

To: Cagen, Stuart Z SCC <szcagen@Shell.Com>
From: Owen, David DE SC-CHSE-DO
</O=SHELL/OU=OPC/CN=RECIPIENTS/CN=SNOW4>
Cc:
Bcc:
Received Date: 2001-07-04 09:08:59 GMT
Subject: RE: Benzene slides

Stuart,
Many thanks for this.
One question:
Are there any details (not in-depth) on what populations are to be studied in the proposed Shanghai study e.g. shoe manufacturers etc/??
David

-----Original Message-----

From: Cagen, Stuart Z SCC
Sent: 03 July 2001 22:43
To: Owen, David DE SC-CHSE-DO
Subject: Benzene slides

David:

Here are a few slides. I tried to send a file earlier - actually I tried 3 times - but I kept getting error messages that the document was too long. This version does not contain 2 fancier slides (lifted from the API web site). I hope this goes through.

Let me know if you have problems, questions

Stuart

<< File: benzenedavidowen.ppt >>

To: Owen, David DE SC-CHSE-DO
<David.E.Owen@OPC.shell.com>
From: Cagen, Stuart Z SCC
</O=SHELL/OU=MSXSCC/CN=RECIPIENTS/CN=SC724012>
Cc:
Bcc:
Received Date: 2001-07-04 17:12:57 GMT
Subject: RE: Benzene slides

David:

Here are some details....

Safe travels

Stuart

Project Description

The proposed project consists of three highly integrated aspects:

- 1) A population-based case control study to investigate the potential relationship between benzene exposure and both NHL and AML including an attempt to define a quantitative potency for the AML response;
- 2) A hospital/clinic-based investigation of the relationship between non-neoplastic diseases of the bone marrow and AML to determine if there is a progression through stages of bone marrow cytotoxicity to an ultimate leukemogenic response. This study would also attempt to define, both a potency and the shape of the dose-response for these "precursor" diseases;
- 3) A "transitional" study to investigate the quantitative relationships between benzene exposure and potential early indicators of both exposure and effect in a focused population of benzene-exposed shoe manufacturing workers.

All three of these aspects are highly integrated in that the potential cases for the case control studies will have their diagnoses confirmed and their subtype and viral status determined by the same laboratory that will conduct the cytogenetic analyses which are part of the third portion of the project. The progression study, the second portion of the project, will use the shared laboratory facilities, and many of the "cases" in the AML case-control study may also be included in the progression study.

Case-Control studies

A collaboration between the US National Cancer Institute and the Chinese Academy of Medicine (the NCI/CAPM study) was published as a cohort study of Chinese workers occupationally exposed to benzene in a number of industries. The NCI/CAPM study reported an association between benzene exposure and Non-Hodgkin's lymphoma. This association has not been reported in any other

study of benzene health effects, and contradicts the general scientific consensus that acute myelogenous leukemia (AML) is the only hematopoietic cancer which can be clearly associated with human exposure to benzene. This publication has already been used to support litigation alleging benzene-induced NHL. The study also has reported an association between benzene exposure and AML, but interpreted the results to indicate that average benzene exposures of around 5 ppm could lead to AML. An association between AML and benzene exposure at these levels has not been reported previously and threatens current occupational standards in Europe, the U.S., and the rest of the world.

This project will initiate a population-based case-control epidemiology study of NHL and AML in the population of Shanghai. The case-control design will allow a focussed examination of the NCI claim that benzene exposure can cause NHL. NHL is not a single disease but, rather, is a collective of over a dozen phenotypically distinct hematopoietic cancers. As has been done traditionally, the NCI/CAPM study looked only at the lumped cancers. The proposed consortium study design includes subtyping each individual case to determine if a positive response is confined to only one component of NHL. In addition, the viral status of each case will be determined because it is known that active infection with any of a number of viruses has been causally related to increased risk of NHL. Confounding by this factor may explain the NCI/CAPM observation. This portion of the project, as well as the other two listed above, will include independent analysis of benzene exposures which will allow a check on the exposure estimation procedures used by the NCI in their publications. If the quality of the exposure data permit, an estimate of the quantitative potency of (slope factor) will be made for any cancer type with a positive association with benzene exposure. Currently, through Dr. Otto Wong, we have contacts with the Departments of Public Health and Hematology of Shanghai Medical University. Through that institution we have contacts with the Shanghai Tumor Registry and the Shanghai Center for Disease Control, which is the governmental repository for workplace exposure information. Protocols are under current development based upon the results of an in-depth feasibility study conducted in August, 1999 by Exxon Biomedical Sciences, Inc. and Dr. Richard Irons of the University of Colorado and funded under the 1999 budget.

Disease Progression/Molecular Epidemiology Study

Researchers, using subsets of workers from the NCI/CAPM cohort study, have published papers that report an association between benzene exposure and a number of chromosomal abnormalities. Some of these abnormalities are reportedly associated with airborne benzene concentrations as low as 5 ppm, close to the current 1 ppm OSHA PEL for benzene. The significance of these studies is difficult to interpret due to problems with exposure assessment in the NCI/CAPM cohort study and with the way in which the exposures are stratified. In addition, dermal exposure to benzene was widely ignored by the previous studies.

One other study from these researchers has reported significant genetic predispositions to benzene-induced hematotoxicity. Although qualitatively plausible, evaluation of the magnitude of the effects is again difficult because of the exposure and stratification issues previously mentioned.

This project will utilize individuals identified as part of the case-control epidemiology study to investigate genetic effects and disruption of regulatory processes on the hematopoietic system. This study will also allow an independent evaluation of the exposure-response nature of these effects in a population more highly exposed than occurs in the U.S. or Europe. This study will identify those individuals with hematopoietic disease, MDS or AML, that can be reliably attributed to benzene exposure, in order to identify unique characteristics of benzene-induced disease. Due to the highly controlled nature of benzene exposure in North America and Western Europe, researchers have not had the opportunity to bring modern medical and molecular biological techniques to bear on a single case of AML, MDS or aplastic anemia in which benzene could be considered the probable etiologic factor. These results may allow a definitive identification of hematopoietic effects unique to benzene exposure, and may establish a link between benzene-induced leukemias and other leukemias secondary to chemical exposure (mainly alkylation chemotherapy) about which much is already known. The study will be performed by Dr. Richard Irons of the University of Colorado with the collaboration and assistance of investigators from the Departments of Hematology and Public Health of Shanghai Medical University.

The above investigators will also be involved in an examination of the relationship between AML and other non-neoplastic hematopoietic diseases. The combination of a relatively stable population (geographically) with both hospital and occupational records of bone marrow related disease has created the possibility of investigating this relationship. Workers in benzene-related areas are monitored for excessive exposure (reported to the Center for Disease Control and Prevention (CDC) as "benzene poisoning") by means of annual blood counts. It has been hypothesized that AML must be preceded by some degree of toxicity to the hematopoietic system. Validation of this hypothesis would provide critical support for a nonlinear (sublinear) dose response of hematopoietic effects due to benzene exposure, and would imply a non-zero threshold exposure to benzene below which there would be no risk of AML, etc. It is not clear at this time how reliably individuals with benzene poisoning can be located, but cases of MDS or aplastic anemia (AA) treated in hospitals may be more easily located. These issues will have to be resolved during the course of the investigations.

Transitional Study of the Shoe Manufacturing Industry

One area of benzene research that has received a lot of attention in the last few years is the attempt to identify early biological indicators that predict a later event such as AML or serious forms of bone marrow toxicity such as MDS or AA. These early indicators have also been referred to as "biomarkers". Some endpoints

which have been measured, such as protein adducts of benzene metabolites, are clearly indicators only of exposure to benzene (although there may be some complicated relationship with biological responses). Some endpoints, such as certain cytogenetic abnormalities, have been claimed to be indicators of future effect. The NCI/CAPM researchers have published several papers investigating both phenomena. However, two problems remain. The first is distinguishing between the two types of indicators. At this time no biological predictor of benzene-induced leukemia has been unequivocally identified. The second problem, as with other portions of the NCI/CAPM studies, is that the benzene exposure information either relies on tenuously justified estimates of retrospective exposure, or has presented current exposure monitoring data in a way that ascribes effects from a wide range of exposures to a single mean value from that range. No publication exists in the scientific literature that has attempted to establish an exposure response relationship for genetic effects that is based upon several sets of data points.

The objective of this series of studies is to investigate the relationship between benzene and various blood dyscrasias and cytogenetic abnormalities in the Shanghai shoe manufacturing industry. The dose-response will be investigated in relation to various types of benzene exposure metrics. This study will take advantage of the wide range of benzene exposures in this occupation, which will maximize the possibility of seeing non-linearity of any dose response that exists. Specific aims of this facet of the overall project are:

- 1) To define benzene dose response patterns for alterations in blood cell counts, bone marrow cytotoxicity and chromosomal alterations;
- 2) To define the most relevant exposure indicators for each of the effects in “1”;
- 3) To assess if the dose response patterns are affected by the presence of other environmental compounds such as toluene or xylene which commonly are co-exposures with benzene;
- 4) To assess if the dose response patterns are altered by the presence of reported susceptibility factors in exposed individuals;
- 5) To define the relationship between external benzene exposure and selected internal measures of exposure.

The extent of specific aim 5 may be affected by ongoing research by the Health Effects Institute which is investigating several of these relationships.

Location

The location for the proposed project is Shanghai, China. Shanghai is a major population center with approximately 14 million individuals living in the local area. Shanghai supplied a large proportion of the individuals studied in the NCI/CAPM epidemiological study, and virtually all of the subjects for the ancillary studies of chromosomal alterations. Shanghai presents the unique situation of a large number of workers with documented exposures to benzene at levels that have not

existed in North America or Western Europe since the 1940's or 50's. A feasibility study group funded by the API Benzene Task Force was shown records of industrial hygiene monitoring of work areas where benzene was routinely used and where airborne benzene concentrations occasionally were in excess of 100 ppm, and where a rare data point could exceed 200 ppm. Although many air samples indicated exposures of less than 10 ppm, concentrations in the range of 10 - 50 ppm were common. The regional agency in charge of maintaining occupational health records, the Center for Disease Control and Prevention, has a computerized database of industrial hygiene (IH) monitoring data extending back to the mid 1980's. In addition to air monitoring data, blood counts of exposed workers are routinely made on an annual basis. These data are also maintained in computerized form by the local CDC offices. Shanghai also contains a major medical school, Shanghai Medical University (SMU), with a School of Public Health and Hematology Department associated with a teaching hospital. This hospital is one of the major hospitals in Shanghai and will serve as a source for identifying potential cases for the proposed studies

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Sent: Wednesday, July 04, 2001 4:09 AM
To: Cagen, Stuart Z SCC
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