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RE: SOCMA HPV Challenge Program test plan for 4-vinylcyclohexene

The following comments on the HPV Challenge Program test plan for 4-vinylcyclohexene are submitted on behalf of the Physicians Committee for Responsible Medicine, People for the Ethical Treatment of Animals, the Humane Society of the United States, the Doris Day Animal League, and Earth Island Institute. These health, animal protection, and environmental organizations have a combined membership of more than ten million Americans.

The Synthetic Organic Chemical Manufacturers Association (SOCMA) 4-Vinylcyclohexene Work Group submitted its HPV Challenge Program test plan for 4-vinylcyclohexene (VCH) (CAS RN 100-40-3) in November of 2006.

SOCMA does not propose any testing for this chemical, which is used as a chemical intermediate in a number of manufacturing processes. While not a true closed-system intermediate in the traditional sense, it appears from the test plan that VCH has almost negligible potential for worker or public exposure. Exposure testing in manufacturing plants indicates that airborne levels are below the current TLV of 0.1 ppm.

SOCMA is to be commended for the test plan submitted for VCH. The data is summarized in a clear and consistent manner, and effort is made to analyze the weight of evidence available for VCH instead of simply checking boxes. Modeled and experimental ecotoxicity data is available, as are studies for acute and repeated dose toxicity for multiple routes. Based on sub-chronic and chronic oral and subchronic inhalation studies, the female reproductive tract is of concern in mice at 1000 ppm, and other toxicological effects at that dose and higher for both species. Oral and inhalation levels of no effect are still many times higher than current human potential exposure levels. The oral chronic toxicity study, conducted by the National Toxicology Program, indicated carcinogenic effects in the mouse ovary.

Reproductive and developmental toxicity endpoints are fulfilled by a long-term continuous breeding study. While not following OECD protocol, the study did assess reproductive function in two generations of mice, the most sensitive species, by the oral route. The test plan could be improved by adding histopathological evaluation of fetal and/or adult tissues, if these data are available. Fetal abnormalities for the F1 and F2 generations were not apparent. Normally, such studies have a limit dose of 1000 mg/kg; however, maternal toxicity was apparent at the highest dose (500 mg/kg). While the primary route of exposure for humans is inhalation, similar toxicological effects were seen in sub-chronic studies for both inhalation and oral routes,

negating any perceived need for reproductive/developmental studies by the inhaled route; in lieu of this, a route-to-route PBPK model may be applied if this is deemed necessary.

Additional data is provided in the form of *in vivo* and *in vitro* metabolism and toxicokinetics. Analyses provided indicate that species differences in metabolic enzyme activity are responsible for the higher sensitivity shown by mice as compared to rats. *In vitro* human and mouse hepatic microsomal fraction data indicate that mice are also much more sensitive to the effects of VCH than humans.

SOCMA presents a complete test plan for this screening-level HPV program. There are multiple additional studies that can be found on the TOXLINE online database to supplement the plan if necessary.

Thank you for your attention to these comments. We can be reached at 510.834.8320 or by e-mail at *kstoick@pcrm.org*.

Sincerely,

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Research Analyst

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