201-16803

PCRM PHYSICIANS COMMITTEE FOR RESPONSIBLE MEDICINE
5100 WISCONSIN AVENUE, N.W. • SUITE 400
WASHINGTON, D.C. 20016
T: (202) 686-2210 • F: (202) 686-2216
PCRM@PCRM.ORG • WWW.PCRM.ORG

July 08, 2009

Lisa Jackson, Administrator
US Environmental Protection Agency
Ariel Rios Building
Room 3000, #1101-A
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Subject: Comments on the HPV test plan for Disulfide Oil (DSO) (CAS# 68955-96-4)

Dear Administrator Jackson:

The following comments on the Petroleum HPV Testing Group's plan for Disulfide Oil (DSO) 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 twelve million Americans.

This test plan uses a compelling category read-across approach, based on existing test data and model predictions, to satisfy data requirements under the HPV Challenge Program. The test plan thoroughly lays out the rationale for category formation; the 10 major dialkyl disulfides, which account for 87% of DSO (w/w), are extremely well-suited to a category approach as they are highly similar in structure, share a common mode of action, and exhibit predictable behavior based on chain length. Because toxicity increases as chain length decreases, the sponsors use existing data from the shortest chain-length category member, DMDS, as a surrogate for the whole group based on the assertion that DMDS represents the worst case scenario for toxicity of the DSO constituents. The test plan provides extensive justification for the worst case assertion, leading them to convincingly posit that the other category members, which comprise 75% of DSO, are not expected to be more toxic than DMDS. Of the remaining 13% of DSO, comprised by 7 other chemicals not in the category, only diisopropyl sulfone is present at greater than 2%. The sponsor argues, with strong supporting evidence, that diisopropyl sulfone is of little concern, because it is derived from the dialkyl disulfides and metabolized similarly. It then follows that toxicity of diisopropyl sulfone is not expected to differ markedly from the dialkyl disulfides.

If the use of DMDS as a surrogate for DSO is acceptable to EPA, then there should be no issues with the acceptability of the DMDS data since they have already been deemed adequate by EPA for meeting the requirements of the HPV Challenge Program in an earlier submission by Arkema Inc, with the exception of two endpoints-stability in water and chronic fish toxicity. The DSO test plan states that these endpoints are being addressed by Arkema Inc, as indicated in its test plan for DMDS. Those results will be applied to the dataset for DSO when they become available. With regard to the chronic fish toxicity testing, we appreciate the efforts of the Petroleum HPV Testing Group to apply ECOSAR, which reportedly does not provide reliable predictions for category members when compared to existing test data. Although the Petroleum HPV Testing Group may have little to do with Arkema's testing, we want to re-iterate other potential alternatives to fish testing including DarT[1, 2, 3] and TETRATOX[4, 5, 6, 7]. If testing is fish testing is pursued, the numbers of fish can be reduced by using the fish acute threshold (step-down) approach[8, 9].

The test plan also does a nice job of discussing the exposure potential of DSO. Because DSO is a byproduct of petroleum refining processes which occurs at only one company, is not sold commercially or used in any downstream products, and is either consumed in the manufacturing of other chemicals or disposed of on site, DSO would appear to be a low priority for additional testing. The sponsors could further clarify the lifecycle of DSO by providing more information on the disposal process.

---

[1] Nagel, R. 2002.DarT: the embryo with the zebrafish *Danio rerio*: A general model in ecotoxicology and toxicology. *ALTEX* 19 Supplement 1, 38-48.

[2] Shulte C., et al. 1996. Testing acute toxicity in the embryo of zebrafish (*Brachydanio rerio*): An alternative to the fish acute toxicity test. *Proceedings of the World Congress on Alternatives and Animal Use in the Life Sciences.* Utrecht.

[3] Friccius, T., et al. 1995. Der Embryotest mid dem Zebrabarbling: Eine neue zur Priifung und Bewertung der von Abwasserproben. *Vom Wasse*r 84, 407-418.

[4] Schultz, T.W. 1997. TETRATOX *Tetrahymena pyriformis* population growth impairment endpoint: A surrogate for fish lethality. *Toxicological Methods* 7, 289-309.

[5] Sinks, G.D. 2001. Correlation of *Tetrahymena* and *Pimephales* toxicity: Evaluation of 100additional compounds. *Environmental Toxicology and Chemistry* 20, 917-921.

[6] Larsen, J. 1997. 'Progress in an ecotoxicological standard protocol with protozoa: results from a pilot ring test with *Tetrahymena pyriformis. Chemosphere* 35, 1023-l 041.

[7] Seward, et al. 2001. Reproducibility of toxicity across mode of toxic action in the *Tetrahymena* population growth impairment assay. *Aquatic Toxicology* 53, 33-47.

[8] Jerama, S., et al. 2005. A strategy to reduce the use of fish in acute ecotoxicity testing of new chemical substances notified in the European Union. *Regulatory Toxicology and Pharmacolog.* 42, 218-224.

[9] Hutchinson, T.H., et al. 2003. A strategy to reduce the numbers of fish used in acute ecotoxicity testing of pharmaceuticals. *Environ. Toxicol. Chem* 22, 303l-3036.

Again, we support the Petroleum HPV Testing Group's detailed test plan and thoughtful use of category formation and read across to meet data requirements. Thank you for your attention to these comments. I may be reached at 202-527-7345 or via e-mail at nbeck@pcrm.org.

Sincerely,

Nancy Beck, Ph.D.
Scientific and Policy Advisor
Toxicology and Regulatory Testing

Chad B. Sandusky, Ph.D.
Director
Toxicology and Regulatory Testing