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Subject: Public Comments on Arizona Chemical Company's HPV Challenge Program Test Plan for Resin Acids and Rosin Acids, Fumarated, Decyl Esters

The following comments on Arizona Chemical Company's test plan for resin acids and rosin acids, esters are submitted on behalf of People for the Ethical Treatment of Animals, the Physicians Committee for Responsible Medicine, 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.

Arizona Chemical Company is proposing to conduct an OECD 422 combined repeat dose/reproductive/developmental toxicity test, and an OECD 203 acute fish toxicity test. If conducted, these tests will kill more than 700 animals.

This test plan violates the following terms of the October 1999 agreement among the EPA, industry, and health, animal protection, and environmental organizations, as well as the December *2000 Federal Register* notice reconfirming that agreement:

2. Participants shall maximize the use of existing and scientifically adequate data to minimize further testing.
3. Participants shall maximize the use of scientifically appropriate categories of related chemicals and structure activity relationships.

Rosins are naturally occurring substances found in pine trees and used commercially for printing inks, adhesives, chewing gums, coatings, soaps, and detergents. The chemical currently being considered is rosin, **fumarated, C9-11 isoalkyl esters, Cl O-rich (rosin, fumarated ester)**. It is closely related to 19 chemicals for which final revised test plans have already been submitted by the Pine Chemicals Association's (PCA) HPV Task Force (of which Arizona Chemical Company is a member). These related chemicals are included in the Rosins and Rosin Salts, Rosin **Adduct** and **Adduct** Salts, and Rosin Esters categories. Rosin, **fumarated** ester is made by first **adducting** rosin with fumaric acid to form a tricarboxylic acid. The resulting fumarated rosin is part of the Rosin **Adduct** and **Adduct** salt category. This is then reacted with "alcohols, C9-1 1-iso, C10-rich" to form the ester. Seven other rosin esters comprise the Rosin

Esters category. Like other rosin esters, rosin, fumarated ester is used primarily as a **tackifier** in adhesives.

Any additional animal testing for rosin, fumarated ester is premature, without first considering data from analogous chemicals with similar toxicity profiles. The PCA (including Arizona Chemical Company) has already tested similar chemicals in the test plans mentioned above. The PCA should have included this rosin ester in the rosin esters category or, preferably, included all of these chemicals in a larger rosins category. All are closely related structurally and have high molecular weight, low water solubility, and high K_{ow} . An expansion of the category would provide greater insight into the relationship between structure and toxicity and, importantly, would reduce the numbers of animals killed in this proposed testing.

As noted in the robust summaries, rosin, fumarated ester is completely non-toxic in acute toxicity testing in rats by both oral and dermal exposure. In each case, at a dose of 5,000 **mg/kg**, all animals appeared active and healthy with no signs of gross toxicity, adverse pharmacologic effects or abnormal behavior. These results are typical of the rosin and rosin compounds in the categories mentioned above. All of the existing data demonstrate that this broad group of chemicals is nontoxic in acute toxicity tests extending to multiple species.

OECD 422 combined repeat dose/reproductive/developmental toxicity tests have already been conducted on representatives of the Rosin **Adduct** and **Adduct Salts** and Rosin Esters categories and their results are reported in the final revised test plans.^{1,2} It is fair to summarize that only minor effects were observed at the highest doses in each case and that even these are most likely due to reduced food consumption and body weight as a consequence of palatability issues. In fact, because of these “severe palatability issues,” parental or reproductive/developmental **NOELs** could not be derived for rosin, methyl ester. This particular pointless test caused the suffering and deaths of hundreds of animals. Given the low acute toxicity of rosin, fumarated ester and its structural similarity to rosin, methyl ester there is every reason to predict that this experience will be repeated if another OECD 422 test is conducted.

The acute fish toxicity test, OECD 203, is also particularly inappropriate for this rosin ester because its insolubility in water ($<3.45 \times 10^{-4}$ g/l) and lack of hydrolysable functional groups hinder the ability to conduct aquatic tests and indicate that this chemical is unlikely to be bioavailable to aquatic life. In addition, alternative methods are readily available, such as ECOSAR or TETRATOX, described in the EPA guidance document “The Use of **Structure-Activity Relationships (SAR)** in the High Production Volume Chemicals Challenge Program”.

Further, the Ecotoxicology Task Force of the European Center for the Validation of Alternative Methods (ECVAM) recently published an evaluation of the applicability of a fish acute threshold (step-down) test concept to new chemical substances.³ Noting that fish are less sensitive than algae or daphnia in acute aquatic toxicity tests roughly 85% of the time⁴, this test sets an upper threshold concentration (UTC) at the lowest EC₅₀ value observed in the algae and daphnia tests. An acute test is carried out at this UTC using five test and five control fish. If no toxicity is observed, no further tests are carried out and the acute fish toxicity result (LC₅₀) is reported as greater than the UTC value. If toxicity is observed, a second test is performed at a step-down concentration using a dilution factor of 3.2, based on a semi-logarithmic concentration series. The testing continues to lower concentrations until no toxicity is observed. The LC₅₀ 96-hour value can be obtained from all step-down threshold test data by applying the binominal method of interpolation. Applying these conditions to data sets drawn from the New Chemicals Database of the European Chemicals Bureau, the ECVAM investigators found that a 53.6–71.2% reduction in the number of fish used would be possible when applying this new testing strategy. An additional refinement could be obtained by terminating the test after 24 hours of exposure, when lethality and/or serious morbidity are observed in two out of five fish. This would contribute significantly to reducing the pain and suffering of the fish. We strongly urge the acceptance of this new testing strategy.

In summary, neither of the animal tests proposed by Arizona Chemical Company is appropriate and we urge the company to reconsider them and the EPA to uphold the principles of thoughtful toxicology. Thank you for your attention to these comments. I can be reached at 610-586-3975 or via e-mail at josephm@peta.org.

Sincerely,

Joseph Manuppello
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¹ U.S. EPA (Environmental Protection Agency). High Production Volume (HPV) Challenge Program. Robust Summaries & Test Plans: Rosin **Adducts** and **Adducts** Salts. Internet address: <http://www.epa.gov/oppt/chemrtk/rosnstrs/c13177tc.htm>

² U.S. EPA (Environmental Protection Agency). High Production Volume (HPV) Challenge Program. Robust Summaries & Test Plans: Rosin Esters. Internet address: <http://www.epa.gov/oppt/chemrtk/rosnstrs/c13552tc.htm>

³ 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 Pharmacology* 42 (2005) 218-224.

⁴ 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**, 3031-3036.