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Robust Summaries & Test Plans: 1,3 Dioxolane Environmental Defense Comments

May 10, 2001

Comments of Environmental Defense on the 1,3-Dioxolane Test Plan and Robust Summary under the High Production Volume Chemical Initiative

(Note: these comments are a slightly revised version of comments earlier submitted on behalf of Environmental Defense, clarifying our views relating to HPV as distinct from possible post-HPV work.)

The Dioxolane Manufacturers' Consortium claim that the toxicological databases for 1,3-dioxolane are adequate and that no additional studies should be conducted. We concur in this conclusion insofar as it relates to the High Production Volume (HPV) initiative. However, as noted below, certain data discussed in the robust summary suggest that it may not be appropriate to regard this chemical as being of low priority for post-HPV consideration. We also offer comments on a few non-HPV endpoints covered in the robust summary. Detailed comments are itemized below.

1. Exposure- There is essentially no consumer exposure to 1,3-dioxolane although exposures in the work place could be as high as 1 ppm. Environmental exposures are low with levels in industrial wastewater ranging from non-detectable to 4 ppm.
2. Acute Toxicity- 1,3-dioxolane exhibits low acute toxicity to rodents and various fish species and the existing database is adequate. We agree that no further acute toxicity tests should be conducted.
3. Repeat dose studies- The most sensitive toxicity endpoint is platelet number and effects on white blood cells. The liver, kidney and CNS also showed effects at high dose levels. The oral NOEL was 75 mg/kg/day and the inhalation NOEL was 500 ppm. These values are 2-3 orders of magnitude higher than worker exposures. We agree that no further repeat dose studies should be conducted.
4. Subchronic studies- These studies are comprehensive and consistent with the repeat dose studies in that liver and the hematopoietic system exhibited toxic effects at high dose levels. The NOEL for inhalation was 300 ppm and 0.5 % in drinking water. Somewhat surprising was the reduction in serum cholinesterase at high doses. However this effect was less sensitive than the effect on blood cells. We agree that no further subchronic studies are needed.
5. Genetic Toxicity- There is considerable information available on the genetic toxicity of 1,3-dioxolane in vitro and in vivo. Results are consistently negative in vitro for a variety of tests including the Ames test and chromosomal aberrations in CHO cells. These in vitro data are sufficient to meet the genetic toxicity data element of HPV, therefore no additional genetic toxicity testing is needed for HPV purposes. However, some of the in vivo tests were positive. Of particular concern was the finding of single strand breaks in rat hepatocytes. Although the sponsors assert that this finding is spurious, their justification

for this claim is far from convincing, particularly inasmuch as positive findings in in vivo genetic toxicity studies are relatively rare. Accordingly, while additional genetic toxicity data are not needed for HPV purposes, dioxolane cannot necessarily be considered "of low priority" for additional work post-HPV. In particular, if no convincing justification for the purportedly spurious positive finding is brought forward, it may be appropriate to do additional in vivo studies using Good Laboratory Practices.

6. Sex related effects -No significant sex-related differences in toxicity were observed and no further studies on sex differences are needed.

7. Reproduction/Development -Developmental effects were observed but only at maternally toxic doses. We agree that the studies on reproductive and developmental effects are complete and no further studies should be conducted.

8. Absorption, /Distribution/Metabolism- Although such data are not required in the HPV initiative, the test plan correctly notes that some information is available. Unfortunately, such data are not dispositive. Therefore, if post-HPV work is conducted, the biological half-life in rodents should be determined. This information is needed to evaluate possible risks from chronic exposures.

9. Lifetime Cancer Bioassay- Though cancer bioassays are not an HPV endpoint, the test plan correctly notes that cancer bioassays have not been conducted. From a purely scientific standpoint, this raises some concern because of the blood cell effect seen in the repeat dose and subchronic studies. However, relatively high doses are required for these effects. The priority for a cancer bioassay, according to NTP standards, would fall between low and moderate.

In sum, we support the sponsor's conclusion that no additional testing is needed as part of the HPV program. However, based on the positive in vivo genetic toxicity test, this chemical cannot necessarily be regarded as of low priority for post-HPV work.

Thank you for this opportunity to comment.

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