VIA FAX

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FROM:

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

memo

Date: August 6, 1997

From: Mary Paxton

To: Benzene Task Force (BTF)

Re: Draft comments on EPA's revision on benzene's cancer potency

Attached is a draft outline of comments to EPA that can provide a strawman for our cnference call tomorrow at 3:00 EDST. I regret that I will be out at an all-day meeting on Friday, so that is not an alternative for rescheduling, but the hour on Thursday can be adjusted.

* * * * *

If you have not already done so, fax to Mary Paxton at 202-682-8270:

_____
(full name)

_____
(company)

____ can participate in the first BTF conference call on Thursday, August 7, at 3:00 EDT;
A better time this week would be:

____ can participate in the second BTF conference call on Thursday, August 14, at 3:00 EDT;
A better time that week would be:

You will be notified if a change from these two times is necessary.

To participate, call 1-800-282-2343 at the appointed time.

____ would like a copy of the Canadian exposure report.

Comments of the American Petroleum Institute

on the

U.S. Environmental Protection Agency's "Carcinogenic Effects of Benzene: An Update"

EPA's goal: Review the adequacy of the current benzene cancer potency factor (cpf) at the request of the Office of Mobil Sources under the 1991 Clean Air Act Amendments.

Is this a worthy goal?
Has EPA achieved its objective in a satisfactory fashion?

API's goal: Be constructive.
Encourage any movement away from low-dose linearity default.
Point out what not considered.

A. Issues posed by EPA to Expert Review Panel:

[Rob Schnatter's submission was focused on addressing these questions.]

1. Is this document successful in "selecting a quantitative approach to estimating benzene risks especially at environmental exposure levels"?

2. Does the document adequately justify use of the Pliofilm cohort ("Rinsky, 1987 cohort") as the basis of its dose-response analysis and risk derivation?

   This raises the issue of deriving a cpf for a pure substance vs. deriving risk estimates for what (e.g., mixtures like gasoline) that most workers and the general population are now exposed to. If the latter is the objective, it would argue for also (or instead) looking at studies of petroleum worker cohorts.

3.1 Does the discussion of the various mode-of-action hypotheses appropriately describe the current thinking and capture consensus where such exists?

   Most, but not all (studies missed pointed out below), of current research into benzene's mechanism of leukemogenesis are alluded to, but are not then really factored into EPA's modeling and quantitative choices. This leads API to pose the long-standing industry query [as also in Section B], How much data does it take to move from EPA's default position?

   Studies missed:

3.2 Is the rationale for specific model selection (e.g., linear at low dose) adequately explained and supported?

The tally of points for and against non-linearity does not really establish the relative merits of the arguments and the overall weight of the evidence.

Super-linearity in relative proportion of toxic to non-toxic metabolites observed at levels where metabolism is saturated does not belie the possibility (in fact, likelihood) that the production of toxic metabolites is sub-linear at the much lower, ambient levels of regulatory concern.

Even if Michalis-Menton kinetics are linear for metabolites all the way to zero from below the high-dose plateau, the relationship for the target event would not be expected to be linear.

EPA equates any type of genotoxicity with low-dose linearity, whereas those specific types of genotoxicity associated with benzene are now generally regarded as having non-linear dose-responses (Preston attachment).

gene conversion in glycophorin assay
clastogenicity
aneuploidy

3.3 Is there another modeling approach that could be supported by consensus information?

July 16 ERP meeting demonstrated consensus that there is adequate evidence to justify the presentation of a range of non-linear estimates to supplement the range of linear estimates as presented in the current EPA draft.

3.4 Is there a scientific rationale for selecting a specific risk estimate from among the range of presented (i.e., low-dose linear risks of 4.7×10^{-3} to 2.5×10^{-2} per ppm, whose upper limit is just less than the current benzene cpf of 2.6×10^{-2} per ppm)?

Without explicit guidance, risk managers and regulators will tend to select the probably overly protective upper limit as the basis of the quantitative judgments. However, EPA's conservative interpretation of the information gathered on benzene over the last decade indicates that, even considering only linear estimates, the risk falls below the existing cpf value. If one were to put aside the strong arguments in favor of non-linearity, the weight of the evidence would support a point within EPA's stated range, thereby effectively reducing the estimated benzene cpf that would be applied in risk assessments by about five-fold. API is well aware that, given the extend of uncertainty surrounding these estimates, a five-fold difference may not represent a "statistically significant difference," but in the implementation of environmental and occupational regulations it represents a very real and practical difference from the engineering point of view.

4. Have major uncertainties and research needs for the next iteration of risk assessment been identified?

   The document concludes with recommendations for further investigation that are unduly focused on age subgroups [as addressed in section D.4]. Current understanding of benzene's metabolism and preliminary findings of genetic heterogeneity suggest that future research related to subpopulations with particular sensitivity to benzene toxicity would be more productively directed at genetic polymorphisms in the enzymes involved in benzene's metabolism.

B. Degree of Success as Implementation of EPA's 1996 Proposed Cancer Risk Assessment Guidelines (r.a. g.l.)

   [The substantive issue of this section will be touched upon in A.3.1 and D.2 or could be tucked in elsewhere. Do we want to keep this issue as a separate section?]

1. In spite of the emphasis in the new r.a. g.l. on integrating multiple routes of exposure, no attention is paid to dermal absorption as a significant source of benzene exposure

2. Both extrapolating from dose-response model (although only linear) and margin of exposure (MOE) approaches were taken, but no resolution firmly stated.

C. Other Technical Issues

1. Question assertion of low-dose linearity for formation of DNA adducts (Reddy attachment).

   protein contamination in Turteltaub's work?
   surprising uniformity of levels in various tissues in Mazzullo's work
   relative sensitivity of methods - suggestion of inconsistency in range of overlap

2. The continuing credence EPA gives to Cronkite's animal model for the human endpoint of concern is outmoded.

3. Exposure estimates applied in MOE approach could be replaced with more current and up-to-date estimates.

   [Information available from Will Ollison.]

D. Process Issues

1. EPA document cites studies that are not publicly available in sufficiently detailed form to permit independent review.

Turteltaub abstract
Zhang submitted article

2. In many places, EPA's conclusions are not adequately developed. Allusions to "other possible pathways" must be specified and accompanied by supporting citations, permitting evaluation of the merits of the assertion. Adhering to a default option on the basis of the existence of some remotely possible alternative puts the impossible onus upon the regulated community to prove the negative that nothing else is possible except, in the case of benzene, the non-linear mechanisms that have been demonstrated.

   [ties back to section B on r.a. g.l.]

3. EPA's current draft represents a good first step toward a revised cpf for benzene, but (as noted in these comments) it could be substantially improved. Unfortunately, the "fixes" will need to go considerably beyond simple editorial changes and insertions, and potentially could have a non-trivial impact on the benzene cpf ultimately settled upon. Therefore, API would encourage another iteration of revision with the ERP. The external review process for this document should be in accord with the FACA process. It would be highly desirable for this ERP to follow the example of CASAC on NAAQS documents, where the experts in the oversight group stay actively involved in the review and revision process until they grant closure.

4. The appended assertion that children and the elderly are likely sensitive sub-population for benzene toxicity is a scientifically unsupported political stance.

E. Editorial Points (Attachment C)

   Straighten out references to particular update of the Pliofilm cohort being referred as the basis of a given analysis instead of using the sloppy nomenclature "Rinsky 1987," which actually only refers to the Pliofilm cohort as updated through 1981, which was not the basis for EPA's 1985 derivation of its current cpf and which is not the most complete data set available on this cohort now available.

F. Conclusion

Attachments

A. Preston on low-dose nonlinearity for various genotoxicity endpoint

B. Reddy on specificity and relative sensitivity of techniques of detecting DNA adducts

C. Editorial Points