

August 26, 2003

Donald A. Lederer  
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Solutia Inc  
PO Box 66760  
St. Louis, MO 63166-6760

Dear Mr. Lederer:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for the Chloronitrobenzenes Category posted on the ChemRTK HPV Challenge Program Web site on April 23, 2003. I commend Solutia, Inc. for their commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed Comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that Solutia advise the Agency, within 60 days of this posting on the Web site, of any modifications to its submission. Please send any electronic revisions or comments to the following addresses: [oppt.ncic@epa.gov](mailto:oppt.ncic@epa.gov) and [chem.rtk@epa.gov](mailto:chem.rtk@epa.gov).

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-564-7649. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at [tsca-hotline@epa.gov](mailto:tsca-hotline@epa.gov).

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

Oscar Hernandez, Director  
Risk Assessment Division

Enclosure

cc: C. Auer  
R. Gonzalez  
W. Penberthy  
M. E. Weber

## **EPA Comments on Chemical RTK HPV Challenge Submission: Chloronitrobenzenes Category**

### **Summary of EPA Comments**

The sponsor, Solutia, Inc., submitted a test plan and robust summaries to EPA for the chloronitrobenzenes category dated April 9, 2003. EPA posted the submission on the ChemRTK HPV Challenge Web site on April 23, 2003. The category consists of three compounds: 1-chloro-2-nitrobenzene (CAS No. 88-73-3), 1-chloro-3-nitrobenzene (CAS No. 121-73-3), and 1-chloro-4-nitrobenzene (CAS No. 100-00-5).

EPA has reviewed this submission and has reached the following conclusions:

1. Category Justification. The submitter's support for grouping the chemicals in this category is adequate.
2. Physicochemical Properties. The data provided by the submitter for melting point, boiling point, vapor pressure, and octanol/water partition coefficient are adequate for the purposes of the HPV Challenge Program. The submitter needs to provide measured water solubility data for at least one additional chemical.
3. Environmental Fate. The data provided by the submitter for these endpoints are adequate for the purposes of the HPV Challenge Program. Although EPA agrees that this chemical is stable in water, the submitter needs to explain this conclusion in the robust summary.
4. Health Effects. EPA reserves judgement on the adequacy of data pending verification of the test substances used in genetic toxicity studies and the correct name and purity of the test substance used in the reproduction toxicity study.
5. Ecological Effects. Adequate data exist to satisfy the fish and invertebrate endpoints for the purposes of the HPV Challenge Program. Although each of the algal studies is limited, when considered together, they are adequate for the purposes of the HPV Challenge Program.

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

### **EPA Comments on the Chloronitrobenzenes Challenge Submission**

#### **Category Definition**

The submitter proposed a category to cover three isomers of monochlorinated nitrobenzenes: 1-chloro-2-nitrobenzene (ONCB, CAS No. 88-73-3), 1-chloro-3-nitrobenzene (MNCB, CAS No. 121-73-3), and 1-chloro-4-nitrobenzene (PNCB, CAS No. 100-00-5). The category definition is clear and unambiguous.

#### **Category Justification**

The submitter's justification of the chloronitrobenzenes category is based on similarities in the chemical structures of the three structural isomers of chloronitrobenzene, which are expected to result in "similar or identical properties" and "similar or identical biological mode[s] of action".

EPA agrees that the physicochemical and environmental fate properties of ONCB, MNCB, and PNCB are reasonably similar. In addition, the mammalian toxicity endpoints demonstrate comparable acute and chronic toxicities and similar primary toxic effects. Although the available acute aquatic toxicological data demonstrate some differences in the magnitude of toxicities of these compounds, the range in values is

sufficiently limited to support the submitter's expectation for similar aquatic toxicological properties for the three isomers. Consequently, the data generally support the category.

## **Test Plan**

### Physicochemical Properties (melting point, boiling point, vapor pressure, partition coefficient and water solubility)

The data provided by the submitter for melting point, boiling point, vapor pressure, and octanol/ water partition coefficient are adequate for the purposes of the HPV Challenge Program.

*Water solubility.* The submitter provided an experimental value of 189.4 mg/L for PNCB, which is adequate for the purposes of the HPV Challenge program. However, the submitter provided calculated values for ONCB and MNCB. According to OECD guidelines, measured (experimental) values need to be provided unless the calculated values are less than 1 µg/L at 25 °C. Therefore, the submitter needs to provide a measured water solubility value for at least one of these chemicals (ONCB or MNCB) so the data can be read across to the third chemical. Ideally, measured data should be provided for the chemicals with the lowest and highest solubilities.

### Environmental Fate (photodegradation, stability in water, biodegradation, fugacity)

The data provided by the submitter for these endpoints are adequate for the purposes of the HPV Challenge Program.

*Stability in water.* The test plan states that these chemicals are stable in water owing to a lack of hydrolyzable functional groups. This is not strictly correct, as the chlorine atoms in ONCB and PNCB are substantially more labile than in simple chlorobenzenes. However, EPA agrees that hydrolysis of the chlorine substituent is unlikely under normal environmental conditions. The submitter needs to explain its conclusion in robust summary format.

*Biodegradation.* The data provided by the submitter are adequate for the purposes of the HPV Challenge Program. The submitter needs to correct the description of biodegradation in the test plan (page 15), which states that the Semi-Continuous Activated Sludge (SCAS) tests "followed similar standards for conduct subsequently codified into OECD guideline 301". This type of test was codified into OECD Guideline 302A (modified SCAS test). EPA agrees with the submitter that these chemicals are not readily biodegradable (test plan, page 16).

### Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity)

Pending verification of some information for genetic and reproductive toxicity, adequate health effects data were submitted for the chloronitrobenzenes category for the purposes of the HPV Challenge Program. Data for all category members were submitted for acute and genetic toxicity endpoints. In addition, data for the ONCB and PNCB were submitted for the repeated-dose, reproductive, and developmental toxicity endpoints. A read-across strategy for MNCB is acceptable for these endpoints.

*Genetic Toxicity.* EPA reserves judgement on the adequacy of the bacterial mutagenesis assays, pending receipt of robust summaries that identify the test compounds by name.

*Reproductive Toxicity.* EPA reserves judgement on the adequacy of this endpoint for ONCB, pending receipt of a revised robust summary that identifies the organs examined for histopathology, and for PNCB, verification of the compound name.

## Ecological Effects (fish, invertebrates, and algae)

Adequate data exist to satisfy the endpoints for acute toxicity to fish and aquatic invertebrates for the chloronitrobenzenes category. When the experimental toxicity values reported from studies on algal toxicity are evaluated together, the data are adequate. The submitter should provide the missing data elements in the robust summary for each endpoint. See the specific comments on robust summaries (below) for details.

*Algae.* Considered separately, the 96-hour tests in *Chlorella pyrenoidosa* are insufficient due to the limited details available (especially the lack of a defined endpoint), and the 48-hour tests are inadequate because at least 72-hour tests are needed to satisfy the algal toxicity endpoint. However, the data are sufficient when considered together because (1) the experimental results and the ECOSAR predictions are similar, (2) the 96-hr studies were conducted according to OECD Guideline 201, and (3) additional studies located by EPA (Canton et al., 1985; Knie et al., 1983) show results similar to the submitted study results.

There were several inconsistencies in the test plan. First, Tables 1, 2, and 3 (pp. 11-13) reported that estimation methods were not available for aquatic toxicity endpoints for ONCB or PNCB or for acute fish toxicity for MNCB. Predicted toxicity values, however, were included in the test plan for each of the three isomers for all three aquatic toxicity endpoints. Second, page 17 reports that ECOSAR predictions were reported for daphnids and algae; however, predictions for fish were also reported. Finally, Table 6 (p. 17) indicates that a 48-hour algal EC<sub>50</sub> was estimated for the MNCB. The estimated EC<sub>50</sub> value, however, was a 96-hour value.

## **Specific Comments on the Robust Summaries**

### Generic Comments

The following comment applies to all the robust summaries provided by the submitter. The submitter should consult EPA guidance documents for the preparation of robust summaries (<http://www.epa.gov/opptintr/chemrtk/guidocs.htm>).

Each summary should clearly identify the test substance by the chemical name.

### Health Effects

Some robust summaries did not identify the test substance at all and others identified the compound only by its acronym. The submitter needs to revise the summaries, especially for the studies that did not identify the test substance.

*Genetic Toxicity.* Robust summaries for mutagenesis assays in *Salmonella typhimurium* for the need to specify the test material.

*Reproductive Toxicity.* A robust summary for a continuous breeding assay in mice exposed to ONCB by gavage needs to identify the organs examined for histopathology and include separate NOAEL fields for systemic and reproductive toxicity.

The submitter needs to identify the test substance in the summary in the PNCB dossier for a two-generation reproductive toxicity assay in rats, which identified the chemical as ONCB under "Test substance" but as PNCB in the results section and PNCB in the reference list. The submitter needs to include separate NOAELs for systemic and reproductive toxicity.

*Developmental Toxicity.* The summary for the ONCB inappropriately used the ">=" symbol rather than the "=" symbol in the NOAEL fields for doses that were not the highest dose levels.

## Ecological Effects

ECOSAR predictions were reported for each chloronitrobenzene isomer for all endpoints; however, no details on the inputs used to generate the predictions were reported. Also, the robust summaries indicated that the SAR for esters was used for all of the predictions although none of the sponsored chemicals are esters. From independent model runs, it appears that the submitter correctly used the SAR for neutral organics for toxicity predictions for MNCB. However, it is not clear how the submitter determined the predicted toxicity values for the other two isomers.

*Fish.* Important details missing from one or more summaries included results based on measured concentrations, values for the actual test concentrations, use and response of controls, mortality data, 95% confidence intervals, statistical methods, and concentration of the solvent (acetone).

*Invertebrates.* Important details missing from one or more robust summaries included test substance identity and purity, mortality data, and the concentration of the solvent.

*Algae.* Important details missing from one or more robust summaries included test substance purity, type of test (*e.g.*, static, semi-static, or flow-through), pH at the beginning and end of the test, water hardness, specific test concentrations (although ranges were provided), type of regression analysis used to determine the EC<sub>50</sub> values, and which endpoint (biomass, etc.) was reported.

## Followup Activity

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

## References

Canton, J.H., et al. 1985. Toxicity, Biodegradability and Accumulation of a Number of Cl/N-Containing Compounds for Classification and Establishing Water Quality Criteria. Regul. Toxicol. Pharmacol. 5: 123-131.

Knie, J., et al. 1983. Results of Studies on Chemical Substances with Four Biotests. (Ergebnisse der Untersuchungen von Chemischen Stoffen mit Vier Biotests.) Dtsch. Gewaesserkd. Mitt. 27(3): 77-79.