

MEMORANDUM

FROM: Jack E. Housenger, Associate Director
Health Effects Division
Office of Pesticide Programs

TO: Paul I. Lewis
Designated Federal Official for the Human Studies Review Board
Office of the Science Adviser

SUBJECT: OPP Comments on the Draft Report of the May 2 – 4, 2006, Meeting of the Human Studies Review Board

We appreciate the opportunity to offer comments on the draft report on the second meeting of the Human Studies Review Board (HSRB), held May 2 – 4, 2006. In general, the report captures the oral comments and conclusions made during the meeting. We also thank the Board members for the timeliness in preparing the report recognizing all the other work they have been tasked to do.

Staff in the Office of Pesticide Programs (OPP) has carefully reviewed the draft to identify any portions that are either unclear or inconsistent with our notes and understandings from the meeting. This memorandum identifies those areas in the draft report we believe could benefit from rewording and/or clarification as well as places in the text that appear to contain typographical or other minor editorial errors. It does not purport to state how EPA plans to act on the HSRB's recommendations. OPP will report to the Board at a future meeting how it has acted on its recommendations.

1. MITC

Page 3, lines 3 – 6

The Board reached its decision based on [the observation that eye irritation LOAELs are often lower than respiratory irritation LOAELs for irritant gases.](#)

Page 27, lines 2 – 5

[Since](#) The animal studies were either long-term inhalation or oral studies [and their use ; they were not considered for a point of departure and therefore](#) would be less protective of human health. [Thus, therefore,](#) the Board recommended the eye irritation [LOAL](#) [LOAEL](#) as a point of departure.

2. Chromium

Page 1, lines 34 – 36

The HSRB concluded there was insufficient information to determine whether the study failed to fully meet specific ethical standards prevalent at the time the research was conducted.

This summary conclusion is worded much stronger than the corresponding conclusion on page 16, lines 16 – 21 and therefore is misleading as a summary of the Board's stated consensus and rationale which reads:

"The Board based these two determinations on its conclusion that this study appeared to have not deviated significantly from the ethical standards prevailing when the study was conducted. However, this conclusion was based, in part, on a process that was hampered by a lack of supporting documentation concerning independent ethical review by the study investigators' home institutions. The Board strongly recommended that for all studies submitted to the HSRB, the Agency make a good faith effort to obtain such documentation in the future."

Page 9, lines 41 – 44

At the public meeting, following welcoming remarks from Agency officials, Celia B. Fisher, HRSB Chair, proposed a set of scientific and ethics criteria consistent with the language of 71 Federal Register 6137 to guide Board evaluation of each ~~protoeol~~ completed study.

Page 14, line 12

The study sponsor was unknown, but is likely to be either the Chem Risk Division of McLaren/Hart.....

Page 14, line 36

The Board concurred with the factual observations of the strengths and weaknesses of the study, as detailed in USEPA (2006a). However, further comments were raised regarding: 1) whether the documentation and process of study subject enrollment was sufficient to meet prevailing standards of voluntary informed consent and 2) whether the ~~repeat high-dose oral three step~~ exposure protocols used were designed to minimize risks to study participants.

Page 16, lines 1 – 3

Thus, the Board believed that there was not ~~was~~ clear and convincing evidence that these studies could have resulted in serious harm based on the knowledge available to the investigators at the time.

Page 27, lines 2 – 5

~~Since~~ The animal studies were either long-term inhalation or oral studies, ~~they were not considered for a point of departure and therefore their use~~ would be less protective of human health. ~~Therefore, they were not considered for a point of departure.~~ Thus, the Board recommended the eye irritation ~~LOAL~~ LOAEL as a point of departure.

3. Carbofuran

Page 21, lines 16 – 17

The Agency proposed to use the RBC cholinesterase data for determination of the ~~BMD_{40L}~~ BMD₁₀.

Page 21, lines 22 -24

As such, although a ~~BMD_{40L}~~ BMD₁₀ could be calculated, the magnitude of the error in the derived values would preclude a reliable, meaningful assessment.

Page 21, lines 22 -24

Therefore, the HSRB reiterated its recommendation that the human data should not be used for calculation of the BMD₁₀.

Page 18, lines 29 – 31

Maximal inhibition of RBC cholinesterase activity at this dose level was ~~45~~ ~~46~~ and 65% in the 2 subjects (4 hours), whereas plasma cholinesterase inhibition was maximal at 24 hours (12 and 16 %, respectively).

Page 20, lines 31 – 33

The weaknesses included the small sample size, the lack of control subjects, the highly variable results for RBC cholinesterase activity and the ~~inappropriate application methods~~ ~~improper dermal loading~~ used in the dermal studies.

Page 25, last line

The second dermal toxicity study was considered significantly deficient by ~~a majority of all~~ Board members ~~and fundamentally unethical by one~~ in that the lack of information provided about the results from the initial dermal toxicity study seriously impaired their informed consent.

4. COMMENTARY ON SCIENTIFIC STANDARDS FOR HUMAN DOSING STUDIES

Page 33

For the heading “Scientific Standards for Human Dosing Studies”, it is unclear whether the Board intends this to apply only to toxicity studies or all human dosing studies. Additionally, it is unclear whether the Board intends to have these scientific standards be applied to completed studies, proposed studies or both.

Page 34, lines 17 – 20

Scientific Standards for Single Dose Level Study

Board definition of single dose level study - individual study that uses one dose level ~~other than a control or placebo, irrespective of the number of subjects; or frequency of dosing, or inclusion of a control or placebo.~~