

201-16196

NCIC OPPT/DC/USEPA/US

Sent by: Geffry King

02/07/2006 09:06 AM

To: NCIC HPV@EPA

cc

bcc

Subject: Re: ERL-4221 

2006 FEB -7 AM 9:31

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OPPT/DC/IC

US Environmental Protection Agency
Office of Pollution Prevention and Toxics Docket
Non-Confidential Information Center (MC 7407T)
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02/06/2006 03:03 PM

To: NCIC OPPT@EPA, Rtk Chem@EPA

cc

Subject: ERL-4221

Dear Sir - Attached please find the response to EPA comments, the revised test plan and tables and the revised dossier. Thanks.

Ken

Ken Nitschke

EH&S Toxicology & Environmental

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e-mail kdnitsch@dow.com The Dow Chemical Company response for ERL-4221.pdf ERI-4221 Revised Test Plan.pdf



ERL-4221 Revised Tables.pdf ERL-4221 dossier Dec 2005.pdf

201-16196A

Cycloaliphatic Epoxy Resin ERL-4221
(ERL-4221)
(CAS# 2386-87-0)

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The Dow Chemical Company thanks the Environmental Protection Agency and Environmental Defense for reviewing and commenting on the draft test plan and dossier for Cycloaliphatic Epoxy Resin ERL-4221 (ERL-4221) (CAS# 2386-87-0). Dow Chemical has repeated the water solubility test and basically repeated the previous study. Given the results of the water solubility test, repeating the daphnia study is considered unnecessary.

Response to Environmental Defense comments.

- If information on environmental contamination or consumer exposure is available, we recommend that it be included in the test plan.

ERL-4221 is reacted to produce coatings and inks. Very little, if any, original material is expected to be released to the environment.

- In the 14-day study, a yellow material was noted in the urogenital area of females after doses of 750 mg/kg/day. This finding was apparently not further evaluated, although it was not reported in a later 28-day study that dosed animals up to 500 mg/kg/day. What is the significance of the yellow material and does it only occur at higher doses for longer exposure periods?

In the 14 day study, the incidence of wet yellow material observed in the urogenital area one-hour after dosing was 8 times in 4 high-dose females and the incidence of dried yellow material observed in the urogenital area one-hour after dosing was 4 times in 3 high-dose females. The total number of female rats in this group was ten and each rat was observed 9 times post-dosing for a total of 90 observations. Thus, although yellow material was observed on the fur, the frequency was quite low.

As stated in the dossier, yellow material on the fur was also observed in the 90-day study at 500 mg/kg/day. The yellow material covered the urogenital area, and occasionally extended to the neck region. During clinical observations of the high dose female rats which occurred daily after dosing, yellow material was observed a total of 43 times during the 90 day study. Thus while it was observed in the 90-day study, the frequency was quite low.

Yellow staining of the fur is commonly observed in animals that inadequately groom themselves.

The low incidence along with the non-specific nature of this observation would not indicate that it would cause a reproductive effect.

- If the sponsor provides an explanation for the finding that indicates that it does not constitute a reproductive effect, then we agree that no further studies are needed. If this explanation is inadequate, then we recommend that the sponsor conduct a reproductive toxicity study.

The Dow Chemical Company has adequately addressed this endpoint.

Response to EPA comments

- Physicochemical Properties. The reported measurements of partition coefficient and water solubility were complicated by competing hydrolysis reactions, and estimated values are preferred.

We have repeated the water solubility study using distilled water. The water solubility was determined at 15°C a temperature which would reduce the rate of hydrolysis. In addition the test material was analyzed by liquid chromatography/mass spectrometry (LC/MS) using positive electrospray ionization. This method used selective detection of parent substance.

The use of LC/MS for residue analysis may have reduced the rate of hydrolysis that may occur when aqueous test solutions are injected into the heated injection port/column of a gas chromatograph. At this lower solution temperature the water solubility was 9798 ± 484 mg/L. This aqueous solubility value is lower than the 13,850 mg/L previously measured at room temperature (20°C).

- Environmental Fate. The submitter needs to provide more information in its hydrolysis robust summary.

This has been provided.

- Health Effects. The submitted data are adequate for the purposes of the HPV Challenge Program. The submitter needs to address some deficiencies in the robust summaries.

This has been provided.

- Ecological Effects. EPA reserves judgment on the adequacy of invertebrate data pending submission of critical information for the submitted study.

This has been provided.

Test Plan

Physicochemical Properties (partition coefficient and water solubility)

The reported measurements of partition coefficient and water solubility were complicated by the competing hydrolysis reactions (see Environmental fate section).

- *Partition coefficient.* The submitter did not discuss how hydrolysis could affect the log K_{ow} determination. EPA estimated a value of 2.37. This value is higher than the measured value, probably owing to hydrolysis during the test. Use of the estimated value for this endpoint is preferred in this case.

Any test material that hydrolyzed in water would have been replaced with test material present in the octanol phase to maintain equilibrium. Thus hydrolysis during the test should not have affected the K_{ow} . However, if the rate of equilibrium were slower than the rate of hydrolysis, this would have raised the K_{ow} , not lowered it.

Water and n-octanol samples were analyzed by gas chromatography for parent material. Although ERL-4221 does hydrolyze in water the

response is slow enough that it should not have had a significant impact on the results. Additional information has been provided in the dossier.

- *Water solubility.* EPA found a water solubility of 0.03% (w/w) at 25 °C (approximately 300 mg/L) reported in Patty's Toxicology and obtained an estimated water solubility of 1,200 mg/L using WSKOW v1.41. The submitter's measured value of 13,850 mg/L after 18 d. is not consistent with either value. The submitter noted the apparent hydrolysis during the test but did not comment on its relevance to the reported result (the hydrolysis products are expected to be more water soluble). The lower values are more reasonable in this case.
As previously mentioned, the Dow Chemical Company has repeated the water solubility and obtained a value of 9798 mg/L at 15°C.

Environmental Fate (stability in water)

- *Stability in water.* The submission provided concentration data for only the initial and final (72 hr) concentrations. From the percent loss after 72 hours, the submitter calculated a half-life assuming first-order kinetics. According to OECD Guideline 111, first-order behavior should be tested by analyzing each reaction solution (pH 4, 7, and 9) at time intervals that provide a minimum of six spaced data points, normally between 20 and 70% of hydrolysis. The submitter also did not state what analytical method was used to follow the reaction. In the test plan, the submitter stated hydrolysis of ERL-4221 will result in cleavage of the ester linkage and opening of the epoxide rings; however, no analytical data were provided for the degradation products. Since the sponsored substance has three hydrolyzable groups, an ester and two epoxides, incomplete hydrolysis can yield up to five products in addition to the two completely hydrolyzed products; analysis of the products is needed to provide insight into the hydrolysis pathway and the aquatic toxicity test results. The submitter needs to provide more details on what was measured and what hydrolysis products were identified and/or measured.

At a pH of approximately 7.2, nine samples were analyzed for parent material as the first run in the water solubility study. These samples were taken approximately 24 to 143 hours after preparing the solution. At pHs of 4 and 9, samples were analyzed only at 0 and 72 hours. Although the studies at these two pH values do not technically meet the guideline, they provide sufficient information to understand this material's stability in water. At the time this study was conducted, 2000, the protocol followed the OECD 111 guideline issued in 1981. Since then a new version of this guideline has been issued which has added identification of hydrolysis products. This was not part of the original guideline and therefore is not necessary. Based on the report, there were no hydrolysis products identified and/or measured.

Health Effects (genetic toxicity)

- *Genetic toxicity.* In the test plan, the reported negative results for the sister chromatid exchange assay in CHO cells need to be revised to reflect the statistically significant positive response reported in the robust summary.
The test plan has been modified. These results were considered to be ambiguous because the studies were repeated three times due to apparent cytotoxicity. This was accidentally omitted from the dossier.

Ecological Effects (invertebrates)

EPA reserves judgment on the adequacy of invertebrate data pending submission of critical information for the submitted invertebrate study.

- *Invertebrate.* The following issues need to be addressed: (1) although this chemical has a hydrolysis half-life of 47hr, the 48-hr measurement showed no loss of chemical in a purported static test; (2) an extremely high water hardness was reported (609 mg/L); (3) the abnormal dose response at higher concentrations. If the submitter cannot resolve these issues, the invertebrate testing should be redone, with reported results based on flow through measured concentrations.
 - 1) While performing the water solubility measurement on ERL-4221, the water solubility in adjusted laboratory dilution water (ALDW) was also determined. This ALDW water is similar to that used for the daphnia studies, in terms of hardness and alkalinity. Although the temperature this study was run at was 15°C, 5°C lower than that typically used for studies of daphnia, it is sufficiently close to demonstrate that the hydrolysis is much slower than reported in the Wallace study (half-life of 47 hr); a saturated aqueous solution showed approximately 20% loss of parent due to hydrolysis over 48 hours (half-life of >150 hr). Thus the rate of hydrolysis of ERL-4221 is much slower than reported previously.

In the daphnia studies the water solutions were changed after 24 hours which would have renewed the concentration of test material.
 - 2) The body of the report states the water hardness was 609 mg/L but the appendix lists a hardness of 221 mg/L as CaCO₃. The dossier has been updated to reflect this.
 - 3) We would agree the dose response is not typical. However, this study was conducted with 7 dose levels. The two lowest concentrations, 5.6 and 10 mg/L (nominal concentration), did not result in any visible effects in the daphnia. Thus, if one were to repeat the study, the LC50 would clearly be above 10 mg/L. This would result in the same classification, 'slightly toxic' as the results of the current study. Thus there is no need to repeat an acute daphnia study.

Specific Comments on the Robust Summaries

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

- *Repeated-dose toxicity.* The robust summary for the 90-day repeated-dose toxicity study (Padgett, 2001) is missing details including age of animals at study initiation; list of organs weighed at necropsy; list of tissues examined microscopically; results of statistical analyses and statistical significance of treatment-related findings.

Additional information has been provided in the dossier.

- *Genetic toxicity.* The robust summary for the reverse mutation assay in *Salmonella typhimurium* and *Escherichia coli* (Machigaki et al., 1995) is missing details including information on statistical analysis and level of statistical significance, and criteria for evaluating a positive or negative response.

Additional information has been provided in the dossier.

- *Developmental toxicity.* The robust summary for the prenatal developmental toxicity study (Varsho, 2003) is missing the following critical details: information on statistical methods and levels of significance; the proportion of fetuses evaluated for external, visceral and skeletal malformations; the magnitude of changes in maternal body weight/body weight gain; maternal kidney weight; fetal body weight; and litter incidence data for skeletal variations.

Additional information has been provided in the dossier.