American Petroleum Institute
1220 L Street, Northwest
Washington, D.C. 20005

memo

Date: October 25, 1993

From: Mary Paxton

To: Benzene Task Force (BTF)

Re: Conference Call on Cox's Revised Proposal

In response to the questions posed at the last BTF meeting, Tony Cox has revised his proposal for implementing a full BBRA model for benzene. His revision and a further addendum he wrote after telephone discussions with Pat Beatty and me are attached for your consideration.

I need to have paperwork underway by November 1 for any contract we want to initiate with 1993 funds. Therefore, I am scheduling a conference call for 2:30 pm EDT on Wednesday, October 27, for the purpose of making a decision about this work. The call-in number is (202)-833-8777. Please return the following form so we will know who to expect on the call. Thank you.

att: 10/12 revision
10/21 addendum

FROM:API-HESD WASH DC TO: VIA XPEDITE (11-1) OCT 25, 1993 9:15AM #180 P.03

Please return to:

Roxie Landry
HESD, API
fax: 202-682-8270

_____
(name)

_____
(company)

_____ will participate

_____ will not participate

in the conference call of the Benzene Task Force on **Cox proposal** at 2:30 pm EDT on Wednesday, October 27, 1993.

To: Dr. Mary Paxton, API
From: Tony Cox, Cox Associates
Re: Proposal to develop a full BBRA model for benzene
Date: 10-12-1993

Thank you for your comments on my 9-18-93 proposal to develop a full BBRA model for benzene. I understand that the committee has two concerns, which can be paraphrased as follows:

(i) *Cost concerns:* My initially proposed budget of $78k is expensive. Is this much work really necessary, and if so, why? (Can't most of the benefits be achieved instead just by integrating the software modules already created in previous years and changing some of their parameter values, without undertaking a large additional effort?)

(ii) *Data concerns:* Are there enough benzene-specific data currently available to make it worthwhile to invest now in completing the BBRA model for benzene? If so, where are these data? (It is almost certainly not worth spending a large amount of research dollars on the problem if the data are not sufficient to produce credible, useful results.)

I am sympathetic to both concerns. This revised proposal tries to address them both. It contains details on the work and some proposed reductions in scope and cost.

A. Background

The computer model to be delivered in this project is intended to achieve the following practical benefits:

(i) *Make biologically based corrections to previous benzene risk assessments* (e.g., by enabling more detailed and credible corrections for high-to-low concentration extrapolations, mouse-to-man extrapolations, and single dose to repeated dose extrapolations than has been possible using previous, less comprehensive models).

(ii) Use simulations of biological processes to *explore mechanistic hypotheses and to develop improved risk and potency estimates*. Improved quantitative understanding of the implications of benzene biology for the dose-response relation may also lead to useful qualitative insights into regulatory and science policy issues, such as whether the benzene dose-response relation is linear or nonlinear at low doses.

(iii) Use the simulated experiments to *guide the design and to interpret the results of empirical (laboratory) experiments* being performed by Professor Rich Irons's team. The model should help to consolidate a number of findings and partial insights into benzene biology and identify areas where reducing scientific uncertainties would most help to improve risk estimates.

To help achieve these benefits, API and WSPA have already funded important building blocks and a substantial amount of methodology development. This prior work will greatly facilitate the cost-effective completion of the current project and will help to assure that we achieve the benefits just outlined. For example, we have already had to confront a number of challenging modeling and methodological challenges, such as those involved in drawing sound, useful, and robust conclusions from models formulated with incomplete (and often inaccurate or imprecise) scientific knowledge. The CP modeling project provided an opportunity to develop practical methods for coping with these challenges. Other key activities completed so far include the following:

o In 1990, we developed a PBPK model for benzene metabolism in rodents and man. (This model looked at total benzene metabolites, but did not include circulating metabolites.)

o In 1991, the PBPK model for benzene was applied to address implications for benzene risk assessment of using internal dose surrogates instead of administered dose in regulatory dose-response modeling.

o In 1992, a biomathematical framework was developed for integrating the PBPK modeling with new models of pharmacodynamic interactions. This work produced a relatively detailed framework for representing the effects of chemical leukemogens on hematotoxicity, cell kinetics, and stochastic AML induction.

o In 1993, the BBRA framework was implemented for cyclophosphamide (CP) as a case study. This project also provided a mathematical basis for describing and exploring (via computer simulation experiments) the quantitative dose-response implications of Dr. Irons' insights into the possible biological mechanisms involved in chemically induced myeloid leukemogenesis.

The purpose of the new work proposed here is build a complete BBRA model for benzene. It will be similar in scope to the CP model, but with much more detailed components. Specifically, it will use a state-of-the-art PBPK model of benzene metabolism (compared to the simple compartmental flow model of CP pharmacokinetics) and will use a hematotoxicity model that includes the granulopoiesis model for CP as one sub-model.

This project is intended to develop a benzene-specific model that has enough detail and credibility to be useful in addressing issues important to science advocacy or science policy debates. It will require using the best available components, including revisting the PBPK model (to address circulating metabolites and transport forms in greater detail) and extending the hematotoxicity model developed for CP to include damage to erythrocytes.

The following tasks and estimated resource requirements are proposed to complete the BBRA model for benzene.

B. Statement of Work

Task 1: Extend the benzene PBPK module to better describe circulating metabolites of benzene.

Discussion: A goal of our effort in 1990-1993 was to develop computer modules (i.e., sub-models) for animals and humans that can be extended and refined as additional data become available. New data on benzene pharmacokinetics and metabolism have become available since 1990 that describe circulating metabolites in rats. (Our 1990 benzene PBPK model used data of Medinsky et al. and Travis et al. did not describe circulating metabolites.) This task will update our PBPK model of benzene to include the new information on production of HQ and other bone marrow benzene metabolites. It will require critically reviewing and synthesizing the benzene metabolism and pharmacokinetics literature published since 1990. Specifically, we will incorporate the benzene-specific PBPK modeling enhancements and metabolite parameter values reported by Smith, Bois, and other recent investigators. For an introduction to recent literature on improved PBPK models of benzene and its principal metabolites, see e.g.

Bois, F.Y., T.J. Woodruff, and R.C. Spear, "Comparison of three physiologically based pharmacokinetic models of benzene disposition," *Toxicology and Applied Pharmacology*, **110**, 79-88, 1991.

Note: We recommend this paper only as a guide to progress in PBPK modeling of benzene since 1993. We do not agree with or endorse its approach to uncertainty and sensitivity analysis, which fails to exploit known constraints on the possible values of quantities.

In developing the human PBPK model for benzene, interspecies comparisons and extrapolations of benzene metabolism (especially from the Fisher rats to humans) will be made in several ways. For example, a human metabolism model with circulating metabolites will initially be developed by using enzyme specific activity levels across species. This methodology has been used in other several other PBPK modeling efforts. The resulting "biologically-based" estimates of metabolic parameter values for human metabolism of benzene will be critically compared to previously published results (due to Henderson, Medinsky, and co-workers) for human benzene metabolism extrapolated from rodent data by allometric scaling. They will also be cross-checked with empirical results on human cell metabolism obtained by Rich Irons's team.

We intend that the PBPK model developed in this task will be the most detailed and best supported model form human benzene metabolism available. It may therefore have applications outside the scope of this BBRA project. For example, it might be used to calculate the internal doses that would have been produced by past occupational exposure scenarios.

Deliverable: PBPK models for benzene and its key circulating and bone marrow metabolites in mice, rats, and humans. (The mouse PBPK model will allow previous risk estimates based on administered doses of benzene and responses in B6C3F1 mice to be recalculated using internal dose surrogates. This will refine our own previous work by supplying better quantitative estimates of specific internal dose surrogates.) Working notes on post-1990 benzene metabolism and pharmacokinetics literature and recent findings will also be made available to the API upon request.

Estimated Resource Requirements: 170 hours, 17k, 4 months. We do not see any opportunities to significantly reduce this level of effort. We will need to replicate the PBPK modeling work already performed for benzene in 1989-1990 for several circulating metabolites, and may have to add transport forms, red blood cell and hematocrit binding, and other details. We will also be adding new compartments for bone marrow metabolism,

involving at least the same level of detail as previous efforts on benzene, and probably more (e.g., based on Rich Irons's quantitative findings on cellular metabolism of benzene in the bone marrow). Whereas our benzene PBPK model with aggregate metabolism was validated with data on benzene levels in blood, urine, and exhaled breath from multiple human volunteers, it will now be necessary to add sensitivity analyses and perhaps some new mathematical techniques (such as a generalization of the AUC conservation theorem developed for linear compartmental models in our cyclophosphamide report) to deal with the uncertainties raised in modeling circulating metabolites.

We believe that 170 hours for this effort reflects great cost-efficiency and significant savings compared to what such a modeling effort would usually require. This savings is based on our existing familiarity with benzene metabolism and biochemistry and on our extensive experience with PBPK extrapolation methods for chemicals. Moreover, we suspect that a well supported, critically examined model of human benzene metabolism and marrow metabolites will be valuable to API in several applications, e.g., in assessing the relative risks associated with various occupational and public health exposure scenarios.

Task 2: Build a hematotoxicity model. Integrate it with the PBPK model.

Discussion: The main challenge in this task will be to develop a model of the hematopoietic system that adequately describes

(i) Bone marrow suppression and inhibition (or stimulation) of hematopoiesis during and following benzene exposure.

(ii) Kinetics of affected hematopoietic cell populations, including stem cells (pre-CFU-GM and earlier) and proliferating cells of the erythroid and granulocytic lineages. Observed compensating proliferation following cessation of benzene exposure must be explained by the model.

(iii) The shift in bone marrow cell composition (e.g., in terms of cumulative stresses experienced by different cell populations) due to prolonged, repetitive exposures.

This model will draw heavily on the hematotoxicity model developed for CP, which will probably be included as a sub-model. Whereas the CP model focused on granulopoiesis, however, the benzene hematotoxicity model must also consider in detail hematotoxic effects

on the erythroid lineage, which is profoundly affected by benzene exposure. The feedback interactions of the GM and erythroid lines in controlling hematopoietic stem cell populations must also be represented.

We anticipate that the benzene hematotoxity model will be more than twice as large as the corresponding CP model. It will provide a solid basis for modeling other hematotoxic agents (excluding those that act on thrombopoiesis), since benzene exposure affects so many hematopoietic cell populations.

Are sufficient benzene-specific data available to justify developing a model of benzene hematotoxicity at this time? We believe that the answer is a strong yes, especially if we continue to use animal data to strengthen and check our modeling. Benzene actually compares favorably to CP in terms of availability of relevant cell kinetics data and quantitative hematotoxicity data. This is especially true if murine data are used. Since murine hematopoiesis and human hematopoiesis parameters are significantly different, however (compared, for example, to normal canine and normal human hematopoiesis), full use of the available benzene-specific murine hematotoxicity data to fit and cross-validate our benzene hematotoxicity model may require implementing a separate model of normal murine hematopoiesis. (Our CP project focused on human hematotoxicity.) Building a combined PBPK/hematotoxicity model for mice as well as for humans will allow us to validate our models with a wealth of detailed animal data compiled by many authors over many years. These include data from Irons's investigations as well as older sources, such as the data reported by Cronkite (*Environmental Health Perspectives*, 1989, pp 99-100), who plotted quantitative data for hematopoietic stem cells and early progenitor cells during and following benzene exposure.

We have reviewed and presented specific data sources on benzene-induced hematotoxicity several times over the past 5 years. A recent source of quantitative cell kinetics and cytotoxicity parameter estimates for benzene is the following paper:

> Scheding, S., M. Loeffler, S. Schmitz, H. J. Seidel, and H. E. Wichmann, "Hematotoxic effects of benzene analyzed by mathematical modeling," *Toxicology*, 72, 265-279, 1992.

We expect to substantially improve upon this previous work by relating hematotoxic effects over time not to the parent compound, benzene, but rather to levels of specific benzene

metabolites in bone marrow, as predicted by the PBPK model. In addition, we will used improved modeling techniques that allow more accurate temporal resolution of the effects of benzene exposure on hematopoiesis.

Deliverable: A combined benzene PBPK hematotoxicity model. As noted above, it may prove necessary to develop separate versions of the combined model, one for mice and one for humans, so as to take full advantage of available data. Based on our experience with CP data, for which fewer data on hematotoxicity are available, we believe that it is realistic to complete a credible, predictively useful model of benzene hematotoxity based on existing data. We expect this model to be more complete and more credible than other published models (such as the one of Scheding et al.) due to its explicit accounting for the roles of benzene metabolites and to its improved level of temporal resolution (hours instead of days), which will permit more extensive comparisons to empirical data.

Estimated Resource Requirements: 380 hours, 38k, 6 months. This will cover the cost of developing a new model of benzene hematotoxicity from original data and modeling efforts. The new model will incorporate the best features of our CP model (e.g., a temporal resolution of hours) and will break new ground, compared to previous models of benzene hematotoxicity, by making toxicity a function of specific metabolite levels instead of benzene levels.

Task 3: Implement a stochastic simulation model of benzene-induced leukemia induction and link it to the PBPK and hematotoxicity models.

Discussion: This task will deliver a stochastic simulation model for leukemogenesis, showing the effects of exposure-related changes in cell kinetics on the resulting age-specific leukemia hazard function. It will be based on the model of leukemogenesis developed during the CP project, which extends the MVK two-stage stochastic model to allow for the "cytotoxic shunt" mechanism discovered by Irons. The new model will also allow for realistic details (discussed but never implemented by Moolgavkar et al., for reasons of mathematical tractability) such as spontaneous extinction of malignant stem cells as well as of initiated ones. Estimates for initiation rates and other parameters will be developed using the most recent data, e.g., those reported in

> G.M. Farris et al., "Carcinogenicity of inhaled benzene in CBA mice," *Fundamental and Applied Toxicology*, **20**, 4, 503-507, 1993.

Since these data (which update earlier experimental investigations by Cronkite) indicate an excess of malignant lymphomas rather than myelogenous leukemias, we will need to use careful biological interpretation in selecting studies and aspects of responses that may be relevant to leukemogenesis in humans. However, the mouse data should be useful in calculating the effective rate of carcinogenic damage occurring in mice under different exposure scenarios. With the help of our mouse PBPK and hematotoxicity models, we should be able to back-calculate approximate potency factors for internal doses. Much of the detailed work in this project will consist of developing credible parameter estimates, seeking ways to cross-validate them (e.g., by applying the same calculations to multiple species or data sets and comparing the results) and critically evaluating and coping with the remaining uncertainties.

Deliverable: A floppy disk containing a stochastic simulation model for predicting leukemia hazard functions (and confidence bands, with enough repetitions) for specified benzene exposure scenarios. The specific deliverables from this task are as follows:

(i) A simulation model that integrates the benzene-specific PBPK, hematotoxicity, and stochastic leukemia induction modules. (This will be delivered on a floppy disk.)

(ii) A technical memorandum summarizing the model structure, the data used, the uncertainty management methodology used to overcome data and knowledge gaps (e.g., sensitivity analyses for the transition rate parameters of the leukemia model), key sensitivities and remaining uncertainties, and the main qualitative insights and quantitative risk estimates obtained by applying the model to various exposure scenarios.

Estimated Resource Requirements: 220 hours, 22k, 4 months. This task combines Tasks 3 and 4 of my September 18 proposal. We have streamlined the deliverables (1 technical memorandum instead of 2) and increased the scope of the memorandum to make it more useful (by including quantitative risk estimates).

Successful completion of this project should produce a wealth of publishable results. Our benzene BBRA risk model will address not only qualitative and scientific questions of importance to benzene risk assessment (e.g., is cumulative exposure a good predictor of risk?), but also specific, quantitative risk predictions (together with uncertainty

intervals) for benzene. Following successful completion of the scope of work outlined here, we will be pleased, at API's discretion, to submit a separate proposal to prepare one or more journal articles based on the results. We expect that the results of the current effort will help to create and gain acceptance for a new paradigm of practical, applied BBRA modeling for chemicals of importance to industry and regulators.

Tasks 1-3 have a combined estimated resource requirement of $77k, compared to the $78k initially proposed. The project can be completed within 8 months. We believe that this represents an extremely cost-effective work plan. After careful thought about the steps that must be taken to complete this work with high enough quality to withstand skeptical (or even hostile) scrutiny from people who are inclided to resist the BBRA approach to risk assessment, I can not find any clear ways to reduce this effort without sacrificing a significant amount of its impact. Further cost reductions could be achieved, especially by uncritically adopting models from the literature rather than creating improved models to replace them. However, the quality of the final model would be compromised.

Please let me know if I can provide further information or change the scope of work to make be more useful to API. I anticipate that the project proposed here, by demonstrating the current practicality of BBRA modeling, can significantly advance the acceptance of "more science in risk assessment". I believe that it would be a mistake to defer completing this project until more data are available. BBRA modeling must be applicable to chemicals with incomplete and uncertain scientific data if it is to be useful as a practical (affordable) alternative to the LMS paradigm. Our uncertainty-management techniques are now well-enough developed to take on an important real problem such as benzene. However, if the committee decides that completing this project is premature, I will be happy to submit a different proposal for a smaller project that focuses on using BBRA modeling to learn from and to guide ongoing research efforts.

FYI.
Tony

To: Dr. Patrick Beatty, WSPA
From: Tony Cox, Cox Associates
Re: Addendum to proposal to develop a full BBRA model for benzene
Date: 10-21-1993

The purpose of this addendum is to summarize and confirm the main points we agreed on today in our telephone conversation about the desired outcome of the benzene BBRA modeling effort. After discussing technical strategies for uncertainty management in the BBRA model, we agreed that the benzene model must do the following things:

Point out which data elements are most important for benzene risk assessment.

Guide further experimentation by showing how eliminating various uncertainties would improve (make more precise or more certain) risk estimates for benzene.

Present (and link the derivation of risk estimates to) testable hypotheses, and identify which ones would be most valuable to test.

We agreed that the modeling effort should not only clarify which specific facts that we don't know now would be most valuable in improving the confidence in, and precision of, BBRA risk estimates, but it must also suggest the empirical measurements and experimental tests of hypotheses that would help to resolve these uncertainties.

I have viewed this active approach to uncertainty management as an intrinsic part of the project. Suggesting what to do about uncertainties, as opposed to merely documenting them, is part the uncertainty and sensitivity analyses buried it in my brief description of the second deliverable from Task 3. Such analyses quantify how the reduced parameters and variables, on which risk depends, might change in light of new data and scientific information. They identify which changes would most affect risk estimates and suggest experiments and information collection opportunities that will reduce the uncertainties to which risk estimates are most sensitive. (Indeed, part of the BBRA approach is the recognition that information, however insight-provoking, that does not affect the reduced parameters or variables is not needed in order to develop confident, accurate estimates of risk.) Rather than leaving this implicit, I commit as part of Task 3 to:

(i) Discuss the model's most important data elements, sensitivities, and uncertainties.

(ii) Identify those uncertainties about facts that most affect the uncertainty in risk estimates.

(iii) Recommend hypotheses, experiments, and measurements to reduce those uncertainties .

Please let me know if I can make this effort more valuable to you in any other way.