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MEMORANDUM

TO: Use of Non-Tumor Data in Cancer Risk Assessment Working Group:

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Dr. Annie Jarabek, USEPA, ORD
Dr. Sheila Galloway, Merck
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Dr. Julian Preston, CIIT
Dr. Steve Robison, Procter & Gamble
Dr. Michael Shelby, NIEHS
Dr. James Swenberg, UNC
Dr. Curtis Travis, Informatica Intl.
Dr. Vickie Dellarco, USEPA, OW

FROM: Gino Scarano (GCNS), ILSI Risk Science Institute

RE: Progress Report on the *Use of Non-Tumor Data in Cancer Risk Assessment* Project

DATE: April 21, 1997

The purpose of this memorandum is to inform you of our progress on the ILSI Risk Science Institute project on the *Use of Non-Tumor Data in Cancer Risk Assessment*. Since our meeting in March of 1996 to develop the scope for the project, the spring and summer of 1996 were spent trying to find adequate funding to carry out the project. By August it was determined that one (aflatoxin) of the four substances identified at our March meeting should be dropped; thus, the project focuses on three case studies (butadiene, vinyl chloride, and benzene) of how to use non-tumor data quantitatively in a cancer risk assessment.

Our last progress report (September 27, 1996) identified the case study participants (listed below) and provided an outline of the project logistics. This document provides an update of project activities since the September report. It is worth noting that the participants elected to participate as equal authors in the effort rather than as primary/secondary authors and reviewers.

Literature searches were performed in October of 1996 for each case study chemical. References from the literature search were distributed to case study participants in March of 1997. Each team is in various stages of discussing strategies, developing outlines, and making writing assignments. Specific information for each case study is provided below.

Butadiene. The team agreed that the epoxide (the mono and/or di-epoxide) metabolites of butadiene are probably responsible for the carcinogenicity of butadiene in rodents, and that the carcinogenic response is different in rats (different sites and at higher exposures) than in mice (different sites and at lower exposures). They further agreed that the reason for the different carcinogenic response between the two rodent species is likely due to differences in butadiene metabolism. They further noted that recent updates of epidemiological studies have been published, and one of these studies suggested an association between occupational exposure to butadiene and various types of

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lymphopoietic cancers in humans. To the best of the team's knowledge, it is likely that any new risk assessments will incorporate the findings of the recent epidemiological studies, but all currently published butadiene cancer risk assessments have been based on either the mouse or rat cancer bioassay studies.

The participants are aware of a number of critical experiments that may be helpful in this exercise which have either recently been completed or are underway. Specifically, experiments on the identification of butadiene-specific DNA adducts in both *in vitro* and *in vivo* assays, *in vivo* mutagenicity studies comparing mice and rats, and identification of biomarkers of exposure and/or effect in humans following exposure to butadiene are being tracked by team members.

The team has tentatively agreed to use both published data and new data on genotoxicity in rodents and see if this accurately predicts rodent cancer data that are available for low exposure levels, and then use human genotoxicity data for butadiene and its metabolites to predict human carcinogenicity and then compare this prediction to the results in published epidemiological studies. At this time, the team has chosen to focus on the following issues: human monitoring data; rodent cancer data; genotoxicity information (point mutations, cytogenicity, and germ cell effects); species differences in metabolism; physiologically-based pharmacokinetic models (PBPK); and DNA adduct data.

Vinyl chloride. Vinyl chloride appears to cause the same specific type of cancer (liver angiosarcoma) in both animals and humans. Published data also suggest that a reactive metabolite of vinyl chloride (chloroethylene oxide) is probably responsible for the carcinogenicity of vinyl chloride, and this reactive metabolite has been shown to form specific DNA adducts in the liver tissue of various animal species. The case study team believes that the concordance among species for tumor type lends weight to the possible use of vinyl chloride specific-DNA adduct data for use in a risk assessment. Therefore, team discussions have centered around the correlation of vinyl halide-specific DNA adduct formation with observed tumor incidence in animals. Other avenues being considered include the use of human (epidemiological) data and *in vivo* genotoxicity data in a vinyl chloride cancer risk assessment.

Benzene. The benzene case study team is interested in incorporating a much broader database into future benzene cancer risk assessments than has been used to date. Specifically, they would like to show how the acute myelogenous leukemia (AML) purported to be associated with human exposure to benzene has been observed in humans as a secondary effect following treatment with certain chemotherapeutic agents. The team proposes that the mechanism of this secondary effect may provide some useful information for benzene cancer risk assessment. In addition, the team is working on comparing and contrasting the use of generic models (LMS vs. stochastic) in benzene cancer risk assessment, and whether or not information from benzene studies in transgenic animals that are in progress at NIEHS may be useful in this exercise.

It is likely that first drafts and initial reviews of all three case studies will be completed by the summer of 1997. At that time, they will be distributed to all Working Group members for comment. Once drafts for all three chemicals have been reviewed and revised, a meeting of all case study participants 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 non-tumor data in cancer risk assessment.

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.ilsi.org).

Case Study Participants

Benzene Team:	Dr. Martyn Smith (U.Cal-Berkeley)	Dr. Richard Irons (U. Colorado)	Dr. Ray Tice (Integr. Lab.Sys.)
Butadiene Team:	Dr. Richard Albertini (U. Vermont)	Dr. Matthew Himmelstein (Dupont)	Dr. Julian Preston (CIIT)
Vinyl Chloride Team:	Dr. Jim Swenberg (U. North Carolina)	Mr. Harvey Clewall (ICF Kaiser)	Dr. Curtis Travis (Informatica Int'l.)