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Date: December 6, 1996

To: Pat Beatty (510)242-7022
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From: George Shevlin

Re: Benzene Task Force Draft Letter

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Dr. Mary Burr Paxton has asked me to forward the attached draft letter to you for your comments. She would like to receive your input by the close of business Thursday, December 12, 1996.

If you have any questions regarding this matter, please direct them to Dr. Paxton. Her telephone number is (202)682-8338.

Thank you.

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Robert T. Drew, Ph.D.
Director, Health and Environmental Sciences Department

DRAFT

December 3, 1996

Dr. Jeffrey Foran
Risk Science Institute
International Sciences Institute
1126 Sixteenth Street, N.W.
Washington, D.C. 20036

Dear Dr. Foran:

Last year, the Benzene Task Force (BTF) of the American Petroleum Institute (API) decided to undertake a project enlisting the aid of several experts to address the issue of additional data needs involving the genetic toxicology of benzene. The BTF decided to focus on the *generic issue of how genetic toxicology data could be used to augment or clarify issues identified in epidemiology studies* of benzene leukemogenesis. A second objective was a *consideration of genetic toxicology data that would be useful in addressing those issues identified by benzene epidemiology studies.*

After initial discussions with Dr. Gino Scarano of ILSI, API agreed to help fund an ILSI workshop on genetic toxicology and risk assessment in which benzene would be one of a limited number of illustrative example compounds. At that time, the Task Force's desire to focus on the use of genetic toxicology as an *adjunct* to epidemiology data was made very clear to Dr. Scarano in an initial meeting and in subsequent discussions with Dr. Mary Paxton of API staff.

API is becoming concerned that during the development of the plans for the ILSI Workshop program, the initial focus of the API project is evolving away from API's initial expectations and desires. Based on the September 27, 1996 memorandum from Dr. Scarano, it appears that the major intent is now to use the case study chemicals in a risk assessment based upon EPA's recently released Cancer Assessment Guidelines. We agree that the proposed guidelines are an important framework for the consideration of human health risk assessment, because they (or an amended form of them) will be what we will probably live with for the next decade. However, API has some serious concerns about some aspects of the charge to authors of the discussion papers as put forth in the 9/27/96 memo.

While the issuance of the proposed guidelines by EPA clearly supplies a framework in which genetic toxicology data are important, the initial API intent was broader. Previous epidemiology studies of benzene exposed worker populations have identified a number of questions or

associations upon which the results of appropriate genetic toxicology data could possibly shed light. As well as the issue of shape of the dose-response relationship, a major question is the choice of the appropriate exposure-response model, *e.g.*, lifetime cumulative dose vs. a measure of peak exposure. Under the current guidance in Dr. Scarano's letter, such an issue would probably not be addressed.

Another area of concern stemming from the use of recent guidelines as a framework for the workshop is the charge to the authors to address the issue of non-tumor data, *i.e.*, genetic toxicology data, to extend the dose-response relationship. We feel that this topic alone is of sufficient complexity and controversy to justify consideration in a separate workshop and that its inclusion in this workshop would detract from an adequate level of consideration of other risk assessment issues. If this issue is to be included, anything beyond a discussion of the generic conditions that must be met for consideration as a biomarker would clearly go beyond the initially agreed upon format upon which API based its support of the workshop.

The third concern is that of using the non-tumor data as a basis for extrapolation of beyond the observable tumor response range (found in section 3 of Dr. Scarano's memo). It should be made explicit to the authors that this section is not intended to generate a dose-response model for extrapolation of the tumor response but, if included at all, should be limited to generic considerations of the pros and cons of this type of activity. This is another area that has already been the subject of separate symposia and workshops. It is API's belief that this topic be dropped from the workshop.

The other component of the API project was to identify genetic toxicity data gaps that would provide valuable information if filled. While the intent was not to generate specific testing recommendations, we did desire to identify those data that would answer specific questions or allow choices to be made between alternative hypotheses. This issue does not appear in the 9/27/96 memo.

API requests that ILSI address the concerns listed above and respond to Dr. Mary Paxton indicating how the instructions to the authors will be modified. If you have any questions or need clarification of any of the points made above, please contact Dr. Paxton at API or Dr. Patrick Beatty, chair of the Benzene Task Force, at (510)-242-7037.

Sincerely,

Robert T. Drew, Ph.D.

ILSI RISK SCIENCE INSTITUTE

International Life Sciences Institute

MEMORANDUM

TO: Dr. Richard Albertini, U. of Vermont; Dr. Vickie Dellarco, U.S. EPA; Dr. D. Jacobson-Kram, Microbiol. Assoc.; Dr. Julian Preston, CIIT; Dr. Michael Shelby, NIEHS; Dr. Curtis Travis, Informatica Intl.; Mr. Harvey Clewell, ICF Kaiser; Dr. Sheila Galloway, Merck; Dr. Mary Paxton, API; Dr. Steve Robison, Procter & Gamble; Dr. James Swenberg, UNC

FROM: Dr. Gino Scarano, ILSI Risk Science Institute

RE: Beginning of the *Use of Non-Tumor Data in Cancer Risk Assessment* Project

DATE: September 27, 1996

The purpose of this memorandum is to let you know that "the project" (*Use of Non-Tumor Data in Cancer Risk Assessment*, formerly called the "genotoxicity project"), is finally getting-off the ground. For your information, I am providing you with the names of the individuals invited to participate in the project and details on how the project is expected to proceed.

Individuals Invited to Participate in the Project

The individuals listed have been contacted and have expressed an interest in participating in the project. Invitation letters have been sent to all individuals.

Chemical	Primary Author	Secondary Author	Reviewer
Benzene	Dr. Martyn Smith (U.Cal-Berkeley)	Dr. Richard Irons (U. Colorado)	Dr. Ray Tice (Integr. Lab.Sys.)
Butadiene	Dr. Richard Albertini (U. Vermont)	Dr. J. Thornton-Manning (Inhal. Tox. Res. Inst.)	Dr. Julian Preston (CIIT)
Vinyl Chloride	Dr. Jim Swenberg (U. North Carolina)	Mr. Harvey Clewall (ICF Kaiser)	Dr. Curtis Travis (Informatica Int'l.)

How the Project Will Proceed

There will be two people involved in the development of a draft document on each chemical (a primary and secondary author) with one person reviewing the draft in detail after it is completed. It is anticipated that the primary and secondary authors will agree upon writing assignments and will

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write a first draft of the case study. It will be the responsibility of the primary author to prepare the first full draft of the document.

Case Study

The starting point for each case study will be the cancer potency estimate derived according to the 1986 U.S. EPA cancer risk assessment guidelines. The estimate will be provided to project participants. From that point, their charge is to develop the following:

1. A cancer potency estimate derived using the dose-response default approaches included in the 1996 proposed revisions to the U.S. EPA cancer risk assessment guidelines (Attachment 3). This will involve modeling tumor data in the observed range to determine whether the effective dose corresponding to the lower 95% limit on a dose associated with a 10% response (LED_{10}) should be used as a point of departure for either extrapolation to the origin as the linear default, or to determine a margin of exposure (MOE) as the non-linear default. Information on such issues as species differences, the slope of the dose-response curve at the point of departure, and other pertinent factors should be discussed.

2. A cancer potency estimate that reflects the use and modeling of non-tumor data (e.g., DNA adducts, mutation, chromosomal aberration, cellular proliferation, hormonal or physiological changes, receptor binding). In the modeling of non-tumor data, the following should be included and/or discussed:

- the evidence that supports the role of the non-tumor data as an element of the agent's carcinogenicity;
- support for selecting a linear versus non-linear extrapolation procedure using the defaults (straight line from LED_{10} or MOE) described in the proposed 1996 guidelines or, if available, a biologically based or case-specific model;
- discussion of whether non-tumor data may be used to extend the tumor response below the range of observation and thus guide the assessment below the observed tumor range; and
- discussion of why it may be more appropriate to model the combined non-tumor and tumor data as an integrated data set, if the non-tumor data are believed to be part of a continuum that leads to the tumor response.

3. A discussion of why, or why not, the tumor precursor response should be modeled and used for extrapolation instead of, or along with, the available tumor data. The discussion should include rationale on why the precursor response is believed to be either obligatory in the carcinogenic process, or more informative of the agent's carcinogenicity.

Following is some other useful information:

- Conference Calls. RSI will coordinate periodic conference calls to monitor the progress of the activity and assure the meeting of all deadlines.

- Time line. The first conference call will be held in the middle of October. The development of the case studies should take approximately five months, with an additional month for the review. Therefore, the working group meeting will likely take place in the in mid-1997.

If you have any questions about the project, please contact me by phone (202-659-3306), fax (202-659-3617), or e-mail (gino@dc.iisi.org).

4. A discussion of the relative importance of non-tumor endpoints that may be available and used in the exercise. For example, if both DNA adduct data and chromosomal aberration data are available for a chemical, should one endpoint be given more "weight" than the other in a cancer risk assessment?

It is critical that there be a clear discussion of the rationale used for each approach taken during the project.

Logistics

The project will consist of the following steps:

- Identification of Data. RSI will conduct a literature search on each of the chemicals and send the results to each author and reviewer of that particular chemical. A conference call will be held among the authors and reviewer to agree upon the data (human and animal) to be used in the project.

- Data Collection and Identification of Assignments. RSI will make sure that all authors/reviewers receive the agreed upon literature. RSI will then coordinate a conference call between the primary and secondary authors to facilitate the identification of writing/analysis assignments.

- Generation of First Draft. Authors will begin work on their respective sections. Any computer runs that may need to be performed (e.g., calculation of cancer potency factors) will be conducted by ICF Kaiser and will be coordinated by RSI. Once the secondary author has completed his/her section, it is to be given to the primary author, who will be responsible for finalizing the draft.

- Review of First Draft. The reviewer will then examine the first draft generated by the authors. Comments will be provided to authors and revisions incorporated as appropriate.

- Meeting of the Authors, Reviewers and Working Group Members. Once drafts for all three chemicals have been reviewed and revised, a meeting of all authors, reviewers and Working Group Members will take place. The purpose of the meeting will be to: 1) discuss the "lessons learned" from the case studies; 2) develop recommendations on the use of non-tumor data in cancer risk assessment; and 3) identify research needs regarding the use of non-tumor data in cancer risk assessment. The product of this project is anticipated to be a report published in the peer-reviewed literature or a stand-alone monograph on the quantitative application of genotoxicity and other data in cancer risk assessment.