

July 21, 1997

Lynn Goldman, M.D., M.P.H.  
Assistant Administrator for  
Prevention, Pesticides and Toxic Substances  
U.S. Environmental Protection Agency  
401 M Street, S.W.  
Washington, D.C. 20460

Dear Dr. Goldman:

The California Environmental Protection Agency's Office of Environmental Health Hazard Assessment (OEHHA), is the lead agency for implementing a California law (the Safe Drinking Water and Toxic Enforcement Act of 1986, more commonly known as "Proposition 65") which requires the Governor to publish and to update at least annually a list of chemicals known to the State to cause cancer or reproductive toxicity.

Under Proposition 65, one of three mechanisms under which a chemical may be listed is if it has been formally identified by an "authoritative body" as a carcinogen or a reproductive toxicant (i.e., a developmental toxicant, male reproductive toxicant, or female reproductive toxicant). The U.S. Environmental Protection Agency (U.S. EPA) has been designated as one of five authoritative bodies, along with the International Agency for Research on Cancer, the National Toxicology Program, the U.S. Food and Drug Administration, and the National Institute for Occupational Safety and Health.

OEHHA staff are currently evaluating a number of chemicals on the U.S. EPA's Toxics Release Inventory (TRI) list as potentially meeting the criteria for an "authoritative body" finding by U.S. EPA that the chemicals cause birth defects or other reproductive harm. These chemicals are: chinomethionat (oxythioquinox), cycloate, cyclohexanol, dicamba, diclofop methyl, 2,4-DB(4-[2,4-dichlorophenoxy] butyric acid, fenoxaprop ethyl, fluazifop butyl, fluvalinate, hydramethylnon (amdro), linuron, metam sodium, molinate, myclobutanil, oxadiazon, oxydemeton methyl, propachlor, propargite, resmethrin, sodium fluoroacetate, sodium nitrite and vinclozolin.

This is the first group of chemicals from the TRI listings that we consider to potentially meet the Proposition 65 "authoritative body" identification criteria, we are seeking information as to whether the U.S. EPA has, through placing these chemicals on the TRI list, formally concluded that any of the aforementioned chemicals are reproductive toxicants. More specifically, we would like to know if your Agency has concluded that, for any of the aforementioned chemicals, either of the following criteria had been satisfied:

- a) studies in humans indicate that there is a causal relationship between the chemical and reproductive toxicity, or

- b) studies in experimental animals indicate that there are sufficient data, taking into account the adequacy of the experimental design and other parameters such as, but not limited to, route of administration, frequency and duration of exposure, numbers of test animals, choice of species, choice of dosage levels, and consideration of material toxicity, indicating that an association between adverse reproductive effects in humans and the toxic agent in question is biologically plausible.

If you are aware of any other U.S. EPA documents in which the agency has formally concluded that any of the aforementioned chemicals cause birth defects or other reproductive harm to humans, or an association between the adverse reproductive effects of the aforementioned chemicals observed in experimental animals is biologically plausible in humans after considering all the parameters cited in (b) above, we would appreciate being advised accordingly.

We thank you for your attention to these matters, and look forward to hearing from you. Should you have any questions regarding this request, please do not hesitate to contact me at (916) 324-2831.

Sincerely,

William A. Vance, Ph.D.  
Deputy Director for Scientific Affairs

DRAFT

August 4, 1997

Mr. Daniel Barolo, Director  
Office of Pesticide Programs  
U. S. Environmental Protection Agency  
410 M Street, S.W. 87501C  
Washington, D.C. 20460

Dear Mr. Barolo:

The California Environmental Protection Agency's Office of Environmental Health Hazard Assessment (OEHHA) is the lead agency for implementing a California law (the Safe Drinking Water and Toxic Enforcement Act of 1986, more commonly known as "Proposition 65") which requires the Governor to publish and to update at least annually a list of chemicals known to the State to cause cancer or reproductive toxicity.

Under Proposition 65, one of three mechanisms under which a chemical may be listed is if it has been formally identified by an "authoritative body" as a carcinogen or a reproductive toxicant (i.e., a developmental toxicant, male reproductive toxicant, or female reproductive toxicant). The U.S. Environmental Protection Agency (U.S. EPA) has been designated as one of five "authoritative bodies," along with the International Agency for Research on Cancer, the National Toxicology Program, the U.S. Food and Drug Administration, and the National Institute for Occupational Safety and Health.

OEHHA is currently evaluating boric acid and its sodium salts, carbon dioxide (by inhalation), and linuron for possible listing as chemicals known to the State of California to cause reproductive and developmental toxicity, based on the following references:

ReRegistration Eligibility Document (R.E.D.) "Boric Acid and its Sodium Salts, EPA-738-R-93-017 USEPA Office of Prevention, Pesticides and Toxic Substances (7508W);

R.E.D. Facts: "Boric Acid," EPA-738-F-93-006 USEPA Office of Prevention, Pesticides and Toxic Substances (7508W) September 1993;

R.E.D.: "Carbon and Carbon Dioxide," EPA-PB92-161926 Office of Pesticides Programs, September 1991; and,

R.E.D. Facts: "Carbon Dioxide," EPA-738-F-91-101 Office of Pesticides and Toxic Substances (7508W), 1991

R.E.D. "Linuron" USEPA Office of Prevention, Pesticides and Toxic Substances, 1995.

The purpose of this letter is to seek information as to whether the U.S. EPA has formally concluded that boric acid and its sodium salts, carbon dioxide by inhalation or linuron are

reproductive toxicants. More specifically, we would like to know if your Agency has concluded that, for these chemicals either of the following criteria have been satisfied:

- a) studies in humans indicate that there is a causal relationship between the chemical and reproductive toxicity, or
- b) studies in experimental animals indicate that there are sufficient data, taking into account the adequacy of the experimental design and other parameters such as, but not limited to, route of administration, frequency and duration of exposure, numbers of test animals, choice of species, choice of dosage levels, and consideration of material toxicity, indicating that an association between adverse reproductive effects in humans and the toxic agent in question is biologically plausible.

In the R.E.D. for boric acid and its salts on pages 25 and 26, U.S. EPA states:

“In chronic oncogenicity studies using mice, rats and beagle dogs, boric acid and borax were found not to be carcinogenic; however, testicular effects and decreases in body weight resulted at high dose levels.” “In reproductive and developmental toxicity studies using rats, mice, and rabbits, maternal liver and kidney effects and decreased weight gain as well as decreased fetal body weights were observed. In two studies, at the highest dose levels, no litters were produced. Prenatal mortality occurred at the highest dose levels in the rabbit study.”

U.S. EPA also summarized that:

“The numbers of corpora lutea were found to be decreased in a multi-generation study conducted in rats, indicating a decreased frequency of ovulation. When treated female rats were mated with control males, there was a decrease in the number of litters produced, and pup survival was compromised.”

Was the intent of these statements in the R.E.D. to formally identify boric acid and its sodium salts as reproductive or developmental toxicants? This would be very significant to the implementation of California’s Proposition 65 as to whether the R.E. D. constitutes a formal identification by U.S. EPA as an "authoritative body."

In the R.E.D. for carbon and carbon dioxide, on pages 8 and 10, U.S. EPA states:

“ . . . chronic studies using test animals resulted in birth defects and adverse effects on sperm production.” Deleterious effects on sperm of various animal species have been reported following exposure to high carbon dioxide atmospheres.” “Serious teratological effects from acute exposure to atmospheres containing more than 10% carbon dioxide have been reported in toxicological studies.”

Was the intent of these statements in the R.E.D. to formally identify carbon dioxide as a reproductive or developmental toxicant? Whether or not an R.E.D. constitutes a formal

identification of carbon dioxide as a reproductive or developmental toxicant by U.S. EPA as an "authoritative body" is important to implementation of California's Proposition 65.

If you are aware of any other U.S. EPA documents in which the Agency concludes that boric acid and its sodium salts or carbon dioxide pose reproductive or developmental hazards to humans, we would appreciate being advised accordingly.

In the R.E.D. for linuron, U.S. EPA states:

for the rat study, "The NOELs for maternal systemic toxicity and developmental toxicity were 125 ppm (12.1 mg/kg/day). The LOEL of 625 ppm (49.8 mg/kg/day) for maternal systemic toxic effects was based upon decreased body weight and food consumption values. The developmental toxicity LOEL of 625 ppm (49.8 mg/kg/day) was based on increased in postimplantation loss and increases in the litter and fetal incidences of resorptions."

for the rabbit study, ". . . a maternal systemic toxicity LOEL was observed at the 25 mg/kg/day level, based upon reduced maternal body weight, thereby defining the NOEL as 5 mg/kg/day. At the high-dose level (100 mg/kg/day) maternal body weight, food consumption, absolute liver weight, and liver-to-body weight ratios were decreased. The developmental toxicity NOEL was determined to be 25mg/kg/day, based upon an increased number of abortions, decreased mean number of fetuses per litter; decreased fetal body weight, and increased incidence of fetuses with skeletal variations of the skull at the 100 mg/kg/day level (the developmental toxicity LOEL)."

Was the intent of these statements in the R.E.D. to formally identify linuron as a reproductive or developmental toxicant? Whether or not an R.E.D. constitutes a formal identification of linuron as a reproductive or developmental toxicant by U.S. EPA as an "authoritative body" is important to implementation of California's Proposition 65.

We thank you for your attention to these matters and look forward to hearing from you.

Sincerely,

William A. Vance, Ph.D.  
Deputy Director for Scientific Affairs

cc: Cynthia Oshita  
Proposition 65 Implementation

August 4, 1997

Fred R. Shank, Ph.D.  
Director  
Center for Food Safety and Applied Nutrition  
Food and Drug Administration (HFS-1)  
200 C Street, S.W., Room 6815B  
Washington, DC 20204.

Dear Dr. Shank:

The California Environmental Protection Agency's Office of Environmental Health Hazard Assessment (OEHHA) is the lead agency for implementing a California law, the Safe Drinking Water and Toxic Enforcement Act of 1986, more commonly known as "Proposition 65." As you may be aware, this law requires the Governor to publish and to update at least annually a list of chemicals known to the State to cause cancer or reproductive toxicity.

Under Proposition 65, one of three mechanisms under which a chemical may be listed is if it has been "formally identified" as a carcinogen or a reproductive toxicant by an "authoritative body." The U.S. Food and Drug Administration (FDA) has been designated as one of five authoritative bodies, along with the International Agency for Research on Cancer (IARC), the National Toxicology Program (NTP), the United States Environmental Protection Agency (U.S. EPA), and the National Institute for Occupational Safety and Health (NIOSH).

OEHHA is currently investigating the possible listing of a number of chemicals as known to the State of California to cause cancer or reproductive toxicity, based upon the conclusions of an authoritative body. Among these chemicals are those listed below, which appear to be subject to FDA regulation when in food or in food contact materials.

***Endpoint of Concern: Carcinogenicity***

<u>Chemical</u>	<u>CAS number</u>
Chloroprene	126-99-8

***Endpoint of Concern: Birth defects or other reproductive harm***

<u>Chemical</u>	<u>CAS number</u>
Avermectin B1	71754-41-2
Borax (Sodium borate)	1303-96-4
	1330-43-4
Boric acid	10043-35-3
Carbon dioxide (by inhalation)	124-38-9
Cyclahexanol	108-93-0
Dibutyl phthalate	84-74-2

Di(2-ethylhexyl)phthalate  
Heptachlor  
Sodium nitrite

117-81-7  
76-44-8  
7632-00-0

As part of our efforts to ensure that our listing decisions are based upon a thorough consideration of all relevant information, we are inquiring about any actions your Agency has taken or plans to take in the near future which involved or may involve an evaluation of the carcinogenicity of chloroprene, or the developmental or reproductive toxicity of the rest of the chemicals listed above. We are particularly interested in any conclusions the FDA has reached regarding whether or not any of the above chemicals is a reproductive toxicant or carcinogen.

More specifically, we would like to know if your Agency has concluded that, for chloroprene, either of the following criteria had been satisfied:

- a) studies in humans indicate that there is a causal relationship between the chemical and cancer, or
- b) studies in experimental animals indicate that there is an increased incidence of malignant tumors or combined malignant and benign tumors in multiple species or strains, in multiple experiments (e.g., with different routes of administration or using different dose levels), or to an unusual degree, in a single experiment with regard to high incidence, site or type of tumor, or age at onset.

For the rest of the chemicals, we would like to know if your Agency has concluded that either of the following criteria had been satisfied:

- a) studies in humans indicate that there is a causal relationship between the chemical and reproductive toxicity, or
- b) studies in experimental animals indicate that there are sufficient data - taking into account the adequacy of the experimental design and other parameters such as, but not limited to, route of administration, frequency and duration of exposure, numbers of test animals, choice of species, consideration of maternal toxicity - indicating that an association between adverse reproductive effects in humans and the toxic agent in question is biologically plausible.

We thank you for your attention to this matter, and look forward to hearing from you. Should you have any questions regarding this request, please call me at (916) 324-2831.

Sincerely,

William A. Vance, Ph.D.  
Deputy Director for Scientific Affairs

cc: Deborah M. Hesse  
Deputy Director of Regulatory Outreach and  
Administrative Program

Cynthia Oshita  
Senior Hazardous Materials Specialist

DRAFT