

**MINUTES OF THE TELECONFERENCE**  
**OF THE PQRI LEACHABLES AND EXTRACTABLES TOXICOLOGISTS ON**  
**17 DECEMBER 2004**

**I. PARTICIPANTS**

Doug Ball (Pfizer)	Ron Wolff (Nektar)
Tim McGovern (FDA)	Mark Vogel (Pfizer)
Roger McClellan (University of New Mexico)	Melinda Munos (IPAC-RS)
James Blanchard (Aradigm)	Lana Lyapustina (IPAC-RS)

**II. OPENING**

Ms. Munos opened the meeting and reminded the participants of the competition guidelines that govern their discussions and cautioned against any reference to commercially sensitive information. Mr. Ball welcomed participants to the Working Group teleconference and reviewed the proposed objectives of the meeting: (i) to discuss the revisions to the Threshold Justification; (ii) to review the SAR Summary; (iii) to plan for presentations and publications; and (iv) to agree on next steps.

**III. DISCUSSION**

*Revisions to Threshold Justification*

Dr. Vogel provided an overview of his revisions to the Threshold Justification showing the implications of setting the SCT at 0.15 µg/day. He explained that this change would have a negligible effect on the threshold, and that the science and rationale presented in the Threshold Justification would support a move to 0.15 µg/day. He reviewed the additional compounds from the CPDB database of SAL positive carcinogens that would fall between a 0.1 µg/day threshold and a 0.15 µg/day threshold, and noted that none of them are likely ingredients in plastics, elastomers, or other container closure system components. Therefore, no compounds would need to be added to the "special concern" list. Moreover, he noted that an SCT of 0.15 µg/day would be consistent with the CFSAN threshold for highly potent carcinogens.

Participants agreed with Dr. Vogel's analysis of the implications of moving the SCT to 0.15 µg/day. They noted that it seemed reasonable to make this change. Ms. Munos informed participants that she had consulted with Dr. Norwood, who had confirmed that moving the SCT to 0.15 µg/day would not be problematic from the chemistry perspective, provided that no compounds were added to the "special concern" list. Participants confirmed that they saw no reason for adding any compounds to this list.

Dr. McClellan reviewed the proposed addition to the Threshold Justification that he had drafted, discussing the SCT in the context of ambient levels of PAHs. He explained that the

paragraph presented data from one of the papers discussed on the previous teleconference. Based on this data, Dr. McClellan explained that he had calculated the TDI of ambient levels of PAHs in California to be 5.2 µg/day, 12 µg/day, and 1.4 µg/day, depending on the site. He noted that while these levels are higher than the proposed SCT, they do not necessarily support raising the SCT to 1.5 µg/day. Because ambient levels of PAHs (and presumably other leachates) are high, the Group should avoid adding to the bio-burden of respiratory patients by minimizing the levels of leachates in OINDP products. He noted that this rationale was reflected in his paragraph.

Participants discussed this data. They agreed that ambient levels of PAHs should not by themselves dictate the level of the SCT, but should instead be viewed in the context of other scientific, policy, and practical considerations. They noted that patients who use OINDP typically have compromised respiratory systems and use the products chronically over their lifetime, increasing their lifetime exposure to any leachates present. They also raised concerns about the potential for irritation or sensitization from some leachates at the 1.5 µg/day level. These scientific considerations call for a conservative approach to setting the level of the SCT. Furthermore, participants noted that from a quality perspective, a less rigorous approach to quality control of elastomers and plastics would be necessary with an SCT of 1.5 µg/day. Current quality control practices are quite rigorous, and have improved significantly over the past 30 years. An SCT at the level of 1.5 µg/day might give the impression that a decline in component quality would be permissible, and would give OINDP manufacturers and suppliers little guidance regarding quality control. Participants agreed that a decline in quality was not desirable.

Based on these considerations, participants agreed that it seemed reasonable and justifiable to move the SCT to 0.15 µg/day rather than 1.5 µg/day. An SCT of 0.15 µg/day would be consistent with current U.S. regulatory practice, as discussed on the previous teleconference, and with the CFSAN threshold for highly potent carcinogens. Dr. McGovern agreed to convey this proposal and these considerations to the relevant chemists and toxicologists at FDA, including Dr. Jacobson-Kram. Participants agreed that a teleconference with the FDA chemists and a teleconference and/or meeting with the FDA toxicologists might be helpful in achieving consensus on this issue. Dr. McGovern agreed to provide the Group with an update on his discussions by January 14, 2005, and to advise the Group at that point whether a teleconference/meeting would be necessary.

Participants agreed that it might be helpful to add Dr. McClellan's paragraph to the Threshold Justification in addition to Dr. Vogel's revisions, but that no changes should be made to the document pending feedback from FDA on the SCT level.

### ***SAR Summary***

Participants discussed the current version of the SAR Summary, dated 24 September 2004. Dr. McGovern noted that this version contains some additional text, which he had provided, in Section III and that this text still needed to be reviewed by the Group. Participants discussed the placement of this document and agreed that it should serve as a bridge between the Threshold Justification and the Chemistry Recommendations. They also noted that it might

be desirable to include a paragraph in the introduction to the SAR Summary or the Threshold Justification (or both) describing the scope of the document and explaining that it is not intended to provide a prescriptive description of how to perform a safety evaluation on a compound. Participants also proposed that a branch could be added to the top of the decision tree describing the treatment of especially toxic leachables. However, they decided that no changes to the document should be made until all toxicologists have re-reviewed both the Threshold Justification and SAR Summary in full. During this review, the toxicologists should note any inconsistencies, errors, or other necessary revisions. These revisions will be discussed on the next call of the toxicologists, following which the documents may be finalized.

### *Presentations and Publications*

Due to time constraints, participants agreed to discuss this item on the next call. Mr. Ball requested, however, that in advance of the next call, participants consider who should be invited to the PQRI L&E Workshop as a speaker or attendee. Furthermore, he noted that the Group would need to begin planning immediately for a presentation at SOT 2006 when calls resume in January.

### *Next Steps*

Participants agreed to re-review both the Threshold Justification and the SAR Summary in full in advance of the next call of the toxicologists. On that call, participants will (i) determine whether any further dialogue with FDA on the level of the SCT is necessary; (ii) discuss any final revisions or additions to the Threshold Justification or SAR Summary; and (iii) discuss the PQRI L&E Workshop and SOT 2006.

## **IV. AGREED ACTIONS**

- The Working Group Toxicologists will review both the Threshold Justification and the SAR Summary in full in advance of the next call and note any necessary revisions or additions;
- Dr. McGovern will discuss moving the SCT to 0.15 µg/day rather than 1.5 µg/day with relevant FDA chemists and toxicologists, will convey to them the rationale for this change, and will provide the Group with an update by January 14, 2004; and
- The Working Group Toxicologists will consider who should be invited to the PQRI L&E Workshop as a speaker or attendee.

## **V. NEXT TELECONFERENCE**

The next teleconference of the toxicologists is scheduled for 1:30 PM EST on 14 January 2005 for 90 minutes.

*Finalized January 24, 2005*