CHEMICALS MEETING THE CRITIERIA FOR LISTING AS DEVELOPMENTAL AND REPRODUCTIVE TOXICANTS (DARTs) VIA THE AUTHORITATIVE BODIES MECHANISM: 5 CHEMICALS IDENTIFIED BY U.S. EPA

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The 5 chemicals listed in the table below meet 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 the chemicals in the table below 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 the chemicals in the table below have 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 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 the chemicals in the table below. 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. 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.

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 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.

Chemical	CAS No.	Endpoints	Pesticide status or usage
2,4-D butyric acid	94-82-6	developmental toxicity male reproductive toxicity	Registered in CA
2,4-D 2-ethylhexyl ester	1928-43-4	developmental toxicity	Registered in CA
2,4-D 2-ethyl-4-methylpentyl ester	53404-37-8 25168-26-7	developmental toxicity	Registered in CA
Propargite	2312-35-8	developmental toxicity	Registered in CA
Triforine	26644-46-2 37273-84-0	developmental toxicity	Registered in CA

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.

2,4-DB (4- [2,4-Dichloro-phenoxy] butyric acid; CAS No. 94-82-6)

Developmental toxicity **has been manifested as morphological abnormalities, stillbirths, and increased post-implantation loss.** ***Male reproductive toxicity*** **has been manifested as aspermatogenesis.**

The U.S. Environmental Protection Agency (U.S. EPA, 1994a and 1994b) concluded that: "…there is sufficient evidence for listing 2,4-DB on EPCRA section 313(d)(2)(B) based on the . . . reproductive and developmental toxicity data for this chemical."

Supporting reproductive documentation for the TRI listing (U.S. EPA, 1993a) states, "animals [dogs] exposed to 25 mg/kg/day (the LOAEL) and higher doses caused [sic] aspermatogenesis within the first 3-9 weeks of treatment (IRIS, 1993 [U.S. EPA, 1997])." In addition, supporting documentation for developmental effects states, "Rats orally exposed to 17 mg/kg during gestation days 1-7 developed unspecified abnormalities; there was also an increase in stillbirths at this dose level (RTECS, 1993 [RTECS, 1997]). In a separate study, rats orally exposed to 416 mg/kg on gestation days 5 or 9 exhibited increased pre-implantation loss and/or fetotoxicity."

The oral RfD is based on the adverse effects observed in the subchronic dog study which are summarized in IRIS (U.S. EPA, 1992). IRIS states that "The two higher doses (25 and 80 mg/kg bw/day) produced frank effects including death, hemorrhage throughout the body, and aspermatogenesis within 3-9 weeks of treatment. Slightly increased liver-to-body weight ratios were observed at both lower dose levels, but no gross or microscopic pathology was evident."

RTECS (1997) referenced the rat developmental toxicity data cited in support of the TRI listing to a study published in the Russian language (Sokolova, 1976). In this study, oral administration of 3.4 mg/kg/day of 2,4-DB throughout pregnancy significantly increased the number of stillborn offspring, and decreased the number of live young per litter, as well as decreasing birth size. Oral administration of 1 mg/kg/day during gestation resulted in increased frequency of hemorrhages into the abdominal cavity; 0.1 mg/kg/day was considered the threshold for embryotoxic effects. Single oral administration of 416 mg/kg at various periods of pregnancy resulted in increased frequency of pre-implantation death when given on either day 4 or 5, increased frequency of post-implantation death when given on day 9, and decreased birth size when given on either day 4, 5, 10 or 14.

It should be noted that the dose at which developmental abnormalities and stillbirths were observed was 3.4 mg/kg, rather than 17 mg/kg as reported in RTECS (1997). Also, the exposure time was translated as "throughout gestation", rather than days 1-7 as reported in RTECS (1997).

With regards to the studies 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 appears to meet the criteria of 22 CFR 12306, and notes the following:

1. **Adequacy of the experimental design:**
   Study a) dog subchronic study - U.S. EPA (1997) gives medium confidence for the principal study,
   Study b) rat teratology studies - core grade unknown, but appears to be supplemental at best.
2. **Route of administration:**
   Study a) dog subchronic study - oral, in diet,
   Study b) rat teratology study - oral gavage, in corn starch solution.
3. **The frequency and duration of exposure:**
   Study a) dog subchronic study - continuous, in diet for 90 days total,
   Study b) rat teratology study - throughout gestation for the low doses (0.1, 1, 3.4 mg/kg/day) and single administration on either day 4, 5, 7, 9, 10, 11, or 14 of gestation for the high dose (416 mg/kg).
4. **The numbers of test animals:**
   Study a) dog subchronic study - 4 per sex per group,
   Study b) rat teratology study - the number of animals per dose group was not given. However, the total number of females, males, fetuses and pups used in the studies were 283, 51, 1615, and 660, respectively.
5. **The choice of species:** The dog and rat are standard test species.
6. **The choice of dosage levels:**
   Study a) dog subchronic study - 0, 2.5, 8.0, 25, 80 mg/kg/day,
   Study b) rat teratology study - 0, 0.1, 1, 3.4 mg/kg/day throughout gestation or single administration of 416 mg/kg during gestation.
7. **Maternal toxicity:**
   Study a) dog subchronic study - not applicable,
   Study b) rat teratology study - At a dose of 3.4 mg/kg/day there was an increase in ascorbic acid levels in maternal brain tissue, but it is unclear whether this could be considered a toxic effect. Maternal toxicity was not discussed in the study following single administration of 416 mg/kg during gestation.

2,4-D 2-ethylhexyl ester (CAS No. 1928-43-4)

Developmental toxicity **has been manifested as fetotoxicity and morphological abnormalities in rats and suppression of growth in rats and mice exposed to 2,4-D isooctyl esters.**

The U.S. Environmental Protection Agency (U.S. EPA, 1994a and 1994b) concluded that, "...there is sufficient evidence for listing 2,4-D 2-ethylhexyl ester on EPCRA section 313 pursuant to EPCRA section 313(d)(2)(B) based on the developmental toxicity data for 2,4-D isooctyl esters, and on the toxic effects of its metabolite 2,4-D."

The proposed rule document (U.S. EPA, 1994a) states, "The 2-ethylhexyl moiety contains eight carbons and, therefore is an isooctyl group. Developmental toxicity following maternal exposure to 2,4-D isooctyl esters has been demonstrated in the rat and mouse." Further details are provided in both the proposed rule document and in the supporting documentation for the TRI listing (U.S. EPA, 1994a and 1993a): "Fetotoxicity occurred in offspring of rats exposed to 528 mg/kg during gestation days 8-11. Rats orally exposed to doses as low as 302 mg/kg during gestation days 9-12 had musculoskeletal abnormalities. Exposure to a lower dose (188 mg/kg) for a longer period during gestation (days 6-15) caused developmental effects on homeostasis and effects on newborn growth statistics. In mice, 438 mg/kg administered orally during gestation days 8-12 also caused effects on newborn growth statistics. Data from OPP's [the U.S. EPA's Office of Pesticide Program's] 'Tox-Oneliner' database supports these findings. Fetotoxic effects including delayed ossification of skull bones and sternabrae, wavy ribs and decreased fetal body weight were observed in rats administered isooctyl esters at 50 mg/kg/day (LOAEL) on GD [gestation days] 6-15; NOAEL was 25 mg/kg/day."

The supporting documentation for the TRI proposed rule (U.S. EPA, 1993a) cites RTECS for most of the studies described. The original references cited by RTECS were retrieved and reviewed. These papers are the source of the study details provided below. It should be noted that RTECS presents dose as a summation of all doses given. That is, a dosing regimen of 10 mg/kg/day repeated on each of 10 days, would be expressed as 100 mg/kg.

With regard to the studies 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 appears to meet the criteria of 22 CCR 12306, and notes the following:

1. **Adequacy of the experimental design**:
   Study a) Schwetz et al. (1971) report on a series of four rat developmental toxicity studies (by reference here as studies 'a1' through 'a4'). The basic protocol and evaluation methods for experiment a1 correspond to standard techniques,
   Study b) Mouse developmental toxicity screen (Kavlock et al., 1987). Study conducted by a screening protocol which yields information useful to hazard identification.
2. **Route of administration:**
   Study a1-a4) Oral, gavage,
   Study b) Oral, gavage.
3. **The frequency and duration of exposure**:
   Study a1) Daily on gestation days 6-15.
   Study a2) Daily on gestation days 5-8.
   Study a3) Daily on gestation days 8-11.
   Study a4) Daily on gestation days 12-15.
   Study b) Daily on gestation days 8-12.
4. **The numbers of test animals**:
   Study a1-a4) 13-21 litters per dose group; 2 control groups, one of 36 and one of 41 litters.
   Study b) 30 litters tested, 43% pregnancy rate.

5. **The choice of species**:
   Rats and mice are standard species used in toxicology testing.
6. **The choice of dosage levels**:
   Study a1) 0, 12.5, 25.0, 50.0, 75.0, 87.0 mg/kg/day*.
   Study a2) 0, 87.0 mg/kg/day*.
   Study a3 & a4) 0, 50.0, 87.5 mg/kg/day*. *doses of isooctyl ester given as molar equivalents to the indicated mg/kg quantity of 2,4-D.
   Study b) 87.5 mg/kg/day.
7. **Maternal toxicity:**
   Study a1-4) Treatment had no effect on maternal weight gain during pregnancy.
   Study b) Study design involved selection of dose to produce minimal maternal toxicity. This was defined as, "a slight (approximately 10%) deficit in weight gain but not more than 10% lethality."

2,4-D 2-ethyl-4-methylpentyl ester (CAS No. 53404-37-8) [synonym: 2,4-D, isooctyl ester, CAS No. 25168-26-7]

Developmental toxicity **has been manifested as fetotoxicity and morphological abnormalities in rats and suppression of growth in rats and mice exposed to 2,4-D isooctyl esters.**

The U.S. Environmental Protection Agency (U.S. EPA, 1994a and 1994b) concluded that, “...there is sufficient evidence for listing 2,4-D 2-ethyl-4-methylpentyl ester on EPCRA section 313 pursuant to EPCRA section 313(d)(2)(B) based on the developmental toxicity data for 2,4-D isooctyl esters, and on the toxic effects of its metabolite 2,4-D.”

The proposed rule document (U.S. EPA, 1994a) states, "The 2-ethyl-4-methylpentyl ester moiety contains eight carbons and, therefore is an isooctyl group. Developmental toxicity following maternal exposure to 2,4-D isooctyl esters has been demonstrated in the rat and mouse." Further information is provided in both the proposed rule document and in the supporting documentation for the TRI listing (U.S. EPA, 1994a and 1993a): "Fetotoxicity occurred in offspring of rats exposed to 528 mg/kg during gestation days 8-11. Rats orally exposed to doses as low as 302 mg/kg during gestation days 9-12 had musculoskeletal abnormalities. Exposure to a lower dose (188 mg/kg) for a longer period during gestation (days 6-15) caused developmental effects on homeostasis and effects on newborn growth statistics. In mice, 438 mg/kg administered orally during gestation days 8-12 also caused effects on newborn growth statistics. Data from OPP’s [the U.S. EPA’s Office of Pesticide Program's] 'Tox-Oneliner' database supports these findings. Fetotoxic effects including delayed ossification of skull bones and sternabrae, wavy ribs and decreased fetal body weight were observed in rats administered isooctyl esters at 50 mg/kg/day (LOAEL) on GD [gestation days] 6-15; NOAEL was 25 mg/kg/day."

The supporting documentation for the TRI proposed rule (U.S. EPA, 1993a) cites RTECS for most of the studies described. The original references cited by RTECS were retrieved

and reviewed. These papers are the source of the study details provided below. It should be noted that RTECS presents dose as a summation of all doses given. That is, a dosing regimen of 10 mg/kg/day repeated on each of 10 days, would be expressed as 100 mg/kg.

With regard to the studies 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 appears to meet the criteria of 22 CCR 12306, and notes the following:

1. **Adequacy of the experimental design**:
   Study a) Schwetz et al. (1971) report on a series of four rat developmental toxicity studies (by reference here as studies 'a1' through 'a4'). The basic protocol and evaluation methods for experiment a1 correspond to standard techniques,
   Study b) Mouse developmental toxicity screen (Kavlock et al., 1987). Study conducted by a screening protocol which yields information useful to hazard identification.
2. **Route of administration:**
   Study a1-a4) Oral, gavage,
   Study b) Oral, gavage.
3. **The frequency and duration of exposure**:
   Study a1) Daily on gestation days 6-15.
   Study a2) Daily on gestation days 5-8.
   Study a3) Daily on gestation days 8-11.
   Study a4) Daily on gestation days 12-15.
   Study b) Daily on gestation days 8-12.
4. **The numbers of test animals**:
   Study a1-a4) 13-21 litters per dose group; 2 control groups, one of 36 and one of 41 litters.
   Study b) 30 litters tested, 43% pregnancy rate.
5. **The choice of species**:
   Rats and mice are standard species used in toxicology testing.
6. **The choice of dosage levels**:
   Study a1) 0, 12.5, 25.0, 50.0, 75.0, 87.0 mg/kg/day*.
   Study a2) 0, 87.0 mg/kg/day*.
   Study a3 & a4) 0, 50.0, 87.5 mg/kg/day*. *doses of isooctyl ester given as molar equivalents to the indicated mg/kg quantity of 2,4-D.
   Study b) 87.5 mg/kg/day.
7. **Maternal toxicity:**
   Study a1-4) Treatment had no effect on maternal weight gain during pregnancy.
   Study b) Study design involved selection of dose to produce minimal maternal toxicity. This was defined as, "a slight (approximately 10%) deficit in weight gain but not more than 10% lethality."

Propargite (CAS No. 2312-35-8)

Developmental toxicity **was evidenced by adverse effects on viability, fetal weights, and ossification of skeletal elements.**

The U.S. Environmental Protection Agency (U.S. EPA, 1994a and 1994b) concluded that: ". . . there is sufficient evidence for listing Propargite 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, 1993a) states, "In the rabbit developmental toxicity study (IRIS, 1993 [U.S. EPA, 1997]) delayed ossification, increased resorption, decreased fetal viability and reductions in fetal body weight were noted in offspring of female rabbits exposed via oral gavage to doses $\geq$ 6 mg/kg/day (fetotoxic LOAEL) during gestation days 6-18. The maternal LOAEL in this study was also 6 mg/kg/day and was based on body weight reductions; the NOEL for maternal and fetal toxicity was 2 mg/kg/day. These developmental effects may have been secondary to the maternal toxicity. Developmental effects (increased incidence of missing sternebrae) were also reported in offspring of rats exposed orally during gestation days 6-15; the fetotoxicity LOAEL was 25 mg/kg/day and the NOAEL was 6 mg/kg/day."

With regards to the studies 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 appears to meet the criteria of 22 CFR 12306, and notes the following:

1. **Adequacy of the experimental design:**
   Study a) rat teratology study - Stated (U.S. EPA, 1997) to be core grade minimum.
   Study b) rabbit teratology study - Stated (U.S. EPA, 1997) to be core grade minimum.
2. **Route of administration:**
   Study a) oral gavage,
   Study b) oral gavage
3. **The frequency and duration of exposure:**
   Study a) each of gestation days 6 - 15,
   Study b) each of gestation days 6 - 18.
4. **The numbers of test animals:**
   Study a) not stated explicitly, but Agency designation as 'core grade minimum' (sufficient for risk assessment) indicates that the study came close to, or met, test guideline requirements of 20 pregnant animals per dose group (U.S. EPA, 1983a),
   Study b) 17 pregnant rabbits per dose group.
5. **The choice of species:**
   Rabbits and rats are standard test species for toxicity studies.
6. **The choice of dosage levels:**
   Study a) 0, 6, 25, 105 mg/kg/day,
   Study b) 0, 2, 6, 10, 18 mg/kg/day.

7. **Maternal toxicity:**
   Study a) maternal toxicity was observed only at doses higher than those associated with adverse effects on development,
   Study b) maternal and developmental toxicity were noted at the same dose levels (NOEL=2 mg/kg/day; LOEL=6 mg/kg/day).

Triforine (CAS No. 26644-46-2 and 37273-84-0)

Developmental toxicity **was evidenced by fetotoxicity in rats and rabbits.**

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

Supporting documentation for the TRI listing (U.S. EPA, 1993b) states, "A decrease in mean relative weight of offspring was observed in rabbits exposed (duration not specified) to 25 mg/kg triforine (the fetotoxicity LOEL). The fetotoxicity NOEL was 5 mg/kg. The LOEL and NOEL for maternal toxicity in this developmental toxicity study were also 25 mg/kg and 5 mg/kg, respectively, and were based on reduced food intake and body weight loss (24 [U.S. EPA, 1993c]). Fetotoxicity (decreased number of fetuses and increased resorptions) was also reported in the offspring of rats fed 1600 mg/kg (the fetotoxicity LOEL) for an unspecified duration. The fetotoxicity NOEL was 800 mg/kg (24 [U.S. EPA, 1993c). Both of these developmental toxicity studies were classified as Core Minimum."

With regard to the studies 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 appears to meet the criteria of 22 CCR 12306, and notes the following:

1. **Adequacy of the experimental design:**
   Study a) rabbit developmental toxicity study, core grade minimum (U.S. EPA, 1993c).
   Study b) rat developmental toxicity study, core grade minimum (U.S. EPA, 1993c).
2. **Route of administration:**
   Not stated for either study, but U.S. EPA test guidelines for developmental toxicity studies (U.S. EPA, 1983a) specify the gavage route of exposure. As both of these studies received acceptable grades, it is presumed that the studies were considered suitable for risk assessment.
3. **The frequency and duration of exposure:**
   Not stated for either study, but U.S. EPA test guidelines for developmental toxicity studies (U.S. EPA, 1983a) specify daily dosing on each of gestation days 6 - 18 for rabbits or days 6 - 15 for rats. As the studies were considered to meet guideline requirements, it is presumed that the studies were considered suitable for risk assessment.

4. **The numbers of test animals:**
   Not stated for either study, but U.S. EPA test guidelines for developmental toxicity studies (U.S. EPA, 1983a) specify a minimum of 12 rabbits or 20 rats per dose group. As both of these studies received acceptable grades, it is presumed that the studies were considered suitable for risk assessment.
5. **The choice of species:**
   Rats and rabbits are standard test species for developmental toxicity.
6. **The choice of dosage levels:**
   Study a) 0, 100, 400, 800, and 1600 mg/kg.
   Study b) 0, 5, 25, and 125 mg/kg.
7. **Maternal toxicity:**
   Study a) Maternal NOEL 5 mg/kg. Maternal LEL, 25 mg/kg (for reduced food intake and body weight loss).
   Study b) maternal toxicity not mentioned.

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