

Dinitrile Category – Comments of Environmental Defense

(Submitted via Internet January 11, 2002.)

Environmental Defense appreciates this opportunity to submit comments on the robust summary/test plan for the Dinitrile Category.

E.I. duPont de Nemours and Company prepared robust summaries and test plans for a proposed category of dinitrile compounds. The proposed category consists of ethylsuccinonitrile (ESN), 2-methylglutaronitrile (2-MGN) and adiponitrile (AND). ESN and 2-MGN are byproducts in the manufacture of 1,3-butadiene.

Existing data and structural comparisons lend support to the category designation and there is no strong evidence that argue against establishment of this category.

In regard to the mammalian toxicity summaries, data for repeat dose studies, reproductive studies and developmental toxicity studies are available for only ADN. In addition a repeat dose study (4-week inhalation) on 2-MGN is in progress. This ongoing study coupled to existing data should provide adequate information for establishing a category for the three dinitrile compounds and if results are similar to ADN no additional studies should be needed. However, if results from the ongoing 2-MGN study differ substantially from those of ADN, then additional studies on ESN and 2-MGN (including reproductive and developmental protocols) would be needed as the category would not be justified in that event.

The existing inhalation repeat dose studies for ADN established a NOAEL of approximately 7 ppm based on blood cell effects in female rats. A two-year drinking water study noted advanced adrenal degeneration in female rats at all doses tested: the lowest drinking water concentration used was 0.5 ppm. The ongoing studies on 2-MGN need to be evaluated in the context of target organ responses for ADN including the adrenal effects. The adrenal response at low drinking water doses raises some safety concerns. The acceptable air exposure limit (AEL) for ADN is 2 ppm for 8 and 12 hour time weighted averages. Although it appears that workers at various ADN plants are exposed to much lower amounts of ADN than are permitted by the AEL, we believe that the drinking water exposures should be subjected to appropriate models for comparing drinking water and inhalation pharmacokinetics and predictions made regarding the inhalation exposure needed to cause the adrenal effects. (We recognize that this analysis is not within the scope of the HPV initiative per se.)

Finally, as we have noted in many previous HPV reviews the assessment of category designations would benefit tremendously by the use of microarray technologies to determine if all members of a proposed category cause the same pattern of gene expression changes in in vitro or in vivo studies.

Thank you for this opportunity to comment.

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