American Petroleum Institute
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April 22, 1988

TO: BENZENE ISSUES GROUP

FROM: R.P. STRIETER

RE: BIG MEETING ON MAY 9, 1988

A meeting of the Benzene Issues Group has been scheduled for Monday May 9, 1988 from 9:00 A.M. to 2:30 P.M. at API Headquarters in room 907. Lunch will be served.

This meeting has two prime objectives:

1. Presentations by Todd Thorslund on progress with the dose-response project at ICF; Curtis Travis on benzene pharmacokinetic modeling at Oak Ridge; and by Richard Irons on benzene mechanism of toxicity research at CIIT; and

2. Review of the overall effort being planned to address the EPA remand of the Section 112 benzene standards.

A tentative agenda is included for your information.

Also enclosed for your information is a copy of the ICF Phase I report recently sent to EPA.

xc:
Benzene mailing list

5/10/88 FYI 005436

TO: PROPOSITION 65 STEERING COMMITTEE

FROM: MIKE WANG

AMERICAN PETROLEUM INSTITUTE
BENZENE ISSUES GROUP
TENTATIVE MEETING AGENDA
API HEADQUARTERS - ROOM 907
MAY 9, 1988
9:00 A.M. TO 2:30 P.M.

I.	INTRODUCTION	C. DIPERNA
II.	OVERVIEW OF THE ICF BENZENE DOSE RESPONSE PROJECT	T. THORSLUND
III.	OVERVIEW OF THE CIIT BENZENE METABOLISM AND TOXICOLOGICAL RESEARCH	R. IRONS
IV.	OVERVIEW OF THE OAK RIDGE NTL. LAB. BENZENE PHARMACOKINETIC MODELING RESEARCH	C. TRAVIS
V.	DISCUSSION OF THE EPA SECTION 112 BENZENE REMAND	C. DIPERNA/ A. SAMPSON
VI.	RESEARCH PLANS TO ADDRESS ACCEPTABLE RISK LEVELS	A. SAMPSON
VII.	ACTIVITIES IN CALIFORNIA	M. CARDIN
	A. RECONSIDERATION OF THE CALIFORNIA BENZENE RISK ASSESSMENT	
	B. PROPOSITION 65 ACTIVITIES	
VIII.	SARA TITLE III RELATED ACTIVITIES	D. RUSSELL
IX.	OTHER BUSINESS	

QUANTITATIVE RE-EVALUATION OF THE HUMAN LEUKEMIA RISK ASSOCIATED WITH INHALATION EXPOSURE TO BENZENE

PHASE 1 REPORT

Supported by:

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April 18, 1988

PREFACE

This document represents the first of a two phased effort to re-evaluate the carcinogenic potency of benzene. Since the last unit risk estimate of cancer potency completed by CAG in 1985, there have been significant advances made in the development of risk assessment methodology, and important new information has become available concerning the effects of benzene on humans and experimental animals.

This phase I report adopts the same theoretical structure used in the EPA (1985) risk models to obtain an upper bound cancer risk estimate but refines the new model by the use of new data and methodological developments. Included in the new estimates are an update of the original epidemiological study by Infante et al. on pliofilm workers, new epidemiological studies conducted in China, and the use of more precise statistical estimation procedures made possible by the availability of exposure and vital status information on individual cohort members. It is important to note that the model developed in this study does not depart substantially from the basic structure of the original CAG model. It incorporates the same one-hit one stage model that was the basis for EPA's (1985) risk assessments. The new estimates reflect the agency's preference for using human data when available, and are based upon parameter estimation techniques which make the most efficient use of the available information.

An observation that demonstrates the consistency of one of the more important underlying assumptions of the model, is that for both the atomic bomb survivors in Japan and workers exposed to benzene in China, the peak leukemia risk for benzene occurs at 5 to 10 years after

initiating the final biological transformation. Thus, in the worst case, the risk of developing leukemia decreases steadily for those people who have had no benzene exposure for more than 10 years. This observation is being confirmed in the pliofilm workers cohort where we see no new cases of leukemia in the additional years of follow-up (1979-1981) included in this report.

The changes made in the model have a pronounced effect upon the unit risk estimate. The upper bound unit risk estimate obtained in this report is 2.7×10^{-3} which is almost an order of magnitude lower than the value of 2.6×10^{-2} that was adopted by EPA in 1985. Another advantage of the new model is that it provides logical way of testing the linear dose-response hypothesis. It was demonstrated that the dose-response relationship exhibited more curvature than could be explained by a simple linear relationship. This demonstration of a curvature, and the probable underestimation of exposure both strongly suggest that the upper bound unit risk estimate is very conservative.

The difference in the cancer potency estimates obtained with the current model compared with the previous approach is primarily due to the type of information used to estimate the model parameters. The present approach uses the vital status and exposure estimates at each point in time for each individual in the cohort as well as information on latency period from other studies. The previous approach grouped individuals into exposure ranges and used the average exposure, observed and expected number of leukemias, and person years in the exposure group in the analysis. The data used in the current study provides much more precise information for the estimation of the

parameters in the dose-response model.

Phase II of this program will involve the use of additional biological and exposure data and a more refined biologically motivated model that takes into consideration benzene's potential mechanisms of action. Since most of benzene's hypothesized mechanisms of action suggest non-linear dose effects, we feel confident the predictions of leukemia risk will be lower than the present upper bound risk estimates.

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I. INTRODUCTION

A complete analysis of the carcinogenic potency of benzene was performed by the U.S. Environmental Protection Agency almost ten years ago. Since this analysis, considerable new and relevant information on benzene has become available and major advances in risk assessment methodology have been achieved. However, a comprehensive reassessment of the carcinogenic potency of benzene has not as yet been undertaken.

In 1985, EPA performed an interim quantitative cancer risk assessment of benzene (EPA 1985). This interim assessment was done in response to a petition and, thus, had severe time constraints that forced the use of a secondary source (Crump and Allen 1984) for deriving the cancer potency estimates which did not permit optimal use of all the available information.

The purpose of this report, which shall be denoted as Phase I or first submittal, is to supply EPA with a new state-of-the-art upper bound estimate of benzene's cancer potency and to inform EPA of the more biologically relevant risk model that is under development which will be referred to as Phase II or second submittal which is scheduled for completion in mid June. The advice and suggestions of agency personnel are sought her for how best to incorporate scientific and regulatory considerations into the new biologically relevant risk model to be developed in Phase II. In the Phase I report, the approaches that were taken to modify and complete EPA's interim cancer potency estimates are described and the approach to be taken in the development of a new more biologically relevant model in Phase II outlined.

The upper bound cancer dose-response model for benzene that is developed in the Phase I report includes the following extensions and improvements of that used in EPA's 1985 report:

(1) Inclusion of additional years of follow-up (1979-1981) from the Rinsky et al. (1981) cohort;

(2) Restricting the analysis to the most relevant data set and functional form of the potential models;

(3) Use of updated U.S. vital statistics to estimate rate of benzene-induced leukemia in the presence of competing mortality;

(4) Corrections and additions of job classification codes that were found on the Rinsky et al. (1981) computer tape to reconcile them with original work records;

(5) Use of actual data from several leukemogens in addition to benzene to define a probability distribution for the time from malignant transformation of the first cancer cell to death due to leukemia; and

(6) Use of more efficient techniques for cancer potency parameter estimation, which is made possible by the availability of information on exposure and vital status for every individual in the Rinsky et al. (1981) cohort.

The new best estimate biologically relevant model that is under development in Phase II will incorporate diverse biomedical information into a biologically based quantitative dose-response model. For example, information from observations of the leukemogenic effects of radiation (atomic bombs, therapeutic), chemotherapeutic agents, and experimental benzene studies will be used to estimate the biological latency period. In addition, the shape of the age-incidence curve for granulocytic leukemia for the general U.S. population

will be used to estimate other model parameters. The approach taken is to derive risk estimates for benzene that are based upon various forms of a two-stage model with clonal expansion of preneoplastic or 1st stage cells (Thorslund et al. 1987).

The two-stage biologically based model can be used to estimate risk from either human or animal data, which is an improvement over the present inconsistent EPA approach of using different models for the two types of data. The new approach has the further advantage of proving a means to incorporate theories of biological mechanisms into the dose response model. For example, we can incorporate benzene's clastogenic effects as well as its effect on cell proliferation into the model.

The following sections of this report provide a more detailed discussion of the approaches that are used here as well as those that are under development.

II. ANALYSIS OF EPA'S 1985 MATHEMATICAL MODELING APPROACHES USED FOR BENZENE

A. General Mathematical Framework

The models that were used in the EPA's cancer risk assessments for benzene (EPA 1985) are based on the implicit assumption that one molecule of benzene can cause the single necessary event that transforms a normal stem or progenitor cell in the bone marrow into a neoplastic cell (i.e., one-stage, one-hit models). The latency period or time between this cellular transformation and death due to leukemia is a variable that is affected by a number of factors such as immunological competence and the stage of hematopoietic maturation of the transformed cell. Thus the time-dependent dose-response model for benzene and leukemia is dependent upon two factors:

1. the dose-response relationship between benzene exposure and the cellular transformation; and
2. the probability distribution of the length of survival (i.e., time between the cellular transformation and death due to leukemia).

This joint biological process is mathematically modeled in a general form in the next section. The manner in which CAG's previous cancer risk models for benzene-induced leukemia fit into this general framework is then described.

1. Development of General Model

In this section, the general EPA cancer dose-response model for benzene is derived mathematically and biologically-based rationales for the model components are proposed.

The relative instantaneous probability that exposure to benzene at time v resulted in death due to leukemia at time t can be expressed as

$$h(v,t) = G[x(v)]w(t-v) \qquad \text{(II-1)}$$

where G[x(v)] is the instantaneous dose-dependent probability that exposure to a specified level of benzene at time v, x(v), will induce the cellular transformation (e.g., chromosomal abnormality) that will lead to leukemia some time in the future; t-v is the length of time between the cellular transformation and death due to leukemia, which is considered to be a random variable with a definable probability distribution w(t-v); and w(t-v) is the probability density or weighting function that defines the relative probabilities of death due to leukemia at time t given that the cellular transformation occurred at time v (i.e., the probability density function of t-v).

The relative probability that a series of exposures to benzene prior to time t will result in death due to leukemia at time t is simply the sum of the effect of the exposures at all individual points in time. Thus, if an individual were subjected to a series of r + 1 exposures (x_0, x_1,...,x_r) occurring at times (v_0, v_1,....,v_r), the instantaneous probability of death due to leukemia at time t is the hazard function or age-specific cancer rate:

$$h(t) = \sum_{j=0}^{r} h(v_j,t) = \sum_{j=0}^{r} G(x_j)w(t-v_j) \qquad \text{(II-2)}$$

The hazard function is illustrated in Figure II-1 for the simple case where the exposure level was x_0 at time v_0 and x_1 at time v_1, the weighting function has the simple unimodal form $w(t-v) = K^2(t-v)\exp\text{-}K(t-v)$, and the cellular transformation function is assumed to be $G(x) = \beta x^2$, which would be the case if the transformation requires two simultaneous one-hit events. An example of a transformation that requires two simultaneous events is reciprocal