Comments from Members of the Chartered SAB on the SAB Draft Report: Science Advisory Board Review of the EPA's Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide (April 27, 2015)

List of comments received as of June 2, 2015

Comments from Lead Reviewers

Comments from Dr. Thomas Burbacher

1) Were the charge questions to the committee adequately addressed?

The Quality Review focused on questions related to 4 aspects of the report on ethylene oxide (EtO) 1) exposure-response modeling, in particular exposure lagging, 2) model selection for breast cancer, 3) model selection for lymphoid cancer, and 4) uncertainty in the cancer risk estimates. In addition, the review provided 5) comments related to the accuracy, objectivity, and transparency of a summary of studies related to the genotoxicity of EtO and an evaluation of responses to a previous (2007) external review, 6) an evaluation of the completeness and clarity of descriptions of new studies and, 7) an evaluation of the responses to scientific issues raised in previous public comments. Overall, I would say that the charge questions to the committee were adequately addressed, although there are a few areas where improvements can be made for charge questions 1, 2, 3, and 4 (see answers below). In general, there were numerous recommendations presented for each of the charge questions, mostly with the intent to strengthen or clarify the proposed approaches (except for the model selection for lymphoid cancer).

2) Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

For charge question 3, the use of categorical results as the preferred model for derivation of the (low exposure) unit risk estimate for lymphoid cancer, the review indicates that rationale for the decision to use categorical results is "lacking and not transparently communicated" and recommends the use a model using individual-level exposure data. It would be helpful for the reviewers to include a summary of the discussion of this issue included in the report and indicate why they believe it is not appropriate. A discussion of this issue on page 4-11of the report indicates that the overall fit of the models using the continuous data resulted in very steep slopes in the low exposure range and that there was "low confidence in the slope given that it is based primarily on a relatively small number of cases in the low-exposure region". It would be appropriate for the review to summarize this information and indicate why there is disagreement with these conclusions.

3) Is the draft report clear and logical?

I would suggest that a summary of recommendations be provided for charge question #1. It is not clear from the comments regarding the CDC 9-11 Working Group Guidelines and the sensitivity analysis recommendations, just what is being requested. Summary recommendations were provided for the other charge questions and it was very helpful. In addition, it would be helpful to indicate that there is support for the EPA's selected model for breast cancer at the beginning of the section for charge question #2, given the extensive discussion of other approaches that is included in this section. For charge question #4, it is unclear to me what limitations there are in accessing the NIOSH data and how those limitations affect risk assessment. There is an extensive discussion of data availability for the NIOSH study. From this discussion, it is clear that the EPA does not have a copy of the NIOSH modeled exposure data, yet the review

recommends a rather extensive summary of these data, assuming they can be obtained. It would seem that after all of these years, that this may not be a good assumption. The review also includes some suggestions for making the discussion regarding deriving risk estimates more appropriate for a “broader audience”, yet it is not clear just who this “broader audience” is and how the suggestions would accomplish this.

4) Are the conclusions drawn or recommendations provided supported by the body of the draft report?

The recommendations are supported by the body of the draft report, except for the issues discussed above.

Comments from Dr. Gina Solomon

1. *Were the charge questions adequately addressed?*

Yes, the charge questions were adequately addressed. The response to question 2a, on the model selection for the breast cancer endpoint, was the only one that was a bit confusing to read. In particular, the paragraph on p. 10, lines 6-25 is not very clear. It's not clear to this reviewer what "more informed use of AIC" means, or what "a better balance between assessment of model fit, a priori considerations regarding the nature of the functional form being applied, and biological considerations of the resulting dose-response estimate" means. These sentences have a bit of a 'read my mind' tone to them, and it's hard to know exactly what the Panel is recommending. This paragraph would probably read more clearly if the section from lines 12-15 were deleted or clarified.

The response to question 2a is also confusing because the subsequent paragraph, starting on line 27 of the same page, also talks about the model, and some of the statements appear to be inconsistent with those in the previous paragraph. It reads as if two different people wrote these paragraphs, and then they were pasted in next to each other. It might be good to try to blend the discussions a bit more and make the flow a bit clearer throughout this section.

In contrast, the response to question 2b is extremely clear and well-written, and the discussion of the AIC on p, 14 is much clearer than in question 2a. Perhaps this discussion could be referenced in the earlier section?

In addition, the slightly confusing language in this section is picked up in the Executive Summary p. 2 lines 1-4, so that might need to be clarified too.

2. *Are there are any technical errors or omissions in the report or issues that are not adequately dealt with in the draft report?*

No, I did not find any technical errors or omissions, or issues that were not adequately addressed.

3. *Is the draft report clear and logical?*

Yes, the flow is very clear and logical, and the letter and ES pick up almost all the key issues.

There is a recommendation on p. 11, lines 32-34, that might be worth including in the Executive Summary, since it's a fairly concrete recommendation.

4. *Are the conclusions drawn or recommendations provided supported by the body of the draft report?*

Yes, the conclusions and recommendations are well-supported.

Comments from Dr. Daniel O. Stram

1. Were the charge questions adequately addressed?

It is clear that the SAB review has been extensive and useful and that the charge questions have been addressed fully. Below I have focused mostly on the few items that I found myself not in close agreement with.

Exposure lagging: The SAB review correctly indicates that sensitivity analyses should be performed and I agree with this recommendation. Lags are a little tricky in my view. Even if hazards are immediately increased it can take years before excess risks are detectable. Moreover identifying lag times (latency times) on the basis of the MLE fit to the dataset being analyzed is somewhat problematic since any given study has considerable uncertainties in the estimate of "best lag". The choice of a lag period for a mutagenic outcome should in principle be based upon an assessment of the amount of time required for a detectable cancer to develop from a damaged single cell; such an assessment would benefit from contributions from a variety of epidemiological and laboratory studies and not simply be based on empirical fitting to the single dataset being considered. **This comment however only reinforces the suggestion that EPA should report on sensitivity analyses employing various lag periods.**

Breast Cancer incidence: The SAB review expresses preference for models that are sensitive to the local behavior of the data so that the estimate of response to low exposures is not unduly influenced by the estimate of high exposure response. While this would be the ideal the available data may not be rich enough to allow this separation. The plot of the data in Fig 4.4 of the IRIS evaluation does seems to indicate a slight non-linearity however this plot may be misleading without error bars for the curves or categories that are being fit. It would appear from the descriptions in the both the published paper by Steenland et al 2003 and in the IRIS evaluation, that the fit (likelihood) of all of the models are really quite similar to each other, and that the response to exposure is only marginally significant in any of them. In such a situation a fall back of an assumption of linearity for a mutagenic exposure, seems useful for estimating low-exposure effects, since the low exposure data itself may be too limited to distinguish between the various models considered.

Selection of knots: For the reasons above I think that more serious consideration should be given to the simplest linear models for breast cancer incidence (linear in cumulative EtO exposure). The procedure for picking a knot is not particularly transparent given that the statistical support for the need of a spline rather than a purely linear exposure-response function is weak.

Lymphoid Cancer: The SAB review makes an excellent suggestion that additional rationale

should be provided for EPA's choice of models and for more display of alternative model results. However I think that the SAB review's preference for the cubic spline and other strikingly non-linear models runs the risk of over-interpreting limited data. Considering the confidence intervals on the points plotted in Fig. 4.1 of the EPA evaluation (confidence intervals for the categories are given in Table 4.2) it would appear that most of the data is consistent with linearity in exposure-response with the possible exception of the largest EtO exposure group. The EPA choice of using the linear fit to the categorical data excluding the largest exposure group is consistent with the general philosophy that (for mutagenic exposures) linear models should be preferred for extrapolation into low exposure regions (where the data itself is too weak to distinguish between response models).

Uncertainty:

The SAB review has identified key uncertainties including

a. The uncertainties in the exposure estimation especially in the construction of the historical estimates (prior to 1975) not based on direct measurements, including the potential for systematic error in the historical estimates which would generally be multiplicative (additive in the log of exposure). These uncertainties are compounded by the evident loss of the data used to develop the exposure model
b. Uncertainties in lag selection to account for latency times
c. Uncertainties due to there being only being one dataset (the NIOSH study) used to estimate effects. However I disagree with the review about the value of the Mikoczy et al (Swedish cohort) at reducing such uncertainty. The doses there are so low (median cumulative exposure is about $1/50^{th}$ of that in the NIOSH study) and the effects so large (and based on so few breast cancer cases) that I feel that these results are if anything best viewed as contradictory to the NIOSH study results rather than complimentary to them.
d. Uncertainty in the "results given the data" which have to do with the many modeling choices (lags, model forms, etc) needed in the modeling.

The SAB review makes some very reasonable recommendations to EPA including obtaining the exposure estimates from NIOSH and providing tables and figures of the distribution of predicted exposures in the NIOSH dataset, as well as summaries of exposures and other relevant variables for cases and controls. A key issue is whether allowance for exposure uncertainty especially for the earlier time periods should affect the interpretation of the apparent non-linearity in response seen especially for lymphoid cancer.

One omission in the discussion of uncertainty then, is that the larger uncertainties in the Hornung et al exposure reconstruction when it is applied to the earlier years may provide a possible reason for the apparent downturn at highest exposures in the cancer response: since higher exposures correspond to earlier employment times when the exposures are least certain. Exposure uncertainty could affect exposure response shape, especially at the higher exposures, and could provide some additional rationale in favor of EPA's dropping the highest exposure category from the overall dose response analysis of this cohort.

Questions 5-6: Overall I feel that these were dealt with very well.

2. Are there are any technical errors or omissions in the report or issues that are not

adequately dealt with in the draft report?

Generally I think that this has been a very extensive and useful review free of errors or major omissions

3. Is the draft report clear and logical?

The report is written clearly and should be easily intelligible to the EPA authors of the EtO evaluation.

4. Are the conclusions drawn or recommendations provided supported by the body of the draft report?
Yes in general the committee has done an excellent job of dealing with the tasks at hand and the recommendations are generally solid. I disagree with one or two, such as advising the EPA to give more weight to highly non-linear models for the lymphoid cancer data. In general I don't think that with the available data from NIOSH it is really possible to separate risk estimation at low exposures from the response seen at higher exposures. If so is then linear extrapolation from high to low exposure for EtO would seem to be consistent with EPA's *Guidelines for Carcinogen Risk Assessment* (2005) as cited on page 4.

Comments from Dr. John Vena

Science Advisory Board (SAB) review of the draft carcinogenicity assessment developed in support of the Integrated Risk 20 Information System, Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide (Revised External 21 Review Draft - August 2014.

1. Were the original charge questions to SAB Standing or Ad Hoc Committees adequately addressed?

I extend my compliments to the Panel for the comprehensiveness and thoroughness of their review. The review is exceptional in content and format. Explicit recommendations are made after very well written responses to the questions, thoughtful critique of document and justification for the recommendations that follow. In my opinion the first three charge questions were very effectively answered. It is noteworthy that they developed well articulated responses and complemented them with very detailed feedback with superb comments and recommendations.

The answer to Charge Question 4 was excellent. However the headings were confusing to me and I suggest clarification: "Uncertainty due to the data (particularly from reliance on a single dataset) and Uncertainty of the results given the data". Charge Question 5 answer was written masterfully.

See below for specific comments and a few corrections. Clarification is requested in the recommendation that inclusion of the new studies would not substantially alter the findings of the assessment, with the exception of the Mikoczy et al. study of Swedish sterilization workers, which can strengthen support for the hazard characterization of EtO and provide support for the

modeling of the NIOSH data. Why not include it if it would strengthen the assessment?

2. Are there are any technical errors or omissions in the report or issues that are not adequately dealt with in the Committee's report?

None that I can tell based on my expertise.

3. Is the Committee's report clear and logical?

The **cover letter** is concise and the text very effectively highlights the major recommendations. The letter captures the sentiments of the full review report.

The **executive summary** is well done and provides an excellent overview of answers to charge questions and recommendations.
Page 5 lines 1-6. Given the fact stated why not include the Swedish study in the assessment?

Page 8 lines 30-33 These statements seem contradictory and the meaning is not clear

Page 10 lines 17-25 excellent comments and well written

Page 11 lines 9-20 very clear and compelling explanation for recommendations regarding model fit

Page 13 lines 17-19 This recommendation is important for clarity and transparency

Page 20 lines 16-19 clarification needed here on what they mean by "highlighting how the study supports the conclusions reached from the NIOSH data?

Page 21 lines 16-19 not sure I agree with this recommendation. it seems to me that this would make the report cumbersome.

4. Are the conclusions drawn or recommendations provided supported by the body of the Committee's report?

Yes. In my opinion the report is very well written and comprehensive in responses to the charge questions.

t

Comments from other SAB Members

Comments from Dr. Joseph Arvai

1. Were the charge questions adequately addressed?

Yes.

2. Are there are any technical errors or omissions in the report or issues that are not adequately dealt with in the draft report?

Not to my knowledge.

3. Is the draft report clear and logical?

Yes.

4. Are the conclusions drawn or recommendations provided supported by the body of the draft report?

Yes.

Comments from Dr. Ingrid Burke

1. Were the charge questions to the committee adequately addressed:

Yes. Each section provided a thorough response to the charge questions.

2. Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

Not that I could see.

3. Is the draft report clear and logical?

Yes. This is among the clearest of the reports that I have read lately.

4. Are the conclusions drawn or recommendations provide supported by the body of the draft report?

I had a little concern with the letter to the Administrator, as I don't think it represents well the

document that it introduces. The bottom of the first page more or less says "good job; implementing these suggestions won't take long". Then the rest of the documents go on to describe fairly serious changes in models that are needed (i.e. from model selection to regression), major justifications or discarding key assumptions (i.e. the "too steep" criterion, which frankly sounds very risky and I'm glad the committee asked for justification), different data sets, and major expansions of discussions. In fact, I was very surprised to read about the depth and breadth of changes the committee was recommending, after reading that introductory statement. It seems to me that the letter to the administrator should be introduced a little more carefully.

Second, if all of these recommendations are equally important, the report is fine as it is, but the committee needs to recognize that they are extensive. If they are not equally important, could some kind of language be used to indicate priority? Is length of time that has gone into the EtO important, given that this is already a re-run? Is there a cost-benefit analysis the committee could use to thinking about the delay that these recommendations would cause, or are they all so important that any amount of time should be used to implement them?

Comments from Dr. Costel Denson

General Comments.
This report is well written, well organized, and uncommonly thorough.

1. Were the charge questions adequately addressed?
    Yes. There were seven complex questions. They were all thoroughly addressed.

2. Are there any technical errors or omissions in the report or issues that are not adequately dealt with in the draft report?
    All issues were adequately addressed. This report is extremely thorough.

3. Is the draft report clear and logical?
    Yes

4. Are the conclusions drawn or recommendations provided supported by the body of the report?
    Yes. Without question.

Comments from Dr. Michael Dourson

1. Were the charge questions adequately addressed?

The committee appears to have addressed several of the given charge questions well.

2. Are there are any technical errors or omissions in the report or issues that are not adequately dealt with in the draft report?

Please see response to question 4.

3. Is the draft report clear and logical?

Yes, the report was very easy to read and it generally made sense.

4. Are the conclusions drawn or recommendations provided supported by the body of the draft report?
Many of the conclusions seemed reasonable. Other lines of thought were not as clear. In particular,
Page 4, line 7. Prior SAB recommendations. Did data occurring in the intervening 7 years resolve this disagreement in the prior SAB? Is the newer SAB panel in complete agreement with excluding these 4 prior recommendations?
Page 8, line 23. On lag time of the models. How much does the use of different lag periods quantitatively affect the cancer hazard identification and dose response assessment? 3-fold? more than 10-fold?
Page 21, line 11. Uncertainty discussion. Whereas the discussions on uncertainties associated with choice of data, exposure profiles and model quantification all seem reasonable, I am surprised that the biological uncertainties associated with the type of tumor evoked and underlying mode of action are not discussed. Did the spectrum of toxicity evoked from EtO exposures in the workplace only result in breast and lymphoid tumors? What kinds of noncancer toxicity may or may not have played a role in tumor formation? How was endogenous exposure factor into this uncertainty discussion? If experimental animal data are being used to fill in some of these data gaps in the human information, how does the toxicokinetic and toxicodynamic differences with humans affect the uncertainty discussion?
Page 22, line 11. Reference to DNA adducts as a key event. My understanding, perhaps incorrect, is that DNA adducts are indicators of exposure, but it is the mutation that is the key event. If so, then reference to DNA adducts throughout this section as a key event is not appropriate, correct?
Page 22, line 31. Regarding genotoxic effects occurring at doses well below those required to induce cytotoxicity. This may be the case, but that does not rule out a dual MOA and different dose response assessment in different parts of the DR curve. See EPA (2005, page 3-22) where it states:
Both linear and nonlinear approaches may be used when there are multiple modes of action. If there are multiple tumor sites, one with a linear and another with a nonlinear mode of action, then the corresponding approach is used at each site. If there are multiple modes of action at a single tumor site, one linear and another nonlinear, then both approaches are used to decouple and consider the respective contributions of each mode of action in different dose ranges. For example, an agent can act predominantly through cytotoxicity at high doses and through mutagenicity at lower doses where cytotoxicity does not occur. Modeling to a low response level can be useful for estimating the response at doses where the high-dose mode of action would be less important.
Page 24, line 30. Lack of noncancer evidence. So what is the noncancer toxicity not occurring in the breast tissue that leads the SAB to conclude this?
Page 26, line 40. Clarity needed. What does this sentence mean? At some point in the low dose extrapolation of exogenous EtO response, the endogenous EtO WILL overwhelm the exogenous

exposures. At what extrapolated risk does this occur please?
Page 27, line 33. Precursor events in humans. Has the lack of precursor data in humans evident in the 2007 SAB review been addressed by additional data? If not, how has this impasse been resolved? If resolved through the use of data from experimental animals, do these animals get the same kinds of tumors as humans? If not, this is a biological uncertainty that should likely be discussed.
Page 32, line 33. Reference to industry comments. This is an *ad hominem* comment that is inappropriate in an SAB report.
Page 33, line 31. Multiple MOAs. In this SAB's opinion, are the data not sufficient to support a dual MOA hypothesis, similar to what is found in EPA (2005, page 3-22), as mentioned above?
Page 35, line 1. On endogenous levels. So is the 10-6 virtually safe dose higher than the expected endogenous level? What is the estimated risk at the endogenous EtO exposure?
Page 35, line 7. EPA's OPP values. So how do the OPP and IRIS cancer slope factors compare? Are these two EPA groups working together, or do we have different risk assessments?

Comments from Dr. Robert J. Johnston

1) Were the charge questions to the committee adequately addressed?

Yes, the report has adequately addressed the charge questions.

2) Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

There are no technical errors or omissions that are not adequately addressed by the draft report.

3) Is the draft report clear and logical?

Yes, the draft report is clear and logical

4) Are the conclusions drawn or recommendations provided supported by the body of the draft report?

Yes.

Comments from Dr. Nancy K. Kim

General Comment

The report was well written and, in general, easy to follow. In a few places, a few additional

summary phrases could be added to make it easier follow for the reader who hasn't read the assessment it self or isn't familiar with technical issues.

1. Were the charge questions to the committee adequately addressed?

Yes.

2. Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

Not that I noticed.

3. Is the draft report clear and logical?

For the most part, yes.

Report

a. Page 9, line 21. Adding one sentence to this paragraph about the lagging recommendations in the previous paragraphs would summarize the response to this charge question nicely.
b. Page 10, line 12. Providing specific advice or examples explaining "more informed use of AIC" would be helpful.
c. Page 13, line 22. If the committee has additional advice about "using somewhat different considerations for comparing AICs" elsewhere in its report, adding that page number here would be helpful.
d. Page 33, paragraph starting on line 31. Assuming I have interpreted this paragraph correctly, adding a phrase such as "and thus the data do not support the claim of a non-mutagenic MOA. Such an addition would help ensure that the reader understood the point the committee was making.

4. Are the conclusions drawn or recommendations provided supported by the body of the draft report?

Yes.

Minor comments

1. Page 11, line 41. Check spacing. May need to add a blank line if line 41 starts a new paragraph.
2. Page 17, line 36. Need to add a blank line after charge question and remove bank line on line 38.
3. Page 28, line 28. Does a blank line need to be added here?
4. Page 33, line 17. Need a blank line.
5. Page 35, line 15. Need a blank line.

Comments from Dr. Lois Lehman-McKeeman

The charge questions have been adequately addressed, and the report is well-organized. A substantive portion of the review focused on the responses to public comments, The review has addressed all of the relevant new information since the 2007 review, and there is a careful, complete response to public comments. The review is very clear, and presented logically, and its

recommendations and suggestions are well articulated. All of the conclusions drawn are supported within the body of the draft report.

The response to the charge question regarding accuracy, objectivity and transparency is very well organized and summarized. The specific suggestions provided (page 23 of the EtO report) will help to further improve this section.

Comments from Dr. Elizabeth Matsui

Were the charge questions adequately addressed?

YES

Are there any technical errors or omissions in the report or issues that are not adequately dealt with in the draft report?

For toxicology- and risk assessment-related content, I will defer to the reviewers with toxicology and risk assessment expertise

Is the draft report report clear and logical?

Yes, overall, the draft report is very clear and logical.

Are the conclusions drawn or recommendations provided supported by body of draft report?

YES

Comments from Dr. James R. Mihelcic

1. Were the charge questions adequately addressed?

Yes

2. Are there are any technical errors or omissions in the report or issues that are not adequately dealt with in the draft report?

No

3. Is the draft report clear and logical?

Yes, for example, responses to the 2007 SAB Comments is clear to logical.

4. Are the conclusions drawn or recommendations provided supported by the body of the draft report?

Yes,

Other issues

Should spaces be added between text on lines 42-43 of page ii (page 6 of pdf), between text on lines 38-39 of page 12 (page 24 of pdf), and text on lines 36-37 of page 17 (line 29 of pdf)?

Comments from Dr. James Opaluch

1) Were the charge questions to the committee adequately addressed?

Yes

2) Are there any technical errors or omissions or issues that are not adequately dealt with in

the draft report?

Not that I am aware of.

3) Is the draft report clear and logical?

Yes

4) Are the conclusions drawn or recommendations provided supported by the body of the draft report?
Yes

Comments from Dr. Amanda D. Rodewald

1) Were the charge questions to the committee adequately addressed?

Yes. The draft report was thorough and provided useful feedback to the Agency.

2) Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

No. I did not find any errors or omissions, but this is outside of my area of expertise.

3) Is the draft report clear and logical?

Yes.
Parsimony could be better defined on lines 31-32 of page 13. Perhaps something like, "given multiple hypotheses, the simplest one (i.e., with fewest parameters) is preferred". I was unclear on what was being suggested in the subsequent sentence on lines 35-37 and recommend clarifying.
Page 14, lines 8-11. I suggest leading with the connection and relevance to the draft report rather than more general statements about statistics.
Page 14, lines 22-30. This section provides useful guidance on the underlying assumptions and requirements of AIC. Another that might be added is that each of the analyses that are associated with competing hypotheses must use the identical dataset, in terms of number of observations.

4) Are the conclusions drawn or recommendations provided supported by the body of the draft report?
Yes.

Comments from Dr. Charles Werth

1) Were the charge questions to the committee adequately addressed?

Yes, they were adequately addressed.

2) Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

I did not find any technical errors or omissions.

3) Is the draft report clear and logical?

Overall it was exceptionally well written, clear and logical. A few minor suggestions are provided for clarity.

i) Page 2, lines 35: Recommend adding sentence to the executive summary noting that "The linear model does not appear appropriate because the risk increases faster at lower exposure." Presently there is not a rationale provided for discounting the linear model in the executive summary and this additional sentence would make the reason more clear.

ii) Page 3, line 13: Should this be "model results" instead of just "results"? If so, please modify.

iii) Page 21, line 25: "rich set of models" seems a bit vague. Should this be more detailed?

4) Are the conclusions drawn or recommendations provided supported by the body of the draft report?

Yes, the conclusions and recommendations are supported by the body of the draft report.

Comments from Dr. Dawn J. Wright

1. Were the charge questions adequately addressed? Yes, as far as I could tell.
2. Are there are any technical errors or omissions in the report or issues that are not adequately dealt with in the draft report? Not that I am aware.
3. Is the draft report clear and logical? Yes
4. Are the conclusions drawn or recommendations provided supported by the body of the draft report? Yes, as far as I could surmise