RE: Scoping of benzene pooled epidemiological analysis

From:

"De Jong, Geert G SI-SHS" <geert.dejong@shell.com>

To:

"Swaen, Gerard (G)" <gswaen@dow.com>, "Tsai, Shan P SHLOIL-SHS" <shan.tsai@shell.com>, "Roythorne, Christopher" <chris.roythorne@uk.bp.com>, "Satin, Ken (KSAT)" <ksat@chevrontexaco.com>, Urbanus Jan <jan.urbanus@concawe.org>, chris.money@exxonmobil.com, rolf.ahlberg@nesteoil.com, jean-philippe.gennart@total.com

Date:

Fri, 03 Jun 2005 10:43:01 +0100

All,

We have a range of opinions on possible way forward. Should we set up a telecom to discuss? If you agree, Jan could you action?

Kind regards,

Geert de Jong
Senior Health Adviser
Shell International B.V.
PO Box 162, 2501 AN The Hague, The Netherlands

Tel: +31 70 377 2516 **Fax:** +31 70 377 2840 **Other Tel:** +31 6 55 124 123 (mobile)
Email: geert.dejong@shell.com
Internet: http://www.shell.com

> -----Original Message-----
> **From:** Swaen, Gerard (G) [mailto:GSwaen@dow.com]
> **Sent:** Friday, June 03, 2005 9:16 AM
> **To:** Tsai, Shan P SHLOIL-SHS; Roythorne, Christopher; Satin, Ken (KSAT); Urbanus Jan; chris.money@exxonmobil.com; De Jong, Geert G SI-SHS; rolf.ahlberg@nesteoil.com; jean-philippe.gennart@total.com
> **Subject:** RE: Scoping of benzene pooled epidemiological analysis
>
> Shan,
>
> I was aware of the possibility that I would propose something against an earlier decision.
> Still I would encourage some more thoughts on including other datasets:
>
> 1. 1. Other datasets are available and getting permission would not delay the project very much.
> 2. 2. The highest exposure to benzene in the petroleum industry is still very low. Some top loading and splash loading of drums may have occurred, but the TWA's would not be higher than a few ppms, I estimate. Now if a dataset with this small dose range will be used to find a threshold, it can never come up with a higher threshold than the highest observed exposure. The point is: Maybe the whole study population is below the threshold and the pooled study can never provide evidence for a threshold.
> 3. 3. Including datasets with higher exposures, in which some small effects have been reported in historical exposure situations, would allow us to evaluate a much wider range of the exposure spectrum. This would provide a much clearer dose-response curve.

Gerard

Gerard Swaen
The Dow Chemical Company
Epidemiology
Health Services
tel: 31-43-3626042

-----Original Message-----
From: Tsai, Shan P SHLOIL-SHS [mailto:Shan.Tsai@shell.com]
Sent: donderdag 2 juni 2005 16:40
To: Swaen, Gerard (G); Roythorne, Christopher; Satin, Ken (KSAT); Urbanus Jan; chris.money@exxonmobil.com; De Jong, Geert G SI-SHS; rolf.ahlberg@nesteoil.com; jean-philippe.gennart@total.com
Subject: RE: Scoping of benzene pooled epidemiological analysis

Gents,

The objectives of the proposed pool study was

1) to improve the analyses and interpretation of the three existing individual studies,
2) to further clarify the potential risk of overall and cell-type specific leukemia from low-level exposures to benzene, and
2) to extablish a threshold for benzene exposures

To achieve the above objectives in a "timely" schedule and minimize the potential complications of exposure assessment, it is important that we should not expand beyond the existing three stuidies, i.e., IOL, IP, and HW.

To extend the follow-up of the IOL and IP would increase the statistical power, however, the time delay (additional 2-3 years) should be a factor to consider. Although the original IOL case-control study includes cases thorugh 1983, the cohort of this nested case-control study has been updated through 1994 (Lewis et al. Occup Environ Med. 2000 Sep;57(9):595-604). One alternative to consider is to add only new cases from the IOL that were identified from the updated IOL study and not include the additional update of the IP.

Regards,

Shan P. Tsai, Ph.D.
Manager, Epidemiology
Shell Health Services
Shell Oil Company
P O Box 2463, Houston, TX 77252-2463, United States of America

Tel: +1-713-241-6078
Fax: +1-713-241-5875
Email: shan.tsai@shell.com
Internet: http://www.shell.com

-----Original Message-----
From: Swaen, Gerard (G) [mailto:GSwaen@dow.com]
Sent: Thursday, June 02, 2005 2:49 AM
To: 'Roythorne, Christopher'; Satin, Ken (KSAT); Urbanus Jan; Tsai, Shan P SHLOIL-SHS; chris.money@exxonmobil.com; De Jong, Geert G SI-SHS; rolf.ahlberg@nesteoil.com; jean-philippe.gennart@total.com
Subject: RE: Scoping of benzene pooled epidemiological analysis

All,

In my perspective Ken and Christopher have both raised some very crucial points and I believe the first step should definitely be to avoid comparing apples with oranges, with respect to the exposure characterization as well as with respect to the outcome parameter. If possible, phase 2 should make sure that all contributing participating institutes have done their best to collect specific data on diagnosis.

In addition to the points made by Ken and Christopher I would like to make the following points:

1. Why is the pooling effort restricted to the three petroleum industry studies? Pooling of only three studies will be less informative than if more studies would be included. There are several other studies on benzene and leukemia with reliable exposure information that also contain relevant information and would increase the exposure range under investigation (indispensable for threshold analyses) and would significantly increase the power. Some other interesting studies that could be included are the Monsanto study, the recent Dow study and the recent DSM study. The advantage of including the Dow study and the Monsanto study is that they report an excess in the high dose group and thus contain information on a possible threshold. The IOL IP and HW do not contain such clear dose-response curves, if any. Even including the pliofilm cohort would have my preference, but I realize we run into trouble because of the different exposure estimates that are available. An extended pooled analysis would also have a better chance of evaluating the relevance of peak exposures. One of the most probable mechanisms for leukemogenesis is thought to work through bone marrow toxicity. Including bone marrow toxicity in the study opens the opportunity to study the relevance of bone marrow toxicity as the mechanism. If we include more studies we can test the hypothesis that increased leukemia rates have been restricted to cohorts or sub cohorts in which bone marrow toxicity has occurred or at least has been reported.
2. If point 1 is no option, I very much support the option to extend the follow-up of the three studies. If no new cases are added to the IOL, IP, and HW current databases a pooled analysis will only have a limited added value.
3. Including cell type information is very important. Given the very small excesses, if any, it is very important to have the outcome parameter as specific as possible. If not, the dose-response analysis will become diluted. In addition, the results can be criticized for not having information on cell type.
4. I do find the estimated costs on the high side. The total is over one million Euro. For such a budget we could have a complete new study done.

With respect to cell types: Have you seen the recent publication on Benzene workers in the UK by Sorahan, Kinlen and Doll in Occupational and Environmental Medicine? He concludes that effects are limited to ANL.

Gerard Swaen

Gerard Swaen

The Dow Chemical Company
Epidemiology
Health Services
tel: 31-43-3626042

-----Original Message-----
From: Roythorne, Christopher [mailto:chris.roythorne@uk.bp.com]
Sent: woensdag 1 juni 2005 09:02
To: Satin, Ken (KSAT); Urbanus Jan; shan.tsai@shell.com; chris.money@exxonmobil.com; Swaen, Gerard (G); geert.dejong@shell.com; rolf.ahlberg@nesteoil.com; jean-philippe.gennart@total.com
Subject: RE: Scoping of benzene pooled epidemiological analysis

All, I think Ken has raised some interesting points and highlighted some significant challenges with respect to exposure and cell type diagnoses which are the two critical factors.
Leaving the exposure issue to one side I see the task of obtaining specific cell type results as a huge task and one that may not be achievable to the extent that would be of value across all of the studies. There is also another aspect to consider, that of original cell type diagnoses. Having recently been in Shanghai my understanding is that the study there is developing what I would describe as very interesting data regarding cell types which will have, in my view, significant implications for previously published studies.
As a consequence, not withstanding the huge practical difficulties of any work, I would be reluctant to embark on any further work until we understand what the implications of the China Study are
Regards
Chris

From: Satin, Ken (KSAT) [mailto:KSAT@chevrontexaco.com]
Sent: 31 May 2005 23:36
To: Urbanus Jan; shan.tsai@shell.com; chris.money@exxonmobil.com; gswaen@dow.com; geert.dejong@shell.com; rolf.ahlberg@nesteoil.com; jean-philippe.gennart@total.com; Roythorne, Christopher
Subject: RE: Scoping of benzene pooled epidemiological analysis

Gentlemen:

Jan's scoping outline pretty much covers the full range of options. I think most are important to consider, but given monetary and time constraints (although at this point in time I don't know what those are), it is likely the entire scope would not be agreed to up front. This suggests a phased approach might be better, with each subsequent phase contingent on the successful completion of the previous. Of course, this could make the whole project take longer and cost more than beginning all aspects at the same time. Nevertheless, assuming a phased approach is most practical, I would suggest the following phases:

1. Rationalize exposure across the studies. We are trying to quantify a relationship so unless we can achieve consistency across studies, there is little basis for combining data and thinking we will obtain a meaningful estimate of effect. This should be the first step. If it can't be done, we need to rethink what outcome we want from the project.

2. We would like leukemia cell-type specific results so the next question is whether we can get this from the data. I would think rationalizing diagnoses across studies would entail obtaining historic medical records. Depending on the availability and access issues related to such data, the goal of this phase may not be achievable. Therefore, I propose a feasibility study to see what additional data could be obtained from a sample of each studies' cases. I would run this pilot concurrently with the exposure rationalization. In the

event this task cannot be completed successfully, it is not necessarily a show stopper to performing a pooled analysis. For example, if cell-specific information was not available, the analysis of the case-control results could be run (as a series of simulations) based on modeling the cell-specific outcomes based on the "usual" cell-type distribution for a given time and study location and seeing how sensitive the results are to the assumed cell-type distribution and number of imprecise or inconsistent leukemia diagnoses such estimating must be applied to.

3. Assuming phases 1 and 2 are successful, the analysis could be run now. This approach would be the least time and money intensive. However, the number of cases in the low exposure range might still be too small to yield the effect resolution we're looking for. Therefore, this is the time to consider further updating the parent cohorts to identify more cases. Note for example, that in the IOL cohort that the case-control study was based on only 11% of the cohort had died (3909/34597). This is a low percentage and may not be representative of the cohort's exposure experience so updating the vital status of cohort members is probably a good idea. To save time, this phase could be started as soon as it appeared that the exposure rationalization was going to be successful.

4. Conduct the pooled case-control analysis using "modern statistical methods". Since the issue here was the elimination of arbitrary exposure categorizations, I suspect the goal is to use a regression technique. My caveat here is that we need to be careful that the analysis is not limited to, or for that matter, even includes, (log) linear models. Instead, a general additive model might be the default used. Note that there is another implication of using nonlinear models -- namely, average or unweighted cumulative exposure metrics will not be particularly meaningful. Consequently, some special modeling may be needed to pursue the application of a nonlinear exposure-response curve. Note that, instead of using regression techniques, the arbitrariness of exposure categorization can be looked at by testing different category cutpoints and seeing the impact on the leukemia risk. I'm not sure how one would interpret the results if we found the effect was very sensitive to the cutpoint, but it might tell us something about our data.

5. Sensitivity modeling of exposure-response curve. While the essence of this task might contained in the analysis as I've described it in Phase 4, I don't think doing a sensitivity analysis for its own sake is worth it. If the modeling results are similar, we've not learned very much other than may be our data is lacking in its ability to achieve the resolution we are interested in. On the other hand, if the results of different exposure-response models are different, we will have interpretability problems since we lack the golden ruler to tell us which is correct. I would pursue sensitivity modeling only if we had leftover funding.

Ken Satin, DrPH

ksat@chevron.com **NEW**
Staff Epidemiologist
Chevron Energy Technology Company **NEW**
100 Chevron Way
Richmond, CA 94802

T: 510 242-1610 F: 510 242-7022

-----Original Message-----
From: Urbanus Jan [mailto:jan.urbanus@concawe.org]
Sent: Tuesday, May 24, 2005 6:21 AM
To: Satin, Ken (KSAT); shan.tsai@shell.com; chris.money@exxonmobil.com; gswaen@dow.com; geert.dejong@shell.com; rolf.ahlberg@nesteoil.com; jean-philippe.gennart@total.com; chris.roythorne@uk.bp.com
Subject: Scoping of benzene pooled epidemiological analysis

Dear Colleagues,

As requested at our recent Health Management Group meeting, I have drafted a first attempt at scoping out a pooled analysis project of the 3 nested case-control studies of

benzene-exposed workers (attached). I would like to encourage you to comment on this via the 'reply all' function, so that we can develop this idea further into a more realistic scope.

Please note I have agreed with Louis Bloemen that he would contribute to the Benzene DCR project as a consultant (after leaving Concawe member company Dow) up to the finalisation of the Phase 1 IOM/IRAS report, and hence he is not part of this next stage. I have included the remaining STF-30 members (Ken and Shan), supplemented with some HMG members – I trust you don't mind, but please advise if you feel we need others to contribute as well.

Jan Urbanus

Technical Coordinator, Health Issues

CONCAWE (the oil companies' European organisation for environment, health & safety)

Boulevard du Souverain, 165

B-1160 Brussels, Belgium

T: +32-2-566 9163

F: +32-2-566 9181

E: jan.urbanus@concawe.org

W: www.concawe.org