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Chad Sandusky <csandusky@pcrm.org> on 10/28/2002 03:50:47 PM

Please respond to csandusky@pcrm.org

To: cford@cardolite.com, Karen Boswell/DC/USEPA/US@EPA, Rtk Chem/DC/USEPA/US@EPA, ChemRTK HPV/DC/USEPA/US@EPA, NCIC OPPT/DC/USEPA/US@EPA

cc:

Subject: Comments on Test Plan for Cashew Nut Shell Liquid

Please find attached (in PDF format) the comments by the animal rights protection community on the above referenced HPV test plan (Cashew Nut Shell Liquid submitted by the Cardolite Corporation).

Sincerely,

Chad B. Sandusky, Ph.D.
Senior Toxicologist
Physicians Committee for Responsible Medicine

- 021028 CNSL HPV Comments.pdf

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

October 28, 2002

Christine Todd Whitman, Administrator
U.S. Environmental Protection Agency
Ariel Rios Building
Room 3000, #1101-A
1200 Pennsylvania Ave., N.W.
Washington, DC 20460

Subject: Comments on the HPV Test Plan for Cashew Nut Shell Liquid

Dear Administrator Whitman:

The following comments on the Cardolite Corporation's High Production Volume (HPV) Challenge test plan for the chemical mixture known as Cashew Nut Shell Liquid (CNSL) 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.

Cardolite submitted its test plan on June 5, 2002. Cardolite is a major importer of CNSL (CAS No. 8007-24-7), a source of naturally occurring alkyl phenols. There are various degrees of "purity" of CNSL, depending on the extent of the refining process. All CSNL, however, are mixtures of phenols with various degrees of unsaturation in the alkyl side-chain (a $C_{15}H_{31}$ chain), plus much smaller amounts of other phenols, less polar substances, and unidentified materials.

Overall, the test plan for CNSL proposes limiting the amount of testing by grouping the various forms of CNSL (depending on the degree of refining) into one testing category. While we agree with this approach, which results in fewer animals being used in the SIDS battery, we are concerned about the remaining tests, particularly the proposed tests for acute oral toxicity (OECD No. 425) and repeat dose and reproductive/developmental screening (OECD No. 422) tests, which are clearly unnecessary. The test plan does not fully utilize information available on CNSL and characteristics of its refining processes, which would further reduce the use of animals in SIDS tests. These items are presented in more detail below.

Furthermore, CNSL could be included in the already-existing Alkylphenols Category, established by Schenectady International in its test plan submitted to the EPA on November 15, 2001. The compounds in this category meet the criteria of having some of the same functional groups as CNSL, showing a similar toxicity pattern, with dermatitis being a primary problematic endpoint, and having low acute oral toxicity testing results (as seen in the Schenectady test plan). This approach is consistent with the EPA's stated goals of maximizing the use of existing data in order to limit additional animal testing. We have encouraged the EPA in past test plan comments to ensure inter-industry cooperation in the development of chemical categories and test plans, including the aforementioned alkylphenols, and also in comments on the American Petroleum Institute Petroleum Coke test plan, the Phosphite Producers HPV Consortium test plan on tris(nonylphenol)phosphite, and the General Electric test plan on p-cumylphenol. We are concerned that the EPA is not encouraging inter-company and inter-industry cooperation in the development of test plans and chemical categories, thus greatly increasing the number of animals killed in the HPV program.

Low Exposure to CNSL: Repeat Dose and Reproductive/Developmental Screening Test

According to the Cardolite test plan, the most likely human exposure during CNSL production is during removal of the kernels from the nuts, which occurs after processing to remove the CNSL. However, there is no shelling of cashews in the U.S. (all CNSL is imported by Cardolite), and, thus, there is no worker exposure in the U.S. during production *per se*. Furthermore, in the U.S. (as stated by Cardolite in its test plan), "workers involved in the further processing of CNSL to manufacture commercial products are likely to have minimal exposure to CNSL as it is expected that good industrial hygiene practices will be followed and personal protective equipment worn to minimize exposure." These measures have been adopted in the U.S., since it is well documented that production workers involved in this "shelling" process overseas may develop sensitization and allergic dermatitis from exposure to CNSL.

Cardolite has proposed unnecessary tests on animals and has failed to recognize the lack of exposure of workers to CNSL. These tests include a combined repeat dose and reproductive/developmental-screening test (OECD No. 422). This test alone will cause the suffering and deaths of 600 animals. In the test plan itself, Cardolite acknowledges that CNSL has a long and well-documented history of causing allergic dermatitis in workers exposed during the production process. Thus, good industrial hygiene practices have been adopted in the U.S. to limit worker exposure during refining and the manufacture of commercial products. Furthermore, because CNSL has a low vapor pressure ($<2 \times 10^{-5}$ Pa = negligible) and no oral exposure occurs during the refining process, clearly the results of any new animal tests will neither affect how CNSL is handled nor result in further limits on worker exposure and risks. In principle, this situation is similar to that outlined in the HPV agreement of October 14, 1999, in which the EPA states that "participants shall not develop sub-chronic or reproductive toxicity data for the HPV chemicals that are solely closed system intermediates" (due to limited exposure).

Furthermore, conducting this test clearly violates Sections 1 and 8 of that agreement and the EPA December 2000 *Federal Register* notice that states a) "In analyzing the adequacy of

data, participants shall conduct a thoughtful, qualitative analysis rather than use a rote checklist approach. Participants may conclude that there are sufficient data, given the totality of what is known about a chemical, including human experience, that certain endpoints need not be tested" and b) "As with all chemicals, before generating new information, participants should further consider whether any additional information obtained would be useful or relevant." The exposure and risk to CNSL are already well controlled due to the need to limit exposure to prevent well-documented dermatitis resulting from dermal exposure to these materials during the production process.

Finally, there is not a data vacuum surrounding CNSL reproductive and developmental toxicity, as extensive testing has already been conducted on similar alkylphenol compounds with some of the same active functional groups, as previously presented in the Schnectady test plan on alkylphenols. With this extensive database, further testing of this compound is unnecessary. An *in-vivo* study using 600 animals in stressful experiments is simply neither warranted nor justified. As an alternative to *in-vivo* testing, and given the aforementioned limited exposure to CNSL, an *in-vitro* embryotoxicity test would be adequate to characterize any possible adverse reproductive effects of this material. If, in fact, Cardolite insists on further exploration of developmental endpoints, we urge it to consider the use of an *in-vitro* test for embryotoxicity (a critical endpoint in developmental toxicity) using the rodent Embryonic Stem Cell Test (EST) protocol that has been validated by the European Centre for the Validation of Alternative Methods (ECVAM). For additional information, please refer to E. Genschow *et. al.*, "The ECVAM international validation study on *in vitro* embryotoxicity tests: results of the definitive phase and evaluation of prediction models" (*Alternatives to Laboratory Animals* 30:151-76, 2002). If a positive result is found, the substance should be treated as a developmental toxicant/teratogen, and no further testing should be conducted under the screening-level HPV program.

In-Vitro Tests: Acute Oral Toxicity Test

Cardolite has proposed conducting an acute toxicity test using the up-and-down procedure (OECD No. 425). This test was proposed because there were no acute data available to meet this SIDS requirement. However, as outlined in the alkylphenols test plan previously submitted by Schnectady, animal testing of similar compounds showed a relatively consistent and low acute oral toxicity (generally >1000 mg/kg/day) in all compounds tested. With this existing data on other alkylphenols, the extensive knowledge base from worker exposure to these compounds in shelling operations, the careful limitation of industrial exposure based on this knowledge, and the consistent toxicological behavior of similar compounds in previously conducted animal tests, further animal testing is redundant, unnecessary, wasteful and cruel.

If Cardolite insists on conducting an acute oral toxicity test for CNSL, we urge it to use the *in-vitro* cytotoxicity assays. This approach was incorporated into the HPV program as a result of the National Toxicology Program- and National Institute of Environmental Health Sciences-sponsored *Workshop on International on in vitro Methods,* held on October 17-20, 2000. This workshop reviewed the validation status of available *in-vitro* methods for predicting acute oral toxicity (among other goals).

As a result of this workshop, the EPA encouraged those participating in the HPV program to "consider using the recommended *in-vitro* tests…as a supplemental component in conducting any new *in-vivo* acute oral toxicity studies,…[and] to note the intention to use these protocols in the HPV Challenge test plans submitted to EPA…." The two *in-vitro* tests recommended are the neutral red uptake assays using the mouse fibroblast cell line BALB/c 3T3 and normal human kerantinocytes. Guidance on these recommended *in-vitro* tests, protocols for their use and a reporting template for results can be found on the ICCVAM Web site at http://iccvam.niehs.nih.gov/docs/docs.htm#invitro.

In particular, since all indications are that these materials will have low acute oral toxicity, any additional *in-vivo* testing is unnecessary and cruel. This is a clear case in which the *in-vitro* cellular toxicity tests can be used to characterize acute hazard and avoid the killing of more animals merely to substantiate low acute oral toxicity.

Summary

It has been well known for many years that CNSL can cause allergic dermatitis and sensitization. Because of this, Cardolite and the end users of CNSL alkyl phenols have long established good industrial hygiene practices to prevent exposure. Furthermore, the test plan indicates "there are no direct consumer applications and therefore no direct sales to the general public." Additional animal testing will not affect how CNSL is handled and used because: a) worker dermal exposure is already limited from the use of good industrial hygiene practices (due to well known dermal effects), b) oral exposure is extremely unlikely, c) the low vapor pressure indicates there is negligible inhalation exposure, and d) there is no exposure to the general public. Because of the well-known characteristics of this hazard, workers are already protected, and additional animal testing will not demonstrate need for additional steps to reduce worker exposure. These additional proposed animal studies are a waste of animals, time, and resources, and Cardolite should not conduct them. *In-vitro* tests are available to characterize acute and reproductive risks, and these should be conducted in lieu of the proposed *in-vivo* tests.

I look forward to a prompt and favorable response to our concerns. I may be reached at 202-686-2210, ext. 302, or via email at CSandusky@PCRM.org.

Sincerely,

Chad B. Sandusky, Ph.D.
Senior Toxicologist