I. PARTICIPANTS

Doug Ball (Pfizer), Chair
Jim Blanchard (Aradigm)
Tim McGovern (FDA)
Lee Nagao (IPAC-RS)
Mark Vogel (Pharmacia)
Ron Wolff (Lilly)

II. OPENING

Mr. Ball opened the teleconference and reviewed the objectives: (i) to discuss the draft Threshold Justification, (ii) to discuss development of a safety qualification decision tree, (iii) to discuss potential peer reviewers of the justification, and (iv) to agree on next steps.

III. DISCUSSION

Dr. Vogel provided an overview of abstracts he had collected, which provide further support to the approaches used to derive the toxicological concern threshold (TCT) in the Justification. These include reference to EPA’s use of the $10^{-6}$ carcinogenicity risk level for water quality criteria for States and Tribes, which EPA believes “reflects an appropriate risk for the general population.” He also noted the World Health Organization’s (WHO) guidelines for drinking water quality, and its use of a less conservative risk level of $10^{-5}$. The publication also notes WHO’s decision not to use scaling factors to adjust for carcinogenic effects in humans from rat and mouse data, and that WHO considers use of such a scaling factor to be “overly conservative.” Participants agreed that text addressing the WHO reference should be included in the Threshold Justification, since such text would add further credence to the Justification, which uses the more conservative $10^{-6}$ carcinogenicity risk level and scaling factors.

Dr. Wolff provided an overview of his approach to deriving typical thresholds for irritants contained in the Justification. He agreed to provide further text describing his approach and rationale. He noted that a larger number of compounds should be examined, and that a curve, analogous to the carcinogenic potency curves generated by Dr. Vogel for the TCT, should be developed to demonstrate safe levels of irritants. Data from the Schaper article, “Development of a database for sensory irritants and its use in establishing occupational exposure limits,” could be used to produce the curve. Dr. Blanchard and Dr. Wolff will speak further with the authors to possibly obtain the data in electronic form.

Participants reviewed other proposed revisions to the Justification, which were agreed to at the 6 February face-to-face meeting of the full Working Group. Participants agreed that
Dr. Nagao will include language in the Justification’s introduction noting that thresholds for compounds with special toxicological concerns such as PNA’s, nitrosamines, mercaptobenzthiozoles, etc. should be determined on a case-by-case basis and that the thresholds proposed by the Working Group will not apply to such compounds. Dr. Nagao also agreed to add language to clarify the purpose of the TCT.

Dr. Vogel will add language addressing OINDP products other than MDIs. He also agreed to clarify the Munro table, which describes development of the FDA’s threshold of regulation. The table, which was originally presented during the 6 February meeting, will eventually be added to the Justification. Clarification will include changing the values to reflect the probability of exceeding a given target risk (either $10^{-6}$ or $10^{-5}$) at different threshold values, and further text to guide the reader through the table.

Mr. Ball agreed to add text addressing residuals from sources other than components (for instance, drawing oils, cleaning solutions, etc.). He will also add language addressing metals and sensitizers. Dr. Blanchard agreed to develop text that addresses the current state of information on safe levels of leachable compounds for children. Dr. Blanchard reminded participants that the toxicologists still need to consider the validity of the position that approaches for development of thresholds for leachables in OINDP have been held to a higher standard than those approaches in the ICH impurity guidelines because leachables are non-drug related impurities.

Participants discussed potential peer-reviewers of the Threshold Justification. Dr. Nagao will compile the list of proposed names for further consideration by the toxicologists.

IV. AGREED ACTIONS

- Participants agreed to revise the Threshold Justification as described above.

V. NEXT TELECONFERENCE/MEETING

The next teleconference of the PQRI Leachables and Extractables Toxicologists will be scheduled for mid to late March.

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