CHEMICAL MEETING THE CRITERIA FOR LISTING AS CAUSING REPRODUCTIVE TOXICITY VIA THE AUTHORITATIVE BODIES MECHANISM

TRIPHENYLTIN HYDROXIDE IDENTIFIED BY U.S. EPA

PACKAGE 11A.1a

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Reproductive and Cancer Hazard Assessment Section
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

Triphenyltin hydroxide (CAS No. 76-87-9) meets the criteria for listing under Proposition 65 via the authoritative bodies listing mechanism. The regulatory guidance for listing by this mechanism is set forth in Title 22, California Code of Regulations (CCR), Section 12306. For example, the regulations include provisions covering the criteria for evaluating the documentation and scientific findings by the authoritative body to determine whether listing under Proposition 65 is required.

The U.S. Environmental Protection Agency (U.S. EPA) has been identified as an authoritative body for purposes of Proposition 65 (22 CCR Section 12306(l)) and has identified triphenyltin hydroxide as causing developmental or reproductive toxicity (DART). This was done by that Agency 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 the basis of identifying chemicals that caused reproductive, developmental and/or other toxicities the U.S. EPA added a number of chemicals to the TRI list. The U.S. EPA published its toxicity findings in the Federal Register (59:1788-1859, 1994 and 59:61432-61485, 1994). In proposing specific chemicals for addition to the TRI list, the Agency stated that a hazard assessment was performed for each candidate, "…in accordance with relevant EPA guidelines for each adverse human health or environmental effect …" Federal Register 59:1790).

OEHHA has found that triphenyltin hydroxide has been "formally identified" as causing reproductive toxicity according to the regulations covering this issue (22 CCR 12306(d)) because the chemical has "been identified as causing … reproductive toxicity by the authoritative body" (i.e., U.S. EPA) "in a document that indicates that such identification is a final action" (e.g., the TRI Final Rule [Federal Register 59:61432]) and have "been included on a list of chemicals causing … reproductive toxicity issued by the authoritative body" "and the document specifically and accurately identifies the chemical" and has been "published by the authoritative body in a publication, such as, but not limited to the federal register…"

OEHHA also finds that the criteria for "as causing reproductive toxicity" given in regulation (22 CCR 12306(g)) have been satisfied for triphenyltin hydroxide. In making

this evaluation, OEHHA relied upon the documents and reports cited by U.S. EPA in making their finding that the specified chemicals cause reproductive toxicity. In some cases, OEHHA consulted additional sources of information on the specific studies cited by U.S. EPA if those sources or studies were part of the administrative record for the TRI process. This was done only where necessary to affirm or clarify details of results and study design for studies cited by U.S. EPA; OEHHA did not review additional studies not relied on by U.S. EPA, nor did OEHHA consider information contained in sources outside of the administrative record.

A major source of information used by the U.S. EPA was the "Tox-Oneliner" database maintained by U.S. EPA's Office of Pesticide Programs (OPP). This database consists of brief summaries of (usually unpublished) data submitted to the U.S. EPA in compliance with regulatory requirements. Many database entries include a notation of "core grade" - a system formerly used by U.S. EPA to indicate the extent to which a study conformed to published test guidelines (U.S. EPA, 1984). Under this scheme, a "core grade guideline" study was considered to meet all guideline requirements; a "core grade minimum" study was considered sufficient for risk assessment; and a "core grade supplementary study" was considered to provide useful supplementary information, but not to be suitable for risk assessment on its own.

Studies cited by U.S. EPA in making findings with regard to reproductive toxicity are briefly described below. The statements in bold reflect data and conclusions which appear to satisfy the criteria for sufficiency of evidence for reproductive toxicity in regulation (22 CCR 12306(g)). Where a notation of "not stated" has been made, OEHHA staff were unable to find an explicit statement of a particular detail such as the number of animals in each dose group. Where NOELs (no-observed-effect-level), LOELs (lowest-observed-effect-level), or LELs (lowest-effect-level) are included in the study descriptions below, they are quoted directly from the cited references.

Studies cited by U.S. EPA in making findings with regard to reproductive toxicity are briefly described below. The statements in bold reflect data and conclusions which satisfy the criteria for sufficiency of evidence for reproductive toxicity in regulation (22 CCR 12306(g)). Where a notation of "not stated" has been made, OEHHA staff were unable to find an explicit statement of a particular detail such as the number of animals in each dose group.

<u>Triphenyltin hydroxide (CAS No. 76-87-9)</u>

The *developmental toxicity* of triphenyltin hydroxide was manifested as decreased embryo/fetal viability in rats.

The U.S. Environmental Protection Agency (U.S. EPA, 1994a and 1994b) concluded that "…there is sufficient evidence for listing triphenyltin hydroxide on EPCRA section 313 pursuant to EPCRA section 313(d)(2)(B) based on the … developmental toxicity data for this chemical."

Supporting documentation for the TRI listing (U.S. EPA, 1993) states, "In a teratogenicity study in rats, oral doses of 15 mg/kg during gestation days 1 - 7 prevented implantation (HSDB 1993); when administered from day 8 and onwards, the compound was fetolethal. Data from OPP's one-liner database support these findings." In addition to the single study cited in HSDB, 13 documents providing supporting data were identified in the one-liner database. The copy of the one-liner database provided to OEHHA by U.S EPA and referenced below (U.S. EPA 1999) was dated 1999; however, all of the documents referenced below were dated prior to the release of the TRI documentation in 1994.

With regard to the documents cited as supporting U.S. EPA's action in adding a chemical to the EPCRA-TRI list, OEHHA finds that the evidence for DART effects meets the criteria of 22 CCR 12306, and notes the following:

1. **Adequacy of the experimental design:**

a) Rat developmental toxicity study: insufficient information provided to assess the quality of the study (HSDB, 1993).
b) Rat developmental toxicity study: core grade minimum (U.S. EPA, 1999) [Batelle Columbus Labs No. 723-0200, 6/25/81].
c) Hamster developmental toxicity study: core grade guideline (U.S. EPA, 1999) [Batelle Columbus Labs No. 723-0100, 2/10/82].
d) Rat developmental toxicity study: core grade minimum (U.S. EPA, 1999) [Cannon Labs Inc. 10/12/76].
e) Rat developmental toxicity study: core grade guideline (U.S. EPA, 1999) [Wil Research Lab. Wil-39011, 4/2/85].
f) Rat developmental toxicity study: core grade supplementary (U.S. EPA, 1999) [Wil Research Lab. Wil-39013, 6/4/85].
g) Rat developmental toxicity study. Unable to determine quality from information in tox one-liner database (U.S. EPA, 1999) [Research Triangle Inst. 1/28/85].
h) Rat developmental toxicity study: core grade supplementary (U.S. EPA, 1999) [Central Inst. Voedingsonderzoek 2/68].
i) Rabbit developmental toxicity study (pilot): core grade supplementary (U.S. EPA, 1999) [Wil Research Lab. Wil-39031, 2/27/87].
j) Rabbit developmental toxicity study: core grade guideline (U.S. EPA, 1999) [Wil Research Lab. Wil-39012, 2/27/87].
k) Rabbit dermal developmental toxicity study: not classified, but noted to be "unsuitable for regulatory purposes" (U.S. EPA, 1999) [Pharmaco LSR; HAG/102, 2/15/93].
l) Rabbit dermal developmental toxicity study: core grade guideline (U.S. EPA, 1999) [Wil Research Lab. Wil-160012, 8/27/93].
m) Rat 1-generation reproduction study: core grade supplementary (range finding study) (U.S. EPA, 1999) [Battelle Memorial Inst. No. 723-0400, 7/22/82].
n) Rat 2-generation reproduction study: core grade guideline (U.S. EPA, 1999) [Wil Research Lab. Wil-39022, 8/28/86].

2. **Route of administration:**

a) Not stated.
b) Gavage.
c) Gavage.
d) Gavage.
e) Not stated, but (due to core grade guideline grading) presumably gavage as specified by U.S. EPA test guidelines (1984) for developmental toxicity studies.
f) Gavage.
g) Not stated.
h) Feeding study.
i) Not stated.
j) Gavage.
k) Dermal.
l) Dermal.
m) Not stated
n) Not stated, but (due to core grade guideline grading) presumably oral as specified as the preferred route by U.S. EPA test guidelines (1984) for reproductive toxicity studies.

3. **The frequency and duration of exposure:**

a) Days 1-7 or 8-14 of gestation (reported in the TRI support document to be days 1-7 of gestation or day 8 and onwards of gestation (U.S. EPA, 1993)).
b) Daily on each of gestation days 5-19.
c) Daily on each of gestation days 5-14.
d) Daily on each of gestation days 6-15.
e) Not stated, but (due to core grade guideline grading) presumably daily on each of gestation days 6-15, as specified by U.S. EPA test guidelines (1984) for developmental toxicity studies.
f) Daily on each of gestation days 6-15.
g) Not stated.
h) Only notation is that feeding was conducted "for 2 and 4 weeks."
i) Not stated.
j) Daily on each of gestation days 6-18.
k) Not stated.
l) Daily on each of gestation days 7-19.
m) Not stated.
n) Not stated, but (due to core grade guideline grading) presumably daily beginning at least 8 weeks prior to the mating period, as specified by U.S. EPA test guidelines (1984) for reproductive toxicity studies.

4. **The numbers of test animals:**

a) Not stated
b) 20 animals per dose group.
c) 20 animals per dose group.
d) 20 animals per dose group.
e) Not stated, but (due to core grade guideline grading) presumably at least 20 pregnant animals per dose group, as specified by U.S. EPA test guidelines for developmental toxicity studies.

f) 40 animals per dose group.
g) Not stated.
h) Not stated.
i) Not stated.
j) Not stated, but (due to core grade guideline grading) presumably at least 12 pregnant animals per dose group, as specified by U.S. EPA test guidelines (1983a) for developmental toxicity studies.
k) Six or less pregnant dams per group at the time of delivery.
l) Not stated, but (due to core grade guideline grading) presumably at least 12 pregnant animals per dose group, as specified by U.S. EPA test guidelines (1984) for developmental toxicity studies.
m) Not stated
n) Not stated, but (due to core grade guideline grading) presumably daily beginning at least 8 weeks prior to the mating period, as specified by U.S. EPA test guidelines (1984) for reproductive toxicity studies.

5. **The choice of species:** Species named in item 1 above. Rats, rabbits, and hamsters are standard species used in developmental toxicity testing.
6. **The choice of dosage levels:**

a) 20 mg/kg on days 1-7 of gestation, not specifically stated for days 8-14 of gestation (reported in the TRI support document to be 15 mg/kg on days 1-7 of gestation, not specifically stated for days 8 and onwards of gestation (U.S. EPA, 1993)).
b) 0, 1, 2.8, 8 mg/kg/day
c) 0, 2.15, 5.08, 12 mg/kg/day
d) 0, 1.25, 5, 8.75, 12.5 mg/kg/day (doses reported in some places in the tox one-liner as ppm rather than mg/kg--same numerical values).
e) 0, 0.35, 1.0, 2.8, 8.0 mg/kg/day.
f) 0, 0.35, 1.0, 2.8, 8.0 mg/kg/day
g) Not stated.
h) 0, 0.5, 1.0, 5.0, 25 ppm.
i) 0, 0.1, 1, 2, 4, 6, 8 mg/kg/day.
j) 0, 0.1, 0.3, 0.9 mg/kg/day.
k) Not stated.
l) 0, 1.5, 2.25, or 3.0 mg/kg/day.
m) 100, 200 ppm (doses of 0, 5, 15.8 and 50 ppm were selected for the definitive study)
n) 0, 5, 18.5, 50 ppm

7. **Developmental toxicity:**

a) Oral doses of 15 mg/kg during gestation days 1 - 7 prevented implantation; when administered from day 8 and onwards, the compound was fetolethal.
b) Terata NOEL < 1.0 mg/kg (LDT), 10% incidence of hydroureter.
c) Fetotoxic LEL = 12 mg/kg (HDT), base on delayed ossification. Decreased number of live fetuses was also noted at this dose.
d) Teratogenic LEL < 1.25 ppm (LDT) based on hydrocephalus and hydronephrosis at 1.25 ppm. Decreased % of live fetuses was noted at 5.08 ppm.

e) Fetotoxic LEL = 8.0 mg/kg/day, increase in unossified sternebrae and decreasing pup weight.
f) Fetotoxic LEL = 2.8 mg/kg/day, kidney weight changes at 2.8 mg/kg/day, poor pup survival at birth at 8.0 mg/kg/day.
g) Equivocal differences in morphological development of ureters in treated fetuses assess just before birth. No differences in pups assessed shortly after weaning.
h) No effects reported.
i) Resorptions and severe pup weight decreases at several dose levels, total resorptions and deaths at some levels of exposure, teratogenicity not fully assessed.
j) Developmental NOEL > 0.9mg/kg/day, the HDT. Slight but not statistically significant body weight decrease at this dose level.
k) High rate of resorptions at all dose levels.
l) Developmental LEL > 3.00mg/kg/day, the HDT. Equivocal findings for certain external malformations at HDT not sufficient to conclude a definite relationship to the test material.
m) Pup deaths and decreased pup body weight at 100 and 200 ppm.
n) Developmental LEL = 18.5 ppm, decrease in live litter size.

8. **Maternal toxicity:**

a) No information provided.
b) Maternal toxicity: NOEL = 2.8 mg/kg, LEL = 8.0 mg/kg (decreased body weight).
c) Maternal toxicity: NOEL = 5.08 mg/kg, LEL = 12 mg/kg (reported to be based on decreased number of live fetuses, rather than a systemic maternal effect).
d) Maternal toxicity: NOEL = 5 ppm, LOAEL = 8.75 ppm (reported to be based on abortion, decreased percent live fetuses, decreased fetal weight and increased resorptions, as well as decreased body weight gain,).
e) Maternal toxicity: NOEL = 1.0 mg/kg/day, LOAEL = 2.8 mg/kg/day (weight loss and decreased food consumption).
f) Maternal toxicity: NOEL = 1.0 mg/kg/day, LOEL = 2.8 mg/kg/day (body weight changes; hair loss and lethargy at 8.0 mg/kg/day).
g) Maternal toxicity not mentioned.
h) Maternal toxicity not mentioned.
i) Maternal toxicity: NOEL > 0.1 mg/kg/day, LOEL = 1.0 mg/kg/day (body weight decreases).
j). Maternal toxicity: NOEL = 0.1 mg/kg/day, LOEL = 0.3 mg/kg/day (decreased body weight).
k) Maternal toxicity not mentioned.
l) Maternal LOEL > 3.0 mg/kg/day.
m) Kidney effects in parents at 100 and 200 ppm.
n) Maternal toxicity: NOEL = 18.5 ppm, LEL = 50 ppm (decreased body weight gain)

References:

Hazardous Substances Data Bank (HSDB, 1993). Triphenyltin hydroxide.

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U.S. Environmental Protection Agency (U.S. EPA, 1994a). Proposed Rule: Addition of Certain Chemicals; Toxic Chemical Release Reporting; Community Right to Kno*w. Federal Register* **59**: 1788.

U.S. Environmental Protection Agency (U.S. EPA, 1994b). Final Rule: Addition of Certain Chemicals; Toxic Chemical Release Reporting; Community Right to Kno*w. Federal Register* **59**(229): 61432.

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