Candidates for Proposition 65 Listing via the Authoritative Bodies Mechanism Found Not to Meet the Scientific Criteria (22 CCR 12306(g))

Office of Environmental Health Hazard Assessment
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The U.S. Environmental Protection Agency (U.S. EPA), an authoritative body for purposes of Proposition 65 (22 CCR Section 12306(l)), identifies chemicals as causing developmental or reproductive toxicity in implementing its Toxic Release Inventory (TRI) program (*i.e.*, Section 313 of the Emergency Planning and Community Right-to-Know Act of 1986 (EPCRA)). On this basis the U.S. EPA, in 1994, added a number of chemicals to the TRI list and published its findings in the *Federal Register* (**59:**1788-1859, 1994 and **59:**61432-61485, 1994). The Office of Environmental Health Hazard Assessment (OEHHA) has reviewed the bases for these TRI chemical additions in the context of the regulatory criteria governing Proposition 65 listing via the authoritative bodies mechanism (Title 22, California Code of Regulations, Section 12306 (22 CCR 12306)).

OEHHA determined for several TRI chemicals that the 22 CCR 12306 regulatory criteria were met and is in the process of placing these chemicals on the Proposition 65 list of chemicals known to cause reproductive toxicity. OEHHA has determined that these same regulatory criteria have not been met for some of the chemicals added by U.S. EPA in 1994 to the TRI list on the basis of reproductive or developmental toxicity. These chemicals are listed in Table 1. In each case the scientific criteria for "as causing reproductive toxicity" given in regulation (22 CCR 12306(g)) were not satisfied, as described below.

In accordance with 22 CCR 12306(i), one of the chemicals in Table 1, propachlor, will be referred to the Developmental and Reproductive Toxicant (DART) Identification Committee of the OEHHA Science Advisory Board because this determination was made subsequent to the issuance of a notice of intent to list (*California Regulatory Notice Register (CRNR)*, December 4, 1998). Therefore, at a future meeting, the DART Identification Committee will opine whether "the chemical has been clearly shown through scientifically valid testing according to generally accepted principles" to cause reproductive toxicity. *CRNR* notices for two other chemicals in Table 1 (tebuthiuron (October 30, 1998); dimethoate (November 20, 1998)) announced that the regulatory criteria for listing may have been met. However, because a notice of intent to list was not issued, these chemicals will not be referred to the DART Identification Committee for its review.

Table 1: TRI chemicals not meeting the scientific criteria (22 CCR 12306(g)) for authoritative bodies listing as causing reproductive toxicity under Proposition 65

Dicamba (CAS No.001918-00-9)
Dimethoate (000060-51-5)
Fenoxycarb (072490-01-8)
Potassium N-methyldithiocarbamate (137-41-7)
Propachlor (001918-16-7)
Sodium dicamba (00198-69-0)
Simazine (000122-34-9)
Tebuthiuron (034014-18-1)
Triphenyltin chloride (000076-87-9)

Dicamba (CAS No. 001918-00-9)

Two rat and one rabbit teratology studies serve as the basis for the TRI identification of developmental toxicity, OEHHA also examined a more recent rabbit study not cited under TRI. As described below, the rat studies provide little or no evidence of developmental toxicity. The rabbit study had equivocal results not replicated in a later study of much better quality performed at higher dose levels. Thus the overall amount of evidence on developmental toxicity is insufficient relative to the listing criteria specified in 22 CCR 12306(g).

The first rat study (Shchitskova et al., *Gig.* Sanit. 6:4-7, 1986 [Russian]) provided data on myocardial toxicity in offspring for some pesticides, but not for dicamba. For the second rat study an equivocal increase in skeletal abnormalies was observed at the lowest dose, with no apparent effects at higher doses (1981; Toxigenetics Study No. 450-0460; MRID 0008424). The U.S. EPA's *Tox One-Liner* cited in the TRI documentation was not available; however, the U.S. EPA, in other documentation (*Integrated Risk Information System [IRIS];* 1988 *Health Advisory*), reported this study as showing no developmental effects. The original rabbit study (Velsicol Chemical Company, 1978, MRID No. 00028236) had several deficiencies including: 1) the combination of data from two experiments because there were not enough pregnancies in the first experiment; 2) no individual data being provided; 3) numerous deaths across all treatment and control groups associated with "pulmonary involvement"; and 4) no analysis of the purity of the dosing solution. This study was reported to show decreased fetal weights and increased post-implantation loss, but the results were equivocal. The later rabbit study (Argus Research Labs., Protocol No. 1819-004, 1992), a higher quality study, conducted at higher dose levels showed only irregular nasal and internasal ossification in the fetuses, the significance of which was unclear.

Dimethoate (CAS No. 000060-51-5)

Two studies served as the basis for the TRI identification of dimethoate as causing developmental toxicity. In a developmental toxicity study in rats (Khera et al., *Bull. Env. Contam. Tox.*, 22:522-529, 1979), the formulation administered was only 47.3% dimethoate, with the remaining constituents unknown; the authors of the study noted that the effects observed could not be attributed to dimethoate. In a multigeneration study in mice (Budreau and Singh, *TAP*, 26:29-38, 1973), the adverse effects observed were postnatal growth and survival of pups, neither of which appeared to be affected until between days 8 and 12 postnatal; thus the effect seems likely to have resulted from postnatal, rather than prenatal, exposure. Under the U.S. EPA Guidelines for Developmental Toxicity Risk Assessment (*Federal Register* 56(234): 63798-63826, 1991), the definition of developmental toxicity includes effects resulting from exposure during the postnatal developmental period, while under the current interpretation, the Proposition 65 statute precludes listing on the basis of developmental effects resulting solely from postnatal exposures.

Fenoxycarb (CAS No. 072490-01-8)

The U.S. EPA based its finding of developmental toxicity on postnatal manifestations of developmental toxicity (pinna unfolding) in a rat reproductive study, following exposures to the chemical throughout pre- and postnatal development. Under the U.S. EPA Guidelines for Developmental Toxicity Risk Assessment (*Federal Register* 56(234): 63798-63826, 1991), the definition of developmental toxicity includes effects resulting from postnatal exposure, while under the current interpretation, the Proposition 65 statute precludes listing on the basis of developmental effects resulting solely from postnatal exposures.

Potassium N-methyldithiocarbamate (CAS No. 137-41-7)

U.S. EPA's identification of this chemical as causing developmental toxicity was based on data for potassium dimethyldithiocarbamate. U.S. EPA based this action on the assumption of a structure-activity relationship between the two chemicals, without referring to metabolic or other data to support this assumption.

Propachlor (CAS No. 001918-16-7)

A developmental toxicity study in rabbits was cited by U.S. EPA as the basis for identification of propachlor as causing developmental toxicity (Miller, 1983, IRDC Corp., as cited in U.S. EPA 1988 *Health Advisory*). The U.S. EPA's 1998 *Reregistration Eligibility Decision* (*RED): Propachlor* identified deficiencies in the study not discussed in the TRI documentation. This study was replicated, and the U.S. EPA in its 1998 *RED* reported this study as showing no evidence of developmental toxicity.

Simazine (CAS. No. 000122-34-9)

The basis for the TRI finding of male reproductive toxicity is a study of necrotic changes in the germinal epithelium of the testis, and disturbances in spermatogenesis in sheep (Dshurov A, *Zentralblatt fur Veterinarmedizin. Reiche A*, 26:44-54, 1979). While suggestive of adverse effects of the test material on the male reproductive system, the study is inconclusive as the test material consisted of only 50% simazine, and was otherwise uncharacterized. The small numbers of animals in each experimental group and the lack of information on systemic toxicity also detract from the study findings.

Sodium dicamba (CAS No. 00198-69-0)

U.S. EPA TRI identification of this chemical as causing developmental toxicity is based entirely on data for dicamba, which does not meet the scientific criteria for listing (see above).

Tebuthiuron (CAS No. 034014-18-1)

U.S. EPA cited several studies as showing developmental toxicity for this chemical, but only in one, a study in rabbits, was the effect clearly attributable to prenatal exposure. Under the U.S. EPA Guidelines for Developmental Toxicity Risk Assessment (*Federal Register* 56(234): 63798-63826, 1991), the definition of developmental toxicity includes effects resulting from postnatal exposure, while under the current interpretation, the Proposition 65 statute precludes listing on the basis of developmental effects resulting solely from postnatal exposures. Thus for Proposition 65 purposes, only the rabbit study supports the finding of developmental toxicity. In this study reduced fetal weights were observed at the high dose, but the U.S. EPA in its 1994 *Reregistration Eligibility Decision: Tebuthiuron (List A, Case 0054),* attributed this effect to litter size and concluded that no compound-related developmental effects were observed.

Triphenyltin chloride (CAS No. 000076-87-9)

The U.S. EPA TRI identification of male reproductive toxicity is based on a rat study (*J. Econ. Entomol.* 61:32, 1968) in which a single dose level was administered. There were 20 animals in the treatment group, and a single control animal. Although various degenerative changes of the testis and 60-70% sterility were reported, no information was provided as to how fertility was assessed. "Drastic" loss in body weight, and effects on blood clotting (including spontaneous bleeding from the mouth and nasal passages) were also reported. Two animals (10% of the test group) were sacrificed early because of excessive blood loss. What appeared to be additional data cited in the *Tox One-Liner* were found to be also from this same study. Thus the overall amount of evidence on male reproductive toxicity is insufficient relative to the listing criteria specified in 22 CCR 12306(g).