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November 17, 2000

The Honorable Carol Browner
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 Irganox 1010 (tetrakis-(methylene-(3,5-di-terbutyl-4-hydrocinnamate)methane)

Dear Administrator Browner:

The following comments on the test plan for Irganox 1010 (tetrakis-(methylene-(3,5-di-terbutyl-4-hydrocinnamate)methane) 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 animal protection and environmental organizations have a combined membership of more than nine million Americans.

The summary submitted by Ciba Specialty Chemicals Corporation appropriately does not call for any additional testing on this well-characterized chemical. The data provided are more than adequate under High Production Volume (HPV) Program guidelines. However, the presentation of the test plan raises some questions regarding compliance with the original HPV framework agreement in which sponsors committed to performing a thorough review of existing data. These concerns include:

- The summary presents minimal data and little discussion of its ability to meet the HPV standards and obviate the need for more tests. No qualitative information on the compound's application and behavior is provided.
- Ciba failed to identify additional existing information Irganox 1010, as several studies in the scientific literature and government databases describe the toxicity, fate, and transport of this chemical.
- This compound is already registered as an FDA food contact substance and more information may be available. Accordingly, we have submitted a Freedom of Information Act (FOIA) request for this information.
- The lack of description of the compound's use, structure, and behavior limits the ability to use the presented data in the development of chemical categories. At minimum, Irganox 1010 could be grouped with the similar compound presented by Ciba, Irganox 1076 (octadecyl 3,5-di(tert)-butyl-4-hydroxyhydrocinnamate).

The EPA needs to play a strong role in requiring that companies perform a thorough review of the literature

and present all available information on the proposed chemicals. The EPA also needs to assume a stronger role in promoting cooperation among participants with respect to chemical category formation. We ask the EPA to inform us how it intends to foster this cooperation in the development of chemical categories so that unnecessary, expensive, and poorly conceived testing is avoided. While Ciba does not call for additional testing, we are concerned that a regulatory review may disagree with Ciba's claim that no additional tests are necessary. We believe that additional testing of this well-understood compound would be redundant and would not contribute to a greater understanding of the public health impact of this chemical. We are therefore providing additional information to support Ciba's claim that no further tests are needed. It should be noted that in the event additional testing is called for, the testing must be deferred until November 2001 or later, as Irganox 1010 is an individual chemical.

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 404, Washington, DC 20016. I look forward to your response on this important issue.

Sincerely,

Nicole Cardello, MHS
Research Coordinator

cc: The Honorable Robert C. Smith
The Honorable F. James Sensenbrenner, Jr.
The Honorable Ken Calvert
The Honorable Jerry Costello
Council on Environmental Quality

General Comments on the Test Plan for Irganox 1010

The Ciba Specialty Chemicals Corporation has provided available in-house study results on Irganox 1010 that addresses each health endpoint of the SIDS battery and therefore appropriately has not called for more tests. However, the summary does raise some concern regarding the original HPV framework agreement in which sponsors committed to conducting a comprehensive review of existing data. We are providing further justification for Ciba's contention that no additional tests are needed under HPV guidelines.

Irganox 1010 is a sterically hindered phenolic antioxidant used as a stabilizer for organic substrates such as plastics. Irganox 1010 is a large, high molecular weight (MW= 1177.649), hydrophobic compound with low volatility. These physicochemical properties most likely explain the relatively low toxicity of Irganox 1010 on animals used in laboratory tests. No toxic effects were seen, even at doses exceeding EPA limit doses. For example, in the acute oral toxicity study, no clinical signs of toxicity were observed even at doses as high as 10,250 mg/kg body weight, two times the EPA limit dose. Irganox 1010 did not produce any eye or skin irritation. This chemical has been thoroughly tested on many animals and any further testing on more animals would not contribute to the understanding of its toxicity.

Several studies in the scientific literature provide additional information on the toxicity, fate, and transport of Irganox 1010 (see Table 1). Inclusion of results from these studies would provide a more comprehensive understanding of the properties and behavior of the compound.

Other Existing Toxicity Studies

As shown in Table 1, a study by the Department of Energy Los Alamos Lab, found acute oral LD-50 values for mice and rats dosed with Irganox 1010 to be greater than the EPA limit dose of 5,000 mg/kg bodyweight. Skin application studies in rabbits showed the material to be nonirritating, while eye irritation studies in the rabbit showed that Irganox 1010 was a mild but transitory irritant. A sensitization study in guinea pigs did not show the material to be deleterious.¹

The Department of Energy conducted an Ames assay on Irganox 1010 and found it to be non-mutagenic.² The tumor-producing potential of Irganox 1010 was also studied. The inhibitory activities on the intercellular gap-junctional communication were investigated using the V79 metabolic cooperation assay. Irganox 1010 did not demonstrate any tumor-producing activity.³

Other Existing Environmental Fate and Transport Studies

The mobility of antioxidant additives from food-packaging material has recently become a subject of interest. Several studies examine the fate and transport of Irganox 1010 from food-packaging substances and are presented in Table 1. These studies indicate that migration is a function of many factors such as molecular

complexity and volatility of the antioxidant, the packaging material, and the food simulant. These studies provide additional information on the environmental fate and transport of this chemical and potential exposure scenarios.⁴⁻⁸

Chemical Categories

Ciba failed to compare Irganox 1010 with other similar chemicals to form a group of phenolic antioxidants. Chemical categories should be formed whenever possible to reduce testing of other similar compounds. Irganox is one of many hindered phenolic stabilizers and could, at minimum, be grouped with another chemical proposed by Ciba, Irganox 1076 (octadecyl 3,5-di(tert)-butyl-4-hydroxyhydrocinnamate). We are asking the EPA to inform us how it intends to foster cooperation in category formation so that unnecessary, expensive, and poorly conceived testing is avoided.

Conclusion

Although Ciba Specialty Chemicals Corporation has presented its in-house data and appropriately not called for any testing, interpretation of study results and a comprehensive review of existing data are needed to provide a complete summary of the chemical's properties, behavior, and toxicity. Additionally, the inclusion of Irganox 1010 into a chemical category should be considered.

References

1. Drake GA, London JE, Smith DM, Thomas RG. Preliminary toxicological study of Irganox 1010. Government Reports Announcements and Index. Issue 18, 1980.
2. Wang SY, Smith, DM. *In vitro* mutagenicity testing. II. Silastic 386 foam elastomer, Irganox 1010, mixture of sylgard 184 with encapsulating resin and curing agent, and dimethylbenzanthracene. Government Reports Announcements and Index. Issue 15, 1980.
3. Tsuchiya T, Fukuhara K, Hata H, et al. Studies on the tumor-promoting activity of additives in biomaterials: Inhibition of metabolic cooperation by phenolic antioxidants involved in rubber materials. *Journal of Biomedical Materials Research* 1995;29:121-6.
4. Schwope AD, Till DE, Ehntholt DJ, et al. Migration of Irganox 1010 from ethylene-vinyl acetate films to foods and food-simulating liquids. *Food Chem Toxicol* 1987;25(4):327-30.
5. Schwope AD, Till DE, Ehntholt DJ, et al. Migration of BHT and Irganox 1010 from low-density polyethylene (LDPE) to foods and food-simulating liquids. *Food Chem Toxicol* 1987;25(4):317-26.
6. Nerin C, Salalfranca J, Rubio C, Cacho J. Multicomponent recycled plastics: considerations about their use in food contact applications. *Food Addit Contam* 1998;15(7):842-54.
7. Lickly TD, Bell CD, Lehr KM. The migration of Irganox 1010 antioxidant from high-density polyethylene and polypropyl series of potential fatty-food simulants. *Food Addit Contam* 1990;7(6):805-14.
8. Garde JA, Catala R, Gavara R. Global and specific migration of antioxidants from polypropylene films into food simulants. *J Food Prot* 1998;61(8):1000-6.

Table 1. Literature Review of Irganox 1010

Author	Title	Source	Subject
Drake <i>et al.</i> , 1980	Preliminary toxicological study of Irganox 1010	Government Reports Announcements and Index	toxicity—acute and irritation
Wang <i>et al.</i> , 1980	In vitro mutagenicity testing.II. Silastic 386 foam elastomer, Irganox 1010, mixture of sylgard 184 with encapsulating resin and curing agent, and dimethybenzanthracene.	Government Reports Announcements and Index	toxicity
Tsuchiya <i>et al.</i> , 1995	Studies on the tumor-promoting activity of additives in biomaterials: inhibition of metabolic cooperation by phenolic antioxidants involved in rubber materials	J Biomed Mat Res	toxicity
Schwoppe <i>et al.</i> , 1987	Migration of Irganox 1010 from ethylene-vinyl acetate films to foods and food-simulating liquids	Food Chem Toxicol	fate/transport, migration to food substances
Schwoppe <i>et al.</i> , 1987	Migration of BHT and Irganox 1010 from low-density polyethylene (LDPE) to foods and food-simulating liquids	Food Chem Toxicol	fate/transport, migration to food substances
Nerin <i>et al.</i> , 1998	Multicomponent recycled plastics: considerations about their use in food contact applications	Food Addit Contam	fate/transport, migration to food substances
Lickly <i>et al.</i> , 1990	The migration of Irganox 1010 antioxidant from high-density polyethylene and polypropyl series of potential fatty-food simulants	Food Addit Contam	fate/transport, migration to food substances
Garde <i>et al.</i> , 1998	Global and specific migration of antioxidants from polypropylene films into food simulants	J Food Prot	fate/transport, migration to food substances