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June 13, 2001

The Honorable 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 Test Plan for Terpenoid Tertiary Alcohols and Related Esters

Dear Administrator Whitman:

The following comments on the test plan for the Terpenoid Tertiary Alcohols and Related Esters (TTARE) 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 nine million Americans.

The Flavor and Fragrance High Production Volume Consortia have developed a well-constructed category and have presented robust summaries that adequately address each health endpoint of the SIDS battery and all but one ecotoxicity endpoint. Any further testing on animals will not contribute to the understanding of the toxicity of the TTARE group. We recommend that no further testing on animals be conducted and that the proposed fish toxicity tests be deleted.

1. The Terpenoid Tertiary Alcohol and Related Esters (TTARE) chemical category is appropriate, well understood, and defensible.

The TTARE category presented by the Flavor and Fragrance Consortia is an example of a logically circumscribed group of chemicals, whose production and metabolism in plants and animals is well understood. The analysis of the group is sophisticated and underscored by a thorough understanding of the biochemical properties of these compounds. This type of category analysis has been applied in internationally accepted safety analyses for decades. In addition, there is a well-developed body of knowledge of the physiologic toxokinetics of these substances, including their hydrolysis in the gastrointestinal tract, gastric absorption rates, and behavior in the liver and other organs. The fundamental building block of these compounds is isoprene (i.e., all are isoprenoid compounds). They are all synthesized along the same biosynthetic pathway, and many of the compounds are naturally derived from each other in these biosynthetic pathways. The primary functional groups of all compounds are closely structurally related to each other, and all the compounds have similar molecular weights. The two complex substances in the group (pine oil and the thermal rearrangement products of linalool and terpenoids) are composed primarily of other compounds in the group. Therefore, biochemical, toxicokinetic, structural, functional, and exposure data all indicate that it is entirely appropriate to include these substances into a single group.

2. Abundant existing data demonstrate the low toxicity of these compounds.

Overall, the compounds in the TTARE group have a very low toxicity. Many of the compounds in the group already occur naturally in common foods. Ten of the 13 compounds in the group are classified as Generally Recognized as Safe by the Food and Drug Administration. Observations of human populations that directly consume millions of pounds of these products in fruits and vegetables indicate that they exhibit very low toxicity.

A series of extensive and, in our view, excessive, irrelevant animal experiments, has already been conducted with these compounds with little or no observed adverse effects. The doses have generally exceeded 1,000 milligrams per kilogram of bodyweight per day, a bolus dose far beyond any typical human exposures. To reemphasize, despite these outrageously high doses administered to animals, few effects have been observed from the compounds in this group. In fact, as outlined in the robust summary, many of the observed effects in these tests have primarily resulted from the test conditions, not from exposure to these compounds. *In vitro* genetic toxicity testing has also demonstrated little effect. Given that these compounds have been consumed by millions of people over many years, the resultant effects, if any, are available from human observation without the need to extrapolate from rodents.

3. The TTARE test plan demonstrates the problem of excluding human exposure assessment from the HPV program.

The TTARE test plan underscores one of the fundamental flaws of the HPV program: excluding exposure from the analysis. The ingestion of the natural form of these substances in fruits and vegetables is more than an order of magnitude greater than the ingestion of the manufactured form of these substances used as food flavoring additives. Because the HPV program has no real mechanism to include this critical exposure information, irrelevant animal testing is being proposed inappropriately.

4. Any aquatic toxicity testing on these chemicals is inappropriate and unnecessary.

As described in previous test plan comments to the Consortia addressing the cinnamyl derivatives, data on aquatic toxicity can be collected by using quantitative structure activity relationships or *in vitro* tests. *In vitro* tests with the protozoan *Tetrahymena* are frequently used as a measure of aquatic toxicity in ecological risk assessments. We have requested a meeting with the EPA to discuss how to incorporate these alternative, nonanimal methods into the HPV program.

Thank you for the opportunity to comment. I look forward to your response. I can be reached via telephone at 202-686-2210, ext. 302, or via e-mail at <ncardello@pcrm.org>. Correspondence should be sent to my attention at the following address: PCRM, 5100 Wisconsin Ave., Suite 400, Washington, DC 20016.

Sincerely,

Nicole Cardello, M.H.S.
Staff Scientist

cc: The Honorable Sherwood Boehlert
The Honorable Ken Calvert
The Honorable Jerry Costello
The Honorable Robert C. Smith