CHEMICALS MEETING THE CRITERIA FOR LISTING VIA THE AUTHORITATIVE BODIES MECHANISM: (2,4-DICHLOROPHENOXY) ACETIC ACID (2,4-D), 2,4-D N-BUTYL ESTER, 2,4-D ISOPROPYL ESTER, 2,4-D ISOOCTYL ESTER, 2,4-D PROPYLENE GLYCOL BUTYL ETHER ESTER (2,4-D PGBE), 2,4-D BUTOXYETHANOL ESTER AND 2,4-D DIMETHYLAMINE SALT

November 2005

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

(2,4-Dichlorophenoxy) acetic acid (2,4-D), 2,4-D n-butyl ester, 2,4-D isopropyl ester, 2,4-D isooctyl ester, 2,4-D propylene glycol butyl ether ester (2,4-D PGBE), 2,4-D butoxyethanol ester and 2,4-D dimethylamine salt 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 this mechanism are set forth in Title 22, California Code of Regulations §12306[1]. The regulations include provisions covering the criteria for evaluating the documentation and scientific findings by the authoritative body which 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 (§12306(1)(3)). U.S. EPA has identified 2,4-D, 2,4-D n-butyl ester, 2,4-D isopropyl ester; 2,4-D isooctyl ester, 2,4-D PGBE, 2,4-D butoxyethanol ester and 2,4-D dimethylamine salt as causing reproductive toxicity. OEHHA has found that these chemicals have been "formally identified" by U.S. EPA as causing reproductive toxicity as required by §12306(d). 2,4-D, 2,4-D n-butyl ester, 2,4-D isopropyl ester, 2,4-D isooctyl ester, 2,4-D PGBE, 2,4-D butoxyethanol ester and 2,4-D dimethylamine salt are the subject of a report published by the authoritative body that concludes that the chemicals cause reproductive toxicity (U.S. EPA 1988). 2,4-D, 2,4-D isopropyl ester, 2,4-D butoxyethanol ester and 2,4-D dimethylamine salt are also otherwise identified as causing reproductive toxicity in a document that indicates that the identification is a final action (U.S EPA 2005). These documents specifically and accurately identify the chemicals and the documents meet one or more of the criteria required by §12306(d)(2).

OEHHA also finds that the criteria in regulation for "as causing reproductive toxicity" (§12306(g)) have been satisfied for 2,4-D, 2,4-D n-butyl ester, 2,4-D isopropyl ester,

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

2,4-D isooctyl ester, 2,4-D propylene glycol butyl ether ester (2,4-D PGBE), 2,4-D butoxyethanol ester and 2,4-D dimethylamine salt. In making this evaluation, OEHHA relied upon the discussion of data by the authoritative body in making it's finding that the specified chemical causes reproductive toxicity. A brief discussion of the relevant reproductive and developmental toxicity studies providing evidence for the findings is presented below.

Chemicals Meeting Criteria for Listing as Reproductive Toxicants

Chemical	CAS No.	Toxicological Endpoints	Identity of chemical	Reference
(2,4-dichlorophenoxy) acetic acid	94-75-7	developmental toxicity	herbicide (2,4-D)	U.S. EPA (1988, 2005[1])
2,4-D n-butyl ester	94-80-4	developmental toxicity	ester of 2,4-D	U.S. EPA (1988)
2,4-D isopropyl ester	94-11-1	developmental toxicity	ester of 2,4-D	U.S. EPA (1988, 2005)
2,4-D isooctyl ester	25168-26-7	developmental toxicity	ester of 2,4-D	U.S. EPA (1988)
Propylene glycol butyl ether ester (of 2,4-D)	1928-45-6	developmental toxicity	ester of 2,4-D	U.S. EPA (1988)
2,4-D butoxyethanol ester	1929-73-3	developmental toxicity	ester of 2,4-D	U.S. EPA (1988, 2005)
2,4-D dimethylamine salt	2008-39-1	developmental toxicity	salt of 2,4-D	U.S. EPA (1988, 2005)

[1] Documents included in the U.S. EPA administrative record that provide additional information on these chemicals (U.S. EPA 2004a,b) are included by reference in U.S. EPA (2005)

A U.S. EPA document entitled *Drinking Water Criteria Document for 2,4-D* (U.S. EPA 1988) meets the criteria for formal identification of 2,4-D and various esters and salts as causing reproductive toxicity (§12306(d) and §12306(g)). This document is provided as Attachment 1. In addition, a recent U.S. EPA Reregistration Eligibility Decision (RED) for 2,4-D and various esters and salts (U.S. EPA 2005) also meets the criteria for formal identification of 2,4-D and various esters and salts, some of which were previously formally identified in U.S. EPA (1988). A related document, the *2,4-D Revised Occupational and Residential Exposure and Risk Assessment and Response to Phase One Comments for the Registration Eligibility Decision (RED) Document* (U.S. EPA 2004a), is incorporated by reference into the RED and reviews the data for developmental and reproductive toxicity of 2,4-D and these various esters and salts. These documents are provided as Attachments 2 and 3.

The ***developmental toxicity*** of 2,4-D and certain of its derivatives has been evidenced by embryotoxicity.

The US Environmental Protection Agency (US EPA, 1988) concluded that, "Teratogenicity testing has been conducted with 2,4-D, several of its esters (n-butyl,

isopropyl, isooctyl, PGBE, butoxyethanol [and] the dimethylamine salt…. in mice, rats and hamsters (Courtney, 1977; Khera and McKinley, 1972; Schwetz et al., 1971; Unger et al., 1981; Konstantinova et al., 1976; Collins and Williams, 1971). Overall these studies indicate that 2,4-D and its derivatives are embryotoxic but only weakly teratogenic or nonteratogenic." All of the studies cited by the EPA document are reviewed in detail. Information such as species and number of animals used; doses, route, and days of treatment; and details of toxicological findings is provided in the document, and is summarized below.

The six research reports cited by U.S. EPA (1988) as containing data on 2,4-D and its esters and salts are referenced as follows:

a. Courtney 1977: 2,4-D; PGBE ester of 2,4-D' n-butylester of 2,4-D, isopropyl ester of 2,4-D, isooctyl ester of 2,4-D
b. Khera and McKinley 1972: 2,4-D; isooctyl ester of 2,4-D; butyl ester of 2,4-D; butoxyethanol ester of 2,4-D; dimethylamine salt of 2,4-D
c. Schwetz et al. 1971: 2,4-D; PGBE ester of 2,4-Disooctyl ester of 2,4-D
d. Unger et al. 1981: PGBE ester of 2,4-D; isooctyl ester of 2,4-D
e. Konstantinova et al. 1976: 2,4-D
f. Collins and Williams 1971: 2,4-D

With regard to the studies cited supporting U.S. EPA's identification of 2,4-D and certain esters and salts as causing developmental toxicity, OEHHA finds that the evidence for DART effects meets the criteria of §12306(g). Relevant parameters of the studies described in Attachment 1 (U.S. EPA 1988) are summarized as follows:

1. **Adequacy of the experimental design:**
   a. Developmental toxicity study with dosing during organogenesis
   b. Developmental toxicity study with dosing during organogenesis
   c. Developmental toxicity study with dosing during organogenesis.
   d. Developmental toxicity study with dosing during organogenesis
   e. Developmental toxicity study with dosing during organogenesis
   f. Developmental toxicity study with dosing during organogenesis

2. **Route of administration:**
   a. CD-1 mouse teratology study- oral-gastric intubation-corn oil or acetone vehicle
   b. Wistar rat teratology study-oral administration , corn oil or aqueous gelatin vehicle
   c. Sprague-Dawley rat teratology study-oral, corn oil vehicle
   d. CD rat teratology study- oral, corn oil vehicle
   e. rat teratology study- oral , gastric intubation, in emulsifying agent
   f. hamster teratology study, oral, in acetone, corn oil or carboxymethyl cellulose

3. **The frequency and duration of exposure:**
   a. gestation day 7 through 15, 12 through 15, or 11 through 13
   b. gestation day 6 through 15
   c. gestation day 6 through 15
   d. gestation day 6 through 15
   e. gestation day 7 through 14
   f. gestation day 6 through 10

4. **The numbers of test animals:**
   a. group size =7 to 16
   b. group size = 4 to 17
   c. group size control = 36 and 41; treated = 13-21
   d. group size control =~35, 37; treated =19-28
   e. group size not stated
   f. group size control=86; treated =7-12

5. **The choice of species:** Rats, mice and hamsters are standard test species for developmental toxicity studies.

6. **The choice of dosage levels:**
   a. 0.56 or 1.0 mM/kg
   b. 25, 50, 100, 150, or 300 mg/kg/day
   c. 12.5, 25, 50, 75 or 87.5 mg/kg/day equimolar to 2,4-D
   d. 6.25, 12.5, 25, 75, or, 87.5 mg/kg/day equimolar to 2,4-D
   e. 50 mg/kg/day
   f. 20, 40, 80, or 100 mg/kg/day

7. **Maternal toxicity:**
   a. no effect on maternal weight gain; increased relative maternal liver weight at some doses
   b. no effects on maternal body weight, except for dimethylamine salt at the highest dose (300 mg/kg/day)
   c. no effects on maternal body weight
   d. no adverse effect on maternal body weight or survival
   e. details of maternal toxicity not reported
   f. details of maternal toxicity not reported

Developmental toxicity, characterized mainly as an increased incidence of skeletal abnormalities in the rat, was observed following exposure to 2,4-D and its amine salts and esters at or above the threshold of saturation of renal clearance.

The U.S. EPA Reregistration Eligibility Decision (RED) for 2,4-D and various esters and salts (U.S. EPA 2005) and the *2,4-D Revised Occupational Residential Exposure and Risk Assessment and Response to Phase One Comments for the Registration Eligibility*

Decision (RED) Document (U. S. EPA 2004a) state that the database for developmental toxicity is considered complete, and identify two studies of prenatal development and one study of reproduction and fertility effects. These studies are all of 2,4-D acid form, which the RED states is representative of all members of the 2,4-D reregistration case (i.e., 2,4-D, 2,4-D dimethylamine salt , 2,4-D isopropyl ester, 2,4-D butoxyethyl ester, 2,4-D isopropylamine salt, 2,4-D sodium salt, 2,4-D diethanolamine salt, 2,4-D triisopropanolamine salt and 2,4-D 2-ethylhexyl ester). As a final action, these documents identify the sole basis for the acute dietary reference dose (RfD) for females 13-50 years of age as the rat developmental toxicity study that demonstrated skeletal abnormalities. In addition, these documents identify the basis for the short term dermal and inhalation RfDs as decreased maternal body-weight gain and skeletal abnormalities in the same rat developmental toxicity study. Additional information on the details of the studies was obtained from the Toxicology Disciplinary Chapter for the Registration Eligibility Decision Document (U.S. EPA 2004b), which is included in the administrative record for the Reregistration Eligibility Decision.

1. **Adequacy of the experimental design:**
   Study a) (MRID 00130407, 00130408 [1983]) prenatal developmental study in Fisher 344 rats. This study was rated Acceptable/Guideline.
   Study b) (MRID 41747601 [1990]) prenatal developmental study in rabbits. This study was rated Acceptable/Guideline.
   Study c) (MRID 00150557, 00163996 [1985]) reproduction and fertility effects study in Fisher 344 rats. This study was rated Acceptable/Guideline.
2. **Route of Administration:**
   Study a) rat prenatal developmental study: gavage.
   Study b) rabbit prenatal developmental study: not stated, but appears to be gavage.
   Study c) rat reproduction and fertility effects study: via diet.
3. **The frequency and duration of exposure:**
   Study a) rat prenatal developmental study: daily on days 6 through 15 of gestation.
   Study b) rabbit prenatal developmental study: daily on days 6 through 18 of gestation.
   Study c) rat reproduction and fertility effects study: from 105 days prior to gestation through gestation and lactation of two litters.
4. **The numbers of test animals:**
   Study a) rat prenatal developmental study: 35 per group.
   Study b) rabbit prenatal developmental study: 20 per group.
   Study c) rat reproduction and fertility effects study: 30 males and 30 females per group.
5. **The choice of species:**
   Rat and rabbit are standard test species.
6. **The choice of dosage levels:**
   Study a) rat prenatal developmental study - 0, 8, 25, 75 mg/kg/day.

Study b) rabbit prenatal developmental study – 0, 10, 30, 90 mg/kg/day (corrected for the 96.1% purity of the test substance).
Study c) rat reproduction and fertility effects study – 0, 5, 20, 80 mg/kg/day highest dose group discontinued due to excess toxicity).

7. **Maternal toxicity:**
Study a) rat prenatal developmental study - maternal body weight gain was decreased at the highest dose tested (75 mg/kg/day), not statistically significant. Survival was not affected.
Study b) rabbit prenatal developmental study – clinical signs (ataxia, decreased motor activity, loss of righting reflex, cold extremities), two abortions, decreased body weight gain at the highest dose tested (90 mg/kg/day), not statistically significant. Survival was not affected.
Study c) rat reproduction and fertility effects study – decreased body weight gain at 20 and 80 mg/kg/day.

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U.S. Environmental Protection Agency (U.S. EPA, 1988) *Drinking Water Criteria Document for 2,4-D.* Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment. (ECAO-CIN-418). [Attachment 1.]

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U.S. Environmental Protection Agency (U.S. EPA 2005). Reregistration Eligibility Decision for 2,4-D. Office of Prevention, Pesticides and Toxic Substances, U.S. Environmental Protection Agency, available at: http://www.epa.gov/oppsrrd1/REDs/24d_red.pdf. [Attachment 2.]