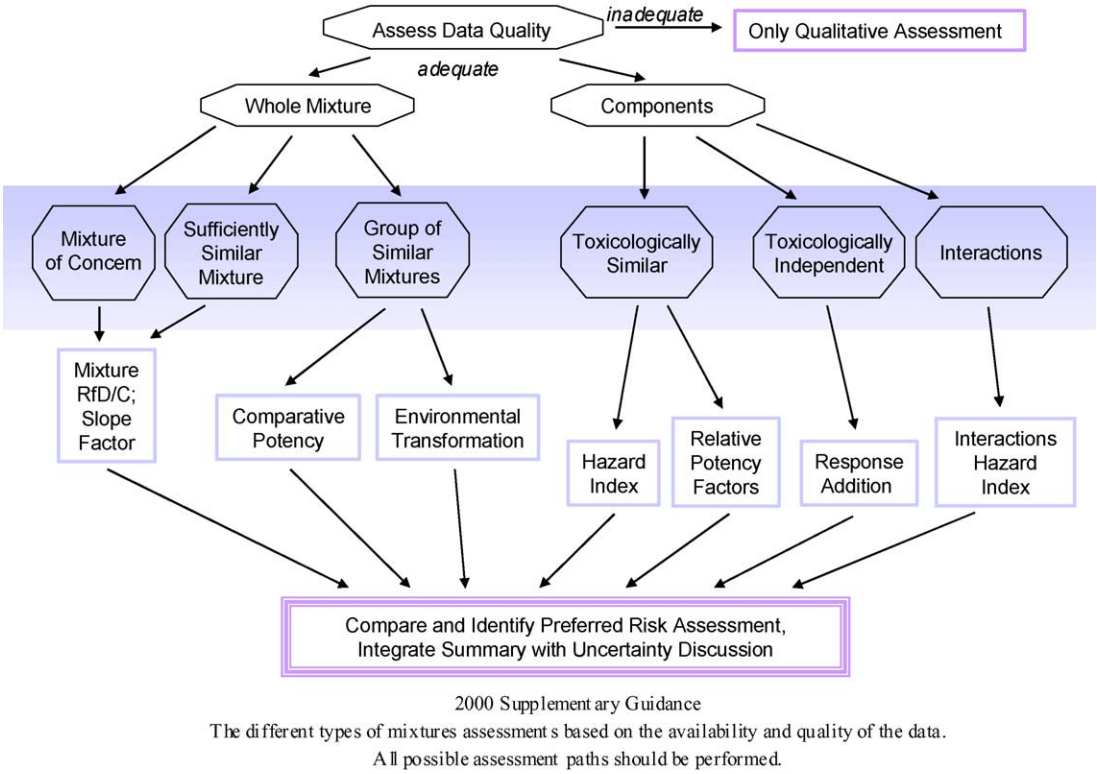


Fig. 5. Flow chart from supplementary guidance for conducting health risk assessment of chemical mixture (U.S. EPA, 2000b).

The emphasis on conducting research in support of risk assessment helps target chemical mixtures research efforts towards useful results. To that end, chemical mixtures risk assessment guidance can be used to shape the nature of research that is conducted. (Conversely, research results also inform the development of new guidance.) For example, methods based on the concept of dose addition require the chemical components of a mixture to share a common toxic mode of action. Thus, toxicologic research can be conducted to determine the toxic mode of action for chemicals that commonly occur together in the environment (e.g., pesticides applied concurrently, drinking water disinfection by-products, metals found in soils), providing the risk assessor with critical information regarding the applicability of dose addition to a specific environmental mixture.

Fig. 5 shows a flow chart from the 2000 mixtures guidance document (U.S. EPA, 2000b) that steers the user through an evaluation of mixtures data to the choice of risk assessment method to employ. During the evaluation of mixtures data, decisions must be made regarding characteristics of toxicological action or chemical composition of a whole mixture or of a mixture's components. For example, the third (highlighted) row of Fig. 5 shows that, under data on 'Components', different component-based risk assessment methods are appropriate depending on whether the component chemicals within a mixture are similar or dissimilar in toxicological mode of action. Also, a new method, the Interaction-Based Hazard Index, can be used to adjust the hazard index based on dose addition by using interactions data on binary combinations of the chemicals within a mixture (see also Hertzberg and Teuschler, 2002).[2] Because these decisions are dependent on good toxicological and pharmacokinetic data on chemicals and chemical pairs, research to fill data gaps and inform decisions on toxicological action can be planned to improve risk assessment capabilities.

## 2. Targeted DBP mixtures research

To illustrate the process of project-level research planning within the EPA as outlined in this paper, research pertaining to complex mixtures of drinking water DBPs is discussed. As an example, the multi-purpose design approach described below was developed explicitly in response to the requirement in the SDWAA to develop new approaches to mixtures found in drinking water. Selection of DBP mixtures was responsive to public interest. The project incorporates design elements (environmentally relevant mixing ratios and low-dose regions of the dose–response curve) subsequently adopted by an expert panel (Teuschler et al., 2002) and was designed so that the

[2] The Interaction-Based Hazard Index was developed to take advantage of data on binary combinations of chemicals, because, the vast majority of available toxicologic interactions data come from experiments using two chemicals. Thus, in applying the method, there is a tacit assumption that interactions data on chemical pairs adequately explains interaction effects for the whole mixture, including higher order interactions among chemicals. U.S. EPA (2000a) encourages risk assessors to apply this new procedure to test data sets so results can be used to further develop and refine the method.

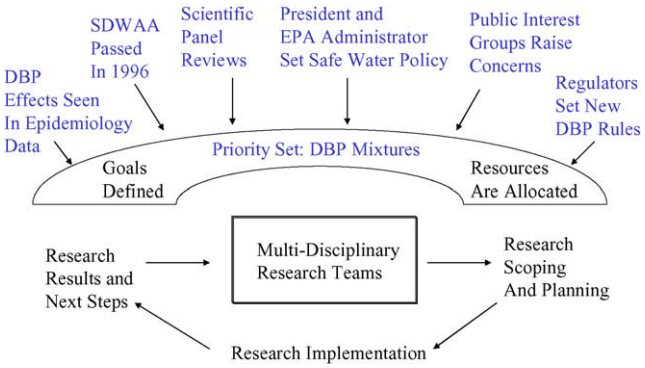


Fig. 6. Example of disinfection by-product (DBP) research planning.

data not only filled data gaps but could also be used for development, refinement, and evaluation of several statistical and risk assessment methods. DBP mixtures health risk became an issue in the 1990s because some positive epidemiological studies were published suggesting associations between chlorinated water and adverse outcomes (e.g., bladder cancer in Cantor et al., 1998; spontaneous abortion in Waller et al., 1998); a great deal of experimental animal data (mostly single chemical, but also mixtures data) also showed effects, generally at high doses (for summaries of both the epidemiologic and toxicologic data, see ILSI, 2001 and U.S. EPA, 2000a). DBP exposures are highly variable, depending primarily on source water composition and type of disinfectant used. About 50% of the amount of DBPs in drinking water consists of material that is unidentified in terms of chemical composition (Weinberg, 1999). The concern was that the majority of the U.S. population is exposed daily to multiple DBPs at low environmental concentrations via multiple routes of exposure; oral, dermal and inhalation.

Fig. 6 shows the influences on research planning for DBP mixtures. The main drivers for this research are the positive epidemiological data and the 1996 SDWWA that impact the need to periodically review and set new DBP rules. One major class of DBPs, regulated as a mixture, is the trihalomethanes (THMs) (chloroform, bromodichloromethane, bromoform, dibromochloromethane). These are known to cause adverse effects in single chemical experiments at high doses, but questions remain regarding their toxicity as mixtures and their potential for interaction effects. Thus, targeted research has been planned and implemented to gather data on THM mixtures. In the evaluation of all DBPs, critical risk assessment issues drive research planning. Some of the most important questions include:

- Is there a risk to human health from exposure to the mixture?
  - Do human health effects occur at environmentally relevant dose levels?
  - How much do classes of DBPs or the unidentified DBPs contribute to risk?
  - Are multiple-route exposures important to risk estimation?
- How do we use animal data?
  - Can we extrapolate to estimate human health risks?
  - Can we identify biological mechanisms of toxicity?
- Can we support use of specific risk assessment methods?
  - Is there evidence regarding toxicological mode of action to support additivity assumptions?
  - Are there interaction effects of concern?
- What is the health risk across drinking water treatment options?
  - Are chlorination DBPs more or less toxic than DBPs produced using ozonation, chloramination, or other forms of disinfection?

Research projects can be structured to answer these questions for various combinations of DBPs. For the four THMs, the EPA developed a targeted research project called the Multiple-Purpose Design Approach (Teuschler et al., 2000; U.S. EPA, 1999), to investigate the toxicity of simple, defined mixtures. Toxicity testing was performed on the single chemicals, the six binary combinations, and eight specific 4-THM mixtures in CD-1 mice (oral gavage 14-day studies on liver/kidney effects). Similar studies were conducted in medaka fish (embryo developmental effects, neurological and circulatory defects, heart beat rate decreases, mortality; cancer studies).

The experiments in the CD-1 mice were specifically designed to satisfy multiple needs in risk assessment, selecting dose levels and mixing ratios strategically.[3] A team of investigators with mixtures expertise in toxicology, statistics, experimental design and analysis, and quantitative risk assessment methods designed the study using data from single chemical hepatotoxicity studies to project likely outcomes for the binary and 4-THM mixtures. Environmentally relevant mixing ratios for the mixtures represented ozone and chlorination treatment systems based on concentrations presented in Krasner et al. (1989). Experimental doses ranged between 0.1 and 3.0 mmol/kg/day, translating into doses in units of body weight of between 12 and 760 mg/kg/day, depending on the composition of the mixture. While these dose levels are still well above doses to which humans may be exposed in the environment, they are relatively small compared with typical ranges in animal studies. Thus, an effort was made to target the lower end of the dose–response curve for hepatotoxicity.

The results of the studies will be used to investigate issues, such as comparing toxicity of chlorination versus ozonation based on their mixing ratios. These experiments were also designed to develop and refine several statistical and risk assessment methods. Goals included the development of efficient experimental designs for mixtures and research on three quantitative methods, testing for departures from additivity

[3] Space limitations preclude fully describing this set of studies in this overview paper. See Teuschler et al. (2000) and U.S. EPA, (1999) for complete details on the study design and reports of some study results. Analysis of data from this project is continuing and will be available in the open literature and through EPA as publications are completed.

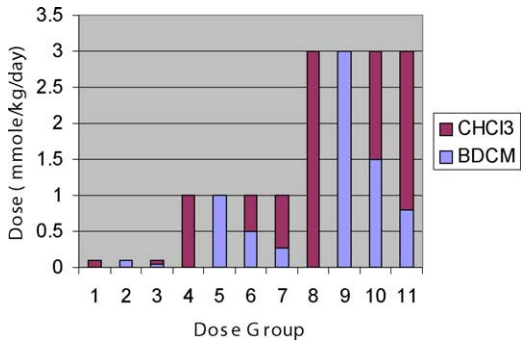


Fig. 7. Example binary experimental design for CD-1 mice chloroform–bromodichloromethane ($CHCL_3$–BDCM).

(Gennings et al., 1997), the Interaction-Based Hazard Index (Hertzberg and Teuschler, 2002), and proportional response addition (U.S. EPA, 1999). The latter two methods combine dose–response information with THM exposure data to express THM mixtures risk. Fig. 7 illustrates the experimental design used for testing the binary combinations in the CD-1 mice experiment. This study is designed for use in multiple analyses as follows:

- Doses are placed below an expected no-observed-adverse-effect level (NOAEL) at 0.1 mmol/kg/day, just above the expected NOAEL at 1.0 mmol/kg/day, and high on the dose–response curve at 3.0 mmol/kg/day for use in a threshold additivity dose–response surface model. The two lower doses bracket the dose from which the estimate of a threshold parameter can be made. The high dose allows the slope parameter to be estimated. The model can then be used to test binary mixtures for departures from additivity.
- Mixing ratios used represent chlorination and ozonation treatment processes, so results can be used to compare variation between these environmentally relevant mixtures.
- Total mixture doses for the binary experiments are held constant at 1.0 and 3.0 mmol/kg/day as proportions of the two chemicals are varied. This facilitates testing of a new mixtures risk assessment method, the proportional response addition approach.
- The highest total dose (3.0 mmol/kg/day) was placed higher on the dose–response curve to increase the likelihood that interactions would occur (i.e., effects greater or less than those observed under additivity) for development of parameters in the Interaction-Based HI method. Dose placement took into consideration that synergy can be difficult to detect when the ‘additive’ response of the chemicals is near the maximum system response and that antagonism can be difficult to detect when the ‘additive’ response of the chemicals is near the background response of the system.

Because of this design, several anticipated uses of these data exist. This efficient experimental design will be available for use in other mixture studies. The nature of THM joint toxicity and interactions can be estimated by combining toxicological judgment of experimental data with statistical evaluations. The toxicity of mixtures using environmentally relevant mixing ratios in the low dose region can be evaluated. Risk assessment methods can be developed and refined using various additivity assumptions as the basis for expressing DBP mixtures risk. Although Fig. 7 shows the design for the CD-1 mouse, a similar set of experiments was conducted using medaka fish. The goals for the medaka fish studies are to establish this assay as a mixture screening assay for relevant endpoints and to conduct preliminary comparisons of the CD-1 mice results with those of the medaka studies to examine interspecies extrapolation.

## 3. Conclusions

EPA research planning is subject to multiple influences and must be responsive to emerging legislation and evolving agency regulatory priorities. Chemical mixtures research is complex in nature, but carefully planned research can yield data useful for several applications. The unique, multidisciplinary structure of ORD is conducive to forming integrated research teams, ideally suited for targeted, multipurpose projects. Optimally, EPA research planning will target critical risk assessment and risk management needs.

## Acknowledgments

The authors thank L. Birnbaum, K. Hammerstrom, L. Papa, G. Suter, and D. Williams for their thoughtful reviews.

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