CHEMICALS MEETING THE CRITIERIA FOR LISTING AS DEVELOPMENTAL AND REPRODUCTIVE TOXICANTS (DARTs) VIA THE AUTHORITATIVE BODIES MECHANISM: THIOBENDAZOLE, IDENTIFIED BY U.S. EPA

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Thiobendazole (CAS No. 148-79-9) 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 thiabendazole as causing developmental or reproductive toxicity. 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 which 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 thiobendazole has been "formally identified" as causing reproductive toxicity according to the regulations covering this issue (22 CCR 12306(d)) because the chemicals have "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" (*i.e.*, the TRI *Final Rule* (*Federal Register* **59:**61432)) and has "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 thiabendazole. In making this evaluation, OEHHA relied upon the documents and reports cited by U.S. EPA in making

their finding that this chemical causes reproductive toxicity (for the developmental endpoint). OEHHA consulted additional sources of information on the specific studies cited by U.S. EPA. This was done only where necessary to affirm or clarify details of results and study design for studies cited by U.S. EPA.

While not the case for thiabendazole, a major source of information used by the U.S. EPA in its TRI evaluations 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 Agency 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 1983a and 1983b). 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 discussed below. The statement in bold reflects 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.

Thiabendazole (CAS No. 148-79-8)

The *developmental toxicity* of thiabendazole has been manifested as decreased fetal weights and increased malformation frequency in mice exposed *in utero.*

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

U.S. EPA (1993) states, "Oral administration of 600 mg/kg/day (LOEL) to rats on days 6 through 15 of gestation produced cleft palate and open eyes (9 [RTECS, 1993]) [a]. Musculoskeletal abnormalities were observed in the offspring of mice orally administered 240 mg/kg on day 9 of gestation (9 [RTECS, 1993]) [b]. Musculoskeletal abnormalities were also observed in the offspring of rats orally administered 296 mg/kg/day on days 8 through 15 of gestation (9 [RTECS, 1993]) [c]. Decreased litter size, and skin abnormalities were observed in the offspring of rats orally administered 667 mg/kg/day on days 8 through 15 of gestation (9 [RTECS, 1993]) [d]. Oral administration of 1,300 mg/kg/day produced musculoskeletal abnormalities and fetal death in the offspring of

mice (9 [RTECS, 1993]) [e]. Oral administration of 2,400 mg/kg/day on day 11 of gestation produced craniofacial abnormalities in the offspring of mice (9 [RTECS, 1993]) [f]."

The supporting document (US EPA, 1993), which referenced RTECS as the citation for these studies, also noted: "The RTECS data cannot be evaluated because of the lack of details." Because of this statement in the TRI supporting documentation (U.S. EPA, 1993), as well as concerns raised by comments received in response to the Request for Relevant Information (OEHHA, October 9, 1998), OEHHA retrieved and evaluated the original reports. Details of these studies are provided below. To facilitate discussion, OEHHA has added the bracketed [letters] to identify individual observations in the citation above.

As OEHHA could not find a corresponding citation in RTECS for observation [a], and the information in U.S. EPA (1994a) was not sufficiently detailed, OEHHA could not adequately evaluate this study in terms of the scientific criteria for authoritative bodies listing (22 CCR 12306). Observation [b] is described in Ogata et al. (1984). Mice were treated with thiabendazole on gestation day 9 at doses ranging from 0 to 2400 mg/kg. Increased skeletal malformations (fusion of vertebral arches and ribs) were found at doses of 240 mg/kg and higher. Additional findings included sporadically occurring limb reduction deformity at doses between 480 and 1157 mg/kg. At doses of 1157 mg/kg and higher, limb reduction defects became a consistent finding. Body weights of live fetuses were also reduced at 240 mg/kg, and at most of the higher doses. Maternal deaths occurred at doses of 1667 mg/kg and higher. The authors stated that reduced maternal weight gain was observed at doses of 1157 mg/kg and higher; and reduced liver, heart, and kidney weights were observed at doses of 1389 mg/kg and higher.

Observations [c], [d], [e], and [f] were described in Ogata et al. (1978, 1984, and 1986). Deficiencies of these studies, including excessive maternal toxicity at developmentally toxic doses, limit the utility of the data for identifying developmental hazards. Therefore, of the studies described in U.S. EPA (1994a), observation [b] is the most critical for judging developmental effects. With regard to this study, OEHHA notes the following:

1. **Adequacy of the experimental design:**
   The original study (Ogata et al., 1984 observation [b]) was reviewed by OEHHA staff, and found to be comparable to the "core grade minimal" standard formerly used by U.S. EPA.
2. **Route of administration:**
   oral, gavage.
3. **The frequency and duration of exposure:**
   once on gestation day 9
4. **The numbers of test animals:**
   21 - 31 mated females per group, per experimental block (some doses were replicated, resulting in up to 50 mated females per dose and 92 controls)
5. **The choice of species:**

The mouse is a standard species used in developmental toxicity testing.

6. **The choice of dosage levels:**
   0, 30, 60, 62, 120, 129, 240, 269, 480, 558, 670, 804, 965, 1157, 1389, 1667, 2000, 2400 mg/kg,
7. **Maternal toxicity:**
   Maternal mortality was 22% at 2400 mg/kg, 10% at 2000 mg/kg, and 6% at 1667 mg/kg. Maternal body weight gains were said to be reduced at 1157-2400 mg/kg. Maternal liver, heart and kidney weights were said to be significantly lower at 1389-2400 mg/kg. Reductions in fetal weights, and increases in malformation frequency, were seen at doses lower than those reported as causing maternal toxicity.

OEHHA also notes that studies submitted in response to a Request for Relevant Information on thiabendazole (*California Regulatory Notice Register,* October 9, 1998) are also indicative of developmental toxicity. In these studies (Nakatsuka 1995a, 1995b), mice were treated with thiabendazole by gavage from gestation day 6 through 15. The "range finding" study (Nakatsuka 1995a) used doses of 0, 25, 100, 200, 400, or 800 mg/kg/d. The main study (Nakatsuka et al. 1995b) used doses of 0, 25, 100, or 200 mg/kg/d, with larger numbers of animals per group. Significantly reduced fetal weight was found in both studies at 100 mg/kg/d and up. Significantly reduced maternal weight gain was found in the range finding study at 200 mg/kg/d and up, and in the main study at 100 and 200 mg/kg/d. The maternal toxicity observed in these studies, at least up to 200 mg/kg/d, would be considered "minimal" by U.S. EPA criteria (U.S. EPA 1991).

References

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