

**CHEMICALS UNDER CONSIDERATION FOR POSSIBLE LISTING
VIA THE AUTHORITATIVE BODIES MECHANISM: THIABENDAZOLE,
THIABENDAZOLE HYPOPHOSPHITE SALT**

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Office of Environmental Health Hazard Assessment
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Thiabendazole, and thiabendazole hypophosphite salt may meet the criteria for listing as known to the State to cause reproductive toxicity under the Safe Drinking Water and Toxic Enforcement Act of 1986 (Health and Safety Code Section 25249.5 et seq.), more commonly known as Proposition 65, via the authoritative bodies mechanism. The regulatory requirements for listing by the authoritative bodies mechanism are set forth in Title 22, California Code of Regulations, section 12306¹. The regulations include the criteria for evaluating the documentation and scientific findings by the authoritative body that the Office of Environmental Health Hazard Assessment (OEHHA) uses to determine whether listing under Proposition 65 is required.

The U.S. Environmental Protection Agency (U.S. EPA) is one of five institutions that have been identified as authoritative bodies for identification of chemicals as causing reproductive toxicity for the purposes of Proposition 65 (Section 12306[1][3]). U.S. EPA has identified thiabendazole and thiabendazole hypophosphite salt as causing reproductive toxicity. OEHHA has found that these chemicals appear to be “formally identified” by U.S. EPA as causing these toxicities as required by Section 12306(d). Thiabendazole and thiabendazole hypophosphite salt are the subject of a document published by the authoritative body that identify the chemicals as causing reproductive toxicity and indicate that the identification is a final action (U.S. EPA 2002). This document specifically and accurately identifies the chemicals and the document meets one or more of the criteria required by Section 12306[d][2]).

OEHHA also finds that the scientific criteria in regulation appear to have been satisfied for “as causing reproductive toxicity” (Section 12306[g]) for thiabendazole, and thiabendazole hypophosphite salt. In making this evaluation, OEHHA relied upon the discussion of data by the authoritative body in making its finding that the specified chemicals cause these toxicities. A brief discussion of the relevant toxicity studies providing evidence for the findings is presented below. Some of the discussion is taken verbatim or paraphrased from U.S. EPA source documents, which are part of the administrative record for these chemicals (U.S. EPA 1999a, 1999b, 2001, 2002). The

¹ All further references are to Title 22 of the California Code of Regulations unless otherwise indicated.

statements in bold reflect data and conclusions that appear to satisfy the criteria for the sufficiency of evidence for reproductive toxicity (Section 12306[g]). The full citations for the authoritative body documents are given later in this document.

Chemicals under Consideration for Possible Listing under Proposition 65

Chemical	CAS No.	Toxicological Endpoints	Chemical Use	Reference
Thiabendazole	148-79-8	developmental toxicity	Used to control a variety of fruit and vegetable diseases caused by various fungi. Registered for use: as a pre-planting dust treatment to potato seed-pieces, sweet potato seed pieces, soybean, and wheat; post-harvest as a dip or spray on citrus fruits, apples, pears, bananas, mangos, papaya, plantain, carrots, avocados, peas, and potatoes; on mushrooms.	U.S. EPA (2002)
Thiabendazole hypophosphite salt	28558-32-9	developmental toxicity	Uses include as a preservative in paints, carpets, adhesives and textiles, and in ready-to-use formulation on ornamental bulbs and elm and sycamore trees	U.S. EPA (2002)

Thiabendazole (CAS No. 148-79-8) and Thiabendazole Hypophosphite Salt (CAS No. 28558-32-9)

U.S. EPA (2002) defines thiabendazole as thiabendazole and its salt, thiabendazole hypophosphate, and refers to both as thiabendazole throughout the document (see e.g., pages iv and 2). Any exposure to the thiabendazole salt results in exposure to thiabendazole.

“Toxicological Dose and Endpoints for Thiabendazole for Use in Human Dietary Risk Assessment” Acute Dietary (females 13+), and Short-Term Residential and Occupational Dermal and Inhalation Exposure Scenarios: Oral Developmental Study - Rat/ decreased fetal body weight (U.S. EPA, 2002, e.g., pages 6, 7, 13, 16)

“The decreased fetal body weight is presumed to occur after a single exposure (dose) and was also seen in studies with other species (mice and rabbits). Therefore, this endpoint is considered to be appropriate for this (acute) risk assessment.” (U.S. EPA, 1999a)

The following study descriptions are adapted from U.S. EPA (1999b)

In a developmental toxicity study (MRID 42842803), thiabendazole (technical, >98.9% a.i.) was administered by gavage to 25 female Sprague-Dawley rats [CrI:CD (SD) BR] in 0.5% methylcellulose at dose levels of 0, 10, 40, or 80 mg/kg/day from days 6 through 17 of gestation. Maternal toxicity was noted at 40 and 80 mg/kg/day and consisted of statistically significant ($p \leq 0.05$) decreases in mean body weight gain of 12 and 26%, respectively, throughout the treatment period. Statistically significant ($p \leq 0.05$) reduction in feed consumption was noted in mid- (11- 15%) and high- (22-28%) dose animals during treatment. No treatment-related changes in body weight gain or feed consumption were noted at 10 mg/kg/day compared to controls. No deaths occurred, there were no treatment-related gross pathologic findings, and no abortions were observed at any treatment level. Clinical signs of toxicity observed during the study consisted of ptosis in 4 dams in the 80 mg/kg/day treatment group on gestational day 6. The maternal LOAEL is 40 mg/kg/day, based on reduced maternal body weight gains and reduced feed consumption. The maternal NOAEL is 10 mg/kg/day. At dose levels of 40 and 80 mg/kg/day, fetal body weights were slightly but significantly ($p \leq 0.05$) reduced (5-6%) in females and were slightly but significantly ($p \leq 0.05$) reduced in males (5%) at 80 mg/kg/day but not at 40 mg/kg/day (3%). No developmental effects were observed at treatment levels of 10 mg/kg/day. There were no treatment-related malformations or variations noted in the fetuses at any dose level. The developmental LOAEL is 40 mg/kg/day, based on decreased fetal body weights. The developmental NOAEL is 10 mg/kg/day. This developmental toxicity study in the rat is classified Acceptable and satisfies the guideline requirements for a developmental toxicity study in rats.

Developmental Toxicity: In the rat developmental study, there were significant decreases in maternal mean body weights and feed consumption noted at 40 and 80 mg/kg/day. Ptosis was present in 3/25 animals at 80 mg/kg/day. The female fetal body weights were decreased at ≥ 40 mg/kg/day and in males at 80 mg/kg/day. Therefore, the rat maternal and developmental LOAEL/NOAEL are 40/10 mg/kg/day.

In the mouse prenatal developmental toxicity study, there were reductions in maternal body weight at mid (100 mg/kg/day) and high dose (200 mg/kg/day) dose treatment groups. There were accompanying reductions in feed consumption in the high dose group. There was decreased fetal body weight at 100 mg/kg/day for both sexes. The mouse maternal and developmental LOAEL/NOAEL are 100/25 mg/kg/day.

In the rabbit developmental study, decreased maternal body weight gains and decreased food consumption were seen in the high dose tested (600 mg/kg/day). There was decreased fetal body weight and increased resorptions at 600 mg/kg/day. The rabbit maternal and developmental LOAEL/NOAEL are 600/150 mg/kg/day.

Reproductive Toxicity: In the two generation reproduction study, the parental systemic LOAEL is based on decreased body weight gain and food consumption seen at 30 mg/kg/day. The NOAEL is 10 mg/kg/day. The offspring LOAEL is based on decreased body weight gain in offspring during lactation seen at 30 mg/kg/day. The NOAEL is 10 mg/kg/day. The reproductive LOAEL is > 90 mg/kg/day. The effects

in the offspring were observed at higher dosages (90 mg/kg/day) than dosages (30 mg/kg/day) causing parental toxicity.

U.S. EPA (1999b) notes other benzimidazole compounds such as parbendazole, cambendazole and mebendazole that possess teratogenic and embryotoxic properties. It also notes studies in the published literature indicate that thiabendazole can cause developmental effects after single in utero exposure of pregnant animals at high doses. These studies are briefly summarized below.

1) In a teratogenicity study in rats (Khera et al., 1979), thiabendazole administered to dams from GD 6-15 at doses ranging from 125 to 500 mg/kg/day produced increased incidence of anomalous fetuses at the highest dose (500 mg/kg/day) level. No details on maternal effects were reported.

2) The developmental toxicity of thiabendazole was assessed in Sprague-Dawley rats and New Zealand (NZB) rabbits (Lankas and Wise, 1993). Rats received thiabendazole at 10, 40, or 80 mg/kg/day and rabbits received thiabendazole orally at doses ranging from 24 to 600 mg/kg/day (in two studies) as an aqueous suspension on GD 6-17. Thiabendazole produced decreased maternal body weight gain (12 to 26%) and decreases in fetal body weights (5-7%) at doses of 30 and 80 mg/kg/day. The NOAEL was 10 mg/kg/day and no teratogenic effects were noted. In rabbits, decreased maternal weight gain and decreased fetal weights were noted at 600 mg/kg/day, but there was no evidence of developmental anomalies. The NOAEL was 120 mg/kg/day.

3) Thiabendazole was administered orally in olive oil (Ogata et al., 1984) to pregnant Jcl:ICR mice at doses of 700, 1300 or 2400 mg/kg/day thiabendazole on GD 7-15. No maternal effects were reported in this study. A dose-dependent increase in external and skeletal anomalies, especially cleft palate (although in a non-dose related manner) and fusion of vertebrae, were observed. In mice given a single dose of 2400 mg/kg/ thiabendazole on any one of the GD 6-13, an increased number of malformations were observed. Various malformations occurred, especially in the mice treated on GD 9: the number of litters with fetuses having shortened limbs and fetuses with skeletal fusion increased in a dose-related manner. Based on these findings the United Nations Food and Agriculture Organization and World Health Organization recommended that the acceptable daily intake (ADI) of thiabendazole should be 0.05 mg/kg.

4) In a 2-Generation reproduction study (Wise et al., 1994), Sprague-Dawley rats received thiabendazole at dietary doses of 10, 30 or 90 mg/kg/day during pre-mating, gestation and lactation. Parental toxicity was seen at ≥ 30 mg/kg/day based on decreased body weight gain (37-46%) and food consumption (3-16%) . The NOAEL was 10 mg/kg/day. Decrease in pup body weight (5-10%) was noted between PND 4 and 21. The NOAEL was 10 mg/kg/day. Thus, no selective sensitivity to thiabendazole was noted in pups.

References

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