

201-14664

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13 August 2003

Ms. Marianne L. Horinko  
US Environmental Protection Agency  
1200 Pennsylvania Ave., N. W.  
Washington, DC 20460

Re: Revision of 2-Pyrrolidone (616-45-5) Documents  
Via Electronic Submission to: [Oppt.ncic@epa.gov](mailto:Oppt.ncic@epa.gov)

Registered with EPA as:  
BPPB Consortium, **Registration Number**

Dear Acting Administrator Horinko;

On behalf of the BPPB Consortium, Toxicology and Regulatory Affairs is hereby responding to the U.S. EPA's comments posted June 19, 2003 on the Chem-RTK HPV Challenge Web site for the Test Plan and Robust Summaries of 2-Pyrrolidone (616-45-5). The U.S. EPA's comments can be broadly grouped into two categories; testing related comments and comments pertaining to information in the Test Plan or Robust Summaries. The following are responses to the U.S. EPA's comments/questions based on these two groups:

#### **Testing Related Issues**

U.S. EPA Comment (1): EPA reserves judgment on the adequacy of available reproductive toxicity data pending receipt of more details of the histopathology on male and female reproductive organs from the submitted 90-day oral study in rats. These data, if adequate, plus data from the oral developmental toxicity study in rats will satisfy the reproductive toxicity endpoint for the purposes of the HPV Challenge Program. The submitter needs to include all relevant data in a separate robust summary for this endpoint.

BPPB Response (1): The reproductive organ histopathology in the 90-day oral study was extensive. Details of the methodology and findings were obtained and an additional robust summary was prepared addressing the histopathology of the reproductive organs. We believe that this additional information in combination with the developmental toxicity fully fills the HPV requirements for reproductive toxicity.

U.S. EPA Comment (2): For the acute fish toxicity study, the submitter needs to express the LC<sub>50</sub> as the geometric mean of the two highest concentrations in order to be consistent with OECD Guideline 203.

BPPB Response (2): The robust summary was modified to express the LC<sub>50</sub> as the geometric mean of the two highest concentrations according to the OECE 203 guidance.

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U.S. EPA Comment (3): The submitter needs to address more fully and, if possible, explain the disagreement between the EC<sub>50</sub> values reported for *Daphnia magna* (48-h EC<sub>50</sub> >500 mg/L and 96-h EC<sub>50</sub> >10,000 mg/L<sup>1</sup>) and *Daphnia pulex* (48-h EC<sub>50</sub> = 13.21 mg/L).

BPPB Response (3): Further investigation did not identify a definitive explanation for the differences in reported EC<sub>50</sub> values for these two species. On a weight of evidence basis, considering the actual data, data from similar compounds and the chemical structure, the low EC<sub>50</sub> value for *pulex* seems to be an outlier. This observation was added to the Test Plan and an extensive footnote was also added providing additional rationale supporting the reliability of the *Daphnia magna* EC<sub>50</sub> values.

### **Test Plan and Robust Summaries**

U.S. EPA Comment (4): Biodegradation. The robust summary of the 2-pyrrolidone study is unclear as to whether this is an inherent or a ready biodegradation study. The methodology is stated as following the Zahn-Wellens test procedure, which is used for testing inherent biodegradation. However, the summary states that it uses "non-adapted sludge flora," which indicates a ready biodegradation study. The summary also states that "...the conditions do not meet the OECD 301 series." The OECD 301 series is for ready biodegradation and the OECD 302 series is for inherent biodegradation. The test temperature was not reported.

BPPB Response (4): As stated, the study in question was a Zahn-Wellens test for inherent biodegradation. This has been further clarified in the robust summary. The temperature was not reported in the test data available. The order of the biodegradation summaries was changed to put the critical study first.

U.S. EPA Comment (5): For the acute mammalian toxicity test, the submitter needs to provide the following information: the length of the observation period, necropsy analyses (if performed), and a range or 95% confidence interval for the LD<sub>50</sub>.

BPPB Response (5): The requested information was added to the robust summary: however, as this was a limit test without mortality a 95% confidence interval cannot be calculated.

U.S. EPA Comment (6): For repeated-dose toxicity, the submitter needs to include the magnitude of the kidney weight changes and identify the organs that were examined for gross pathology and histopathology, especially those associated with reproduction.

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<sup>1</sup> The >10,000 mg/L value in the EPA comment is apparently a typo as the reported value is 96-hr LC<sub>50</sub> > 1,000 mg/L, not >10,000 mg/L.

BPPB Response (6): The requested information about kidney weight was added to the robust summary, as were complete lists of tissues examined at necropsy and examined microscopically. The reproductive organs were included in the lists and a more extensive description of the reproductive organ evaluation and results has been added in a separate robust summary under "fertility".

U.S. EPA Comment (7): The submitter needs to indicate whether the toxicity values from critical studies were based on measured or nominal concentrations and provide missing information on GLP compliance in the summary of the acute invertebrate study.

BPPB Response (7): The requested information was added to the robust summaries.

The Test Plan and Robust Summaries have been revised to incorporate the changes noted above. This completes the BPPB Consortium's commitment for 2-Pryollidone. Please contact me at (618) 539-5280 if you have any questions or comments.

Sincerely,

Elmer Rauckman, PhD, DABT  
Consulting Toxicologist

Attachments:

Testing Plan            616-45-5-Rev Test Plan.pdf

Robust Summaries    616-45-5-Rev RS.pdf