To: George Woodall; 'BenzConsort-OC@listserve.api.org'; 'BenzConsort-TC@listserve.api.org'
Cc: Cagen, Stuart Z SCC; Tsai, Shan SP SHLOIL-SPS
Subject: RE: SRP Status Update; Ballot on Statistician

George, Oversight Committee, Technical Review Committee: Shell votes to go to the next name on the list. I include comments from Stu and Shan regarding the composition of the SRP and the September 27 meeting.

Like Shan, I (Stu) know nothing about Kopecky, but he seems acceptable from the earlier description we were given; regardless, my notes indicate that we said OK to him in the previous ballot.

I would not hold things up looking for another European for its own sake as there is coverage already.

My concern at this point is the percentage of SRP members who will be present at the 27 September meeting - either in person or present with comments submitted ahead of time - and whether this level of review will be adequate to move forward at the rapid rate needed for the University of Colorado review in October or November.

What I stated during the last technical review committee conference call was that moving ahead at the rapid pace was agreeable if: 1) a sufficient number of reviewers were enjoined, 2) they had sufficient time to review the protocols and that 3) their reviews were favorable enough to move forward. If the above conditions are met I would agree we could comfortably move forward. Right now I am assuming this is an uphill battle and would need to be shown otherwise. Even though I cannot attend the meeting on the 27th I would need to be shown evidence of a favorable review by a sufficient quorum.

Shell would appreciate consideration of these points.

Patsy

Patsy M. Clegg

Product Steward, HSE

Shell Chemical Company, PO Box 4320, Houston, TX 77002

Phone: 713-241-2521 FAX: 713-241-3325

e-mail: pmclegg@shellus.com

-----Original Message-----
From: George Woodall [mailto:Woodallg@api.org]
Sent: Tuesday, August 21, 2001 12:33 PM
To: 'BenzConsort-OC@listserve.api.org'; 'BenzConsort-TC@listserve.api.org'
Subject: SRP Status Update; Ballot on Statistician
Importance: High

Benzene Health Research Oversight and Technical Committees; The current status of the Scientific Review Panel (SRP) is as shown on the attached PDF file. The one slot for which we do not have any representation prior to the Protocol Review Meeting on September 27 is a statistician. I have tried to contact Richard Peto several times to no avail. In a conversation I had with Patrick Beatty today, he suggested that with the addition of Helmut Greim and John Cherrie as European representatives along with Jerry Rice of IARC, we now have significant European participation. He also suggested that having an American as a statistician would also help to control travel costs. Another consideration is that Dr. Peto is extremely busy and that someone else in this position may be able to provide more time to a review. The question to the Committees is as follows (please indicate your companies preference for the next course of action): ___ X __ 1) Go to the next nominee on the list for a statistician. _____ 2) Convene a conference call to discuss (tentatively for 1:00 - 2:00 PM EDT on Tuesday, August 28) Also indicate your availability for a conference call at the proposed time, or alternate availability for early next week. Regards, George M. Woodall, Ph.D. Senior Toxicologist American Petroleum Institute 1220 L Street, NW Washington, DC 20005 Tel. (202)682-8067 Fax. (202)682-8031 ********** Coming Soon! The New **www.api.org**

From: Cagen, Stuart Z SCC [szcagen@Shell.Com]
Sent: Friday, August 24, 2001 5:56 AM
To: 'George Woodall'
Cc: Lorraine Twerdok; Paula Podhasky; John Wagner; Bill Frick;
'burnetdm@bp.com'; 'burnetdm@bp.com'; 'bondtj@bp.com';
'michael.d.johnston@usa.conoco.com';
'carol.a.fairbrother@exxonmobil.com'; 'lynn.b.russo@exxon.com';
'pwbe@chevron.com'; 'twerdokl@api.org'; 'pmclegg@shellus.com';
'woodallg@api.org'; 'roythorc@bp.com'; 'burnetdm@bp.com';
'bondtj@bp.com'; 'bill.d.broddle@usa.conoco.com';
'carol.a.fairbrother@exxonmobil.com'; 'pwbe@chevron.com';
'roythorc@bp.com'; 'sptsai@shellus.com'; 'woodallg@api.org';
'szcagen@ShellUS.Com'
Subject: RE: Benzene Consortium Status Update

George:

A note to confirm what we discussed yesterday:

I am comfortable and quite excited about the depth of the peer review that is expected prior to and during the Scientific Review Panel meeting, which includes at least one individual from each discipline, with the exception, so far, of a biostatisician.

As we discussed, I would highly recommend a formalized process for the peer review whereby there is designated a chair of the Scientific Review Panel (perhaps Dr. Larson ?) and that a product of the meeting on the 27th of September should be a report from the Scientific Review Panel to the investigators (cc: the technical review committee). The chair would author the report but all of the members of the Scientific Review Panel should review and approve draft(s). I suppose that most of the members of the Scientific Review Panel would resist taking on the role of the chair because of a perceived extra load of work, but you could possibly reassure them that you can help with the compiling of individual review comments, possibly, but not necessarily, as a rappatour for the Panel (I hope you would agree to this). Regardless, this should not be a role of any of the industry members - neither oversight nor technical committees. I would ask, however, that the technical committee be included in the correspondence between the Scientific Review Panel and the investigators so there is sponsor understanding of the review as well as investigator responses or recommended program adjustments.

Finally, as mentioned before, I would like to included in discussions regarding the implementation of this program, and hope that my willingness to be an active member of the technical committee is viewed as an asset. Regardless, it is an expectation on my end.

Thanks

Best wishes

Stuart

> -----Original Message-----
> From: George Woodall [SMTP:Woodallg@api.org]
> Sent: Thursday, August 23, 2001 5:50 PM
> To: BenzConsort@listserve.api.org
> Cc: Lorraine Twerdok; Paula Podhasky; John Wagner; Bill Frick; Stuart
> Cagen Ph.D. (E-mail)
> Subject: Benzene Consortium Status Update
>
> To all interested parties;
>
> Please forward this message to anyone not on the attached list that should
> be included.
>
> This e-mail is being sent to foster better communications. Much has
> happened in the past few weeks and more will need to happen in order to
> make this consortium work.
>
> * List of Committees - I have attached a Word document that lists all
> the members and ex-officio members of the consortium committees, and a
> separate list of "interested parties" that should include everyone on the
> other three lists along with others. This document also includes the list
> server e-mail addresses for each group, along with the e-mail addresses
> for each individual.
> * Legal Workgroup - A Legal Workgroup was formed to try to iron out
> the issues associated with developing the consortium agreement. This is a
> very time-sensitive issue since many of the contributing companies have
> tied having a finalized and signed contract in place prior to honoring any
> invoices for the consortium. As it now stands, we have had communication
> from 4 of the 5 companies indicating that they prefer the bilateral
> contract arrangement over the option for the consortium to incorporate
> separately. The attached e-mail from John Wagner includes the latest
> draft of the agreement document.
> * Scientific Review Panel - The candidates for the SRP that have
> accepted include: Jerry Rice (IARC - General Toxicolgy), Helmut Greim
> (University of Munich - General Toxicolgy), Li Guilan (Chinese Academy of
> Preventative Medicine - Genetic Toxicolgy), Richard Larson (Univ. of
> Chicago - Hematology), Robert Herrick (Harvard - Industrial Hygiene), John
> Cherrie (University of Aberdeen- Industrial Hygiene), and Nancy Mueller
> (Harvard - Epidemiology). The following have been invited to participate
> but have not yet indicated acceptance: Martha Linet (NCI - Epidemiology),
> Mark Minden (Ontario Cancer Center - Hematology), Richard Brunning
> (University of Minnesota - Hematopatholgy), and Kenneth Kopecky
> (University of Washington - Statistics and Study Design).
> * Protocol Review Meeting - Scheduled for September 27 in Chicago.
> The panel that will review the protocols include all of the SRP members
> that have accepted, as well as Elizabeth Delzell (University of Alabama at
> Birmingham - Epidemiologist) and Richard Albertini (University of Vermont
> - Genetic Toxicology), both of whom were retained prior to the development
> of the SRP. Not all of the members of the SRP will be able to attend, but
> have promised to at least provide written comments prior to the meeting.
> * Contracts with the Researchers - API is in the process of developing
> separate contracts with American Health Sciences (Dr. Otto Wong) and Fudan
> University (Dr. Fu Hua) for the Case-Control portion of the project. A
> larger grant to the University of Colorado Health Sciences Center (Dr.

> Richard Irons) is also in process which will include the funding for the
> parts of the Molecular Epidmiology and Disease Progression studies being
> done at Fudan University, and the other Chinese agencies in Shanghai. A
> separate contract with Dr. Richard Irons' consulting company is being
> drafted to cover project-related expenses that could not be included in an
> agreement with the University of Colorado (travel for UCHSC staff, housing
> in China, etc.). At present, much of this can only go to the draft stage
> until the funding to support the contract/grant is on the ledger at API.
>
> I hope this helps to keep you updated. If there is additional information
> that you feel needs to be communicated, please send me an e-mail or give
> me a call.
>
> Best regards,
>
> George M. Woodall, Ph.D.
> Senior Scientist
> American Petroleum Institute
> 1220 L Street, NW
> Washington, DC 20005
>
> Tel. (202)682-8067
> Fax. (202)682-8031
> ---------- << File:
> BenzeneConsortiumCommittee.doc >> << Message: Benzene Consortium
> Agreement >>

Jerry M. Rice, PhD
Chair, Scientific Review Panel
3213 Coquelin Terrace
Chevy Chase, Maryland 20815
Tel: +1-301-986-0659
Fax: +1-301-986-5438
E-mail: jmricewas@aol.com

SHANGHAI HEALTH STUDY

Memorandum

To: Technical Oversight Committee and Members of the Consortium

From: Jerry M. Rice, Ph.D., Chair, Scientific Review Panel

Date: October 17, 2003

Subject: Conclusions of the Scientific Research Panel –
Annual Research Meeting, Asilomar, California, August 2003

Executive Summary

- A fully equipped and staffed Central Diagnostic Laboratory has been satisfactorily established. This is an important first milestone for all three (CC, DP & ME) studies.
- The next milestones to be monitored are:
    1. Progress in recruitment of cases and controls for all studies;
    2. Cost-effective implementation of HIV serology for control subjects in the case-control study;
    3. Timely peer-reviewed publication of findings in the scientific literature.
- Additional endpoints have been identified, which the investigators should consider (with external funding if required).
- The SRP and ERP have jointly decided to hold future panel meetings during annual research meetings, and to defer recruitment for 3 SRP vacancies. These actions will significantly reduce the budget required for the two external Panels in future years.

Current status of investigations in view of the formal objectives and goals previously proposed and accepted for funding by sponsors of the Shanghai Health Study

Establishment of the central diagnostic laboratory as a functioning reality, and expanding the number of cooperating institutions to include 23 of the 24 major Shanghai hospitals, are major achievements. It is especially significant that the hospitals that have most recently joined the Study are those that treat the majority of benzene poisoning cases in Shanghai. The enrollment of cases, which has just commenced (July 2003), constitutes a highly significant milestone in this overall research program. The investigators are now in an excellent position to accomplish the specific goals of their respective protocols. As these studies progress, a transition plan for identified cases and an ongoing local role for the clinical laboratory should be considered.

For the NHL component of the case-control study, it is imperative to document exposures of both cases and controls to all risk factors for NHL other than benzene, notably to HIV. For HIV, a questionnaire alone is insufficient. Performing the requisite blood test should not be a technical difficulty for the diagnostic laboratory, but the current case-control protocol does not provide for blood samples from controls, and is not funded to do this. As an action item, Drs. Irons and Wong agreed to confer and propose an approach to obtaining HIV data from control subjects.

Suggestions for further and/or expanded future studies

As the goals of the current studies are progressively reached in future years, the investigators should give consideration to exploring new sources of funding for additional studies that lie outside the work scopes of the current protocols:

1. Establish a Leukemia Tissue Bank

An established leukemia tissue bank, consisting of stored frozen cells and serum, will provide a major international resource for future research. These clinically and biologically well characterized tissues could be made available to future studies of many kinds and thus provide a significant asset to the investigators and their institutions. A mechanism should be developed for other investigators to apply for access to these preserved tissues. The National Cancer Institute Clinical Cooperative Groups have developed and published criteria for reviewing concepts or research proposals from other laboratory investigators for access to their tissue

banks. [See: Schilsky RL, Dressler LM, Bucci D, Monovich L, Jewell S, Suster S, Caligiuri MA, Kantoff PW, Compton C. Cooperative group tissue banks as research resources: the Cancer and Leukemia Group B tissue repositories. Clin Cancer Res. 2002 May; 8(5): 943-8].

2. Include Commonly Evaluated Benzene Biomarkers

The current studies of benzene toxicity and carcinogenicity in many ways will be the most sophisticated ever undertaken, notably in the application of modern diagnostic criteria. It is highly desirable that the results of these studies be directly comparable to results of previous studies. This can best be accomplished by adding commonly evaluated biomarkers of benzene exposure and effect. All three of the study protocols describe dose response, and the study protocol of the Molecular Epidemiology Study describes identification of sensitive biomarkers, as a specific aim. These include specific metabolites of benzene present in urine, and chromosome aberrations assessed in peripheral blood lymphocytes by conventional methods. Enumerations of peripheral blood granulocytes and lymphocytes are already being made by standard hematological assays. The urinary concentrations of S-phenylmercapturic acid (S-PMA) and trans, trans-muconic acid (T,T-MA), which are minor metabolites of benzene, have recently been validated as highly specific biomarkers of recent benzene exposures (Qu et al. HEI Report #11, 2003). Correlations with external exposures, as measured by personal monitors, have been excellent, with linear relationships even between 0.1 to 1.0 ppm. Other benzene metabolites, such as phenol, catechol and hydroquinone do not show such sensitivity or specificity. It is recommended to include at least urinary excretion of S-PMA in studies that investigate acutely exposed workers.

In this same study, conventional chromosome analyses of peripheral blood lymphocyte metaphase spreads also were correlated with benzene exposures. Furthermore, chromosome aberrations and chromatid breaks were correlated also with long term cumulative benzene exposures, as assessed by work histories, etc. FISH analyses of interphase cells (granulocytes and non-stimulated lymphocytes), as well as of metaphase spreads of cultured lymphocytes, showed more variability, suggesting that these newer methods require additional development. Decreases in peripheral blood granulocyte and lymphocyte numbers were also correlated with measured

benzene exposures, even though the white blood cell numbers did not drop below normal levels.

The reason for including these additional biomarkers in this component of the overall study is to assess benzene internal doses by the best-validated methods currently available. This will add validity to the estimates of (current) external benzene exposures being made by worker histories, work area measurements, etc., that are now the only measures of current exposure levels for the subjects in the Molecular Epidemiological Study. As these latter measures are also those being used to quantify benzene exposures retrospectively in the other two components of the overall study, *i.e.* the Disease Progression Study and the Case Control Study, the Molecular Epidemiology Study will serve as an internal validation study of the methods, adding credibility to them and thereby to the exposure assessment in the other two studies.

Conventional chromosome aberration studies using peripheral blood lymphocytes will not be as sensitive or specific for benzene exposures as the urine metabolite concentrations, but good correlations have traditionally been shown between frequencies of chromosome aberrations and chromatid breaks and benzene – as again verified in the Qu study. This biomarker will link the SHS with the many other studies of benzene's human effects that have preceded it. Furthermore, chromosome aberration frequencies are also correlated with long term benzene exposure levels – something that cannot be assessed using the urine metabolites. Finally, chromosome aberrations appear to have predictive value for the subsequent occurrence of cancer, as shown by studies of Hagman and Bonassi over recent decades. (Note: these chromosome studies will not be mechanistic probes; they will be used as biomarkers of exposure to add validity to the methods currently used to assess exposure.)

These biomarker suggestions apply to the Molecular Epidemiology Study only. Urinary metabolites will have no use for measuring the distant past benzene exposures of relevance in the other two studies of the overall SHS, and chromosome changes, although reflecting long-term cumulative exposures, will be difficult to interpret in patients with leukemia and associated diseases.

Participants

Richard Albertini
Patrick Beatty (*observer*)
Stuart Cagen (*observer*)
Harvey Checkoway
John Cherrie
Helmut Greim
Robert Herrick
Juhana E. Idänpään-Heikkilä
Bruce Jarnot (*API staff*)
Richard Larson
Guilan Li
Jerry Rice
Howard Rockette
Zong-Liang Xu