

**CHEMICALS UNDER CONSIDERATION FOR POSSIBLE LISTING
AS DEVELOPMENTAL AND REPRODUCTIVE TOXICANTS
(DARTs) VIA THE AUTHORITATIVE BODIES MECHANISM:
10 CHEMICALS IDENTIFIED BY US EPA**

**PACKAGE 11b:
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Reproductive and Cancer Hazard Assessment Section
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

The 10 chemicals listed in the table below may 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.

US 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 Toxics 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 US EPA added a number of chemicals to the TRI list. The US 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.*, US 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]) appear to have been satisfied for the chemicals in the table below. In making this evaluation, OEHHA relied upon the documents and reports cited

by US 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 US EPA. This was done only where necessary to affirm or clarify details of results and study design for studies cited by US EPA; OEHHA did not review additional studies not relied on by US EPA.

A major source of information used by the US EPA was the "Tox-Oneliner" database maintained by US 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 US EPA to indicate the extent to which a study conformed to published test guidelines (US 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
Bromacil lithium salt	5340419-6	developmental 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; synonym 2,4-D, isooctyl ester	53404-37-8 or 25168-26-7	developmental toxicity	Registered in CA
Diazinon	333-41-5	developmental toxicity	Registered in CA
Dichlorophene	97-23-4	developmental toxicity	Not currently registered in CA
2,4-DP (dichloroprop)	120-36-5	developmental toxicity	Not currently registered in CA
Dimethoate	60-51-5	developmental toxicity	Registered in CA
Diuron	330-54-1	developmental toxicity	Registered in CA
Naled	300-76-5	female reproductive toxicity	Registered in CA
Triforine	26644-46-2 & 37273-84-0	developmental toxicity	Registered in CA

Studies cited by US 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.

Bromacil lithium salt (CAS No. 5340419-6)

Developmental toxicity has been manifested as morphological abnormalities.

The US Environmental Protection Agency (US EPA, 1994a and 1994b) concluded that: "...there is sufficient evidence for listing bromacil lithium salt on EPCRA section 313 pursuant to EPCRA section 313(d)(2)(B) based on the available developmental ...toxicity data."

In supporting the decision to add bromacil lithium salt to the TRI list, US EPA (1994a) notes that, "Bromacil lithium salt will dissociate into bromacil, which is soluble in aqueous systems, and lithium ion." Therefore, developmental toxicity studies on other lithium salts, such as lithium chloride, are considered an appropriate basis for determining the hazard posed by bromacil lithium salt. It should be noted that two lithium salts, lithium carbonate and lithium citrate, are currently listed under California's Proposition 65 as developmental toxicants. These listings were based on warnings formally required by the US Food and Drug Administration to accompany pharmaceutical preparations containing these compounds.

Supporting documentation for the TRI listing (US EPA, 1993b) states, "Defects of the palate[,] eye and external ear were reported in the offspring of rats administered 50 mg lithium chloride intraperitoneally on gestation days 1, 4, 7, and 9 followed by 20 mg/day until day 17th [sic] (6 [Shepard, 1992]). Cleft palates were also observed in mouse fetuses when mothers were gavaged with 300 to 465 mg/kg/day lithium carbonate on gestation days 6 to 15. An increase in Esbstein's [sic] anomaly was reported among offspring of women taking lithium. Cardiovascular defects were found in 212 offspring exposed *in utero* to lithium therapy (6 [Shepard, 1992])."

Weinstein (1979), summarized by Shepard (1992), reports on a series of 212 lithium-exposed infants, 17 of whom had cardiovascular defects. Of these 17, there were 6 cases of Ebstein's anomaly, 10 of other major cardiovascular abnormalities, and one case of an abnormal umbilical artery. According to the author, among the general population, the ratio of congenital heart disease to all nontrivial malformations is about 1:8. Among the infants on the Register of Lithium Babies, however, the ratio of congenital heart disease to all non-trivial malformations was 1:1.4. The author concluded, "We cannot say with certainty that congenital cardiovascular anomalies occur more often in lithium-exposed infants than in the non-exposed, but it is likely that they do."

In the case of lithium, none of the individual studies were considered adequate for risk assessment. Taken together, however, the weight of evidence supports the conclusion that a hazard for developmental toxicity is posed by this chemical.

With regard to the studies cited as supporting US 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) rat developmental toxicity study (Wright et al., 1971). The low numbers of animals used and the use of a single dose of lithium render this study unsuitable for risk assessment purposes. However, the high frequency of lithium-induced malformations observed in this study are indicative of hazard.

Study b) mouse developmental toxicity study (Szabo, 1970). Two experiments are reported in this study. Neither experiment alone is suitable for risk assessment purposes. Taken together, the results of these experiments were consistent with each other, and are indicative of hazard.

Study c) human case reports (Nora et al., 1974).

Study d) Retrospective epidemiological study (Weinstein, 1979).

2. Route of administration:

Study a) ip injection.

Study b) oral, gavage

Study c) not stated, presumably oral.

Study d) not stated, presumably oral

3. The frequency and duration of exposure:

Study a) beginning on gestation day 1, 4, 7, or 9, daily through day 16.

Study b) daily on each of gestation days 6 - 15

Study c) throughout at least the first trimester of pregnancy

Study d) throughout at least the first trimester of pregnancy.

4. The numbers of test animals:

Study a) 3 pregnant animals in each test group, 3 sham controls, and 6 untreated controls.

Study b) 1) 3 - 4 pregnant animals per dose group. 2) 15 - 20 pregnant animals per dose group.

Study c) not relevant - paper presents two case reports of babies having Ebstein's anomaly being born to mothers undergoing lithium therapy.

Study d) Series of 212 infants on the "Register of Lithium Babies".

5. The choice of species:

Study a) rats

Study b) mice

Study c) humans

Study d) humans

6. The choice of dosage levels:

Study a) The dose chosen was considered to be the maximum sublethal dosage. Initial dose was 50 mg LiCl/rat (approximately 213 mg/kg bw), subsequent doses were 20 mg LiCl/rat (approximately 85 mg/kg bw).

Study b) 200, 300, 465 mg lithium carbonate/kg bw. 2) 0, 200, 465 mg lithium carbonate/kg bw.

Study c) Therapeutic dosages of lithium.

Study d) Therapeutic dosages of lithium.

7. Maternal toxicity:

Study a) Not relevant - as lithium was known to be an appetite suppressant, any animals losing weight were given caloric supplementation.

Study b) 1) 37% maternal death at the high dose of 465 mg lithium carbonate/kg bw.

Study c) not relevant.

Study d) not relevant.

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 US Environmental Protection Agency (US 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 (US 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 (US EPA, 1994a and 1993b): "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 US 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 cites RTECS (1993) 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 US 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 study (Courtney, 1977). Not conducted by standard techniques, but study does contain information useful to hazard identification.

Study c) Mouse developmental toxicity screen (Kavlock et al., 1987). Study conducted by a screening protocol which yields information useful to hazard identification.

Study d1 & d2) Rat developmental toxicity study (NTIS, 1981). Appears to have been conducted by standard techniques. In the d2 part of the study, some animals were allowed to deliver their litters, and the pups examined at birth and followed postnatally.

Study e) Mouse developmental toxicity study (NTIS, 1968). Not graded. Not conducted by standard techniques, but study does contain useful supplementary information.

2. Route of administration:

Study a1-a4) Oral, gavage.

Study b) Oral, gavage.

Study c) Oral, gavage.

Studies d) Oral, gavage.

Study e) Subcutaneous injection.

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 7-15 (in this study, the day a seminal plug was detected was designated as GD-1, rather than GD-0).

Study c) Daily on gestation days 8-12.

Studies d) Daily, on each of gestation days 6-15.

Study e) Not stated directly, but the general protocol (for a large number of chemicals summarized in the publication) indicates that treatment was given daily on each of gestation days 6-14 or 6-15.

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) 11 litters.

Study c) 30 litters tested, 43% pregnancy rate.

Study d) 21-34 litters per group.

Study e) Not stated.

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) 0, 0.56 mM/kg.

Study c) 87.5 mg/kg/day.

Study d) 0, 6.25, 12.25, 12.5, 25.0, 87.5 mg/kg/day*. *doses of isooctyl ester given as molar equivalents to the indicated mg/kg quantity of 2,4-D. For the postnatal follow-up part of the study, animals were taken only from the 0, 12.5 or 87.5 mg/kg/day groups.

Study e) Several separate experiments were conducted, with doses stated as 24, or 48, or 130 mg/kg/day (it is not clear whether multiple dose levels were tested in any single experiment).

7. **Maternal toxicity:**

Study a1-4) Treatment had no effect on maternal weight gain during pregnancy.

Study b) Treated dams showed a significant increase in the ratio of liver weight to body weight.

Study c) 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."

Study d) "No adverse effects were observed on maternal welfare...."

Study e) Not discussed, although in the general protocol information, it is stated that maternal weights at various timepoints were recorded.

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 US Environmental Protection Agency (US 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 (US 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 (US EPA, 1994a and 1993b): "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 US 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 cites RTECS (1993) 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 US 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 study (Courtney, 1977). Not conducted by standard techniques, but study does contain information useful to hazard identification.
- Study c) Mouse developmental toxicity screen (Kavlock et al., 1987). Study conducted by a screening protocol which yields information useful to hazard identification.
- Study d1 & d2) Rat developmental toxicity study (NTIS, 1981). Appears to have been conducted by standard techniques. In the d2 part of the study, some animals were allowed to deliver their litters, and the pups examined at birth and followed postnatally.
- Study e) Mouse developmental toxicity study (NTIS, 1968). Not graded. Not conducted by standard techniques, but study does contain useful supplementary information.

2. Route of administration:

- Study a1-a4) Oral, gavage.
- Study b) Oral, gavage.
- Study c) Oral, gavage.

- Study d) Oral, gavage.
Study e) Subcutaneous injection.
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 7-15 (in this study, the day a seminal plug was detected was designated as GD-1, rather than GD-0).
Study c) Daily on gestation days 8-12.
Study d) Daily, on each of gestation days 6-15.
Study e) Not stated directly, but the general protocol (for a large number of chemicals summarized in the publication) indicates that treatment was given daily on each of gestation days 6-14 or 6-15.
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) 11 litters.
Study c) 30 litters tested, 43% pregnancy rate.
Study d) 21-34 litters per group.
Study e) Not stated.
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) 0, 0.56 mM/kg.
Study c) 87.5 mg/kg/day.
Study d) 0, 6.25, 12.25, 12.5, 25.0, 87.5 mg/kg/day*. *doses of isooctyl ester given as molar equivalents to the indicated mg/kg quantity of 2,4-D. For the postnatal follow-up part of the study, animals were taken only from the 0, 12.5 or 87.5 mg/kg/day groups.
Study e) Several separate experiments were conducted, with doses stated as 24, or 48, or 130 mg/kg/day (it is not clear whether multiple dose levels were tested in any single experiment).
7. **Maternal toxicity:**
Study a1-4) Treatment had no effect on maternal weight gain during pregnancy.
Study b) Treated dams showed a significant increase in the ratio of liver weight to body weight.
Study c) 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."

Study d) "No adverse effects were observed on maternal welfare...."
Study e) Not discussed, although in the general protocol information, it is stated that maternal weights at various timepoints were recorded.

Diazinon (CAS No. 333-41-5)

Developmental toxicity has been manifested in offspring as morphological defects, increased post-implantation mortality, decreased litter size, and behavioral abnormalities.

The US Environmental Protection Agency (US EPA, 1994a and 1994b) concluded that: "...there is sufficient evidence for listing diazinon 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 (US EPA, 1993a) states, "In rats, diazinon induced defects in the urogenital system in offspring when administered orally to mothers at doses of 26.4 mg/kg on days 12-15 of gestation. Diazinon also induced musculoskeletal abnormalities in offspring when administered orally to mothers at doses of 45 mg/kg on days 8-12 days of gestation. Post-implantation mortality was increased in female rats administered 63.5 mg/kg on day 10 of gestation (RTECS, 1993). Similar reproductive and developmental effects were observed in mice. Oral administration of 3.96 mg/kg of diazinon (days 1-22 of gestation) caused decreased litter size and delayed behavioral effects in the newborn. Doses of 0.210 mg/kg and 3.78 mg/kg administered orally day 1-21 of gestation caused abnormalities in the immune and reticuloendothelial system and biochemical and metabolic abnormalities of the offspring, respectively (RTECS, 1993). Additional information from EPA/OPP's 'Tox-Oneliner' database confirms these findings."

The TRI listing is based on a brief summary of results presented in RTECS (1993) from four published studies. The rat teratology data originated from a published study by Dobbins (1967). 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. The actual administered doses which produced a higher incidence of urogenital effects (hydronephrosis and hydroureter) were 16.5 and 6.6 mg/kg given daily during days 12-15 of gestation (reported as 26.4 mg/kg in RTECS). The actual administered dose which induced musculoskeletal abnormalities (irregular ribs, short and wavy ribs) was 9.0 mg/kg given daily during days 8-12 of gestation (reported as 45 mg/kg in RTECS). Each of these treated groups was comprised of only 1 or 2 litters. Thus, the study contributes some supplementary data for hazard identification, but cannot be considered useful in itself for quantitative risk assessment purposes.

The mouse teratology data originated from three published studies (Spyker and Avery, 1977; Cranmer et al., 1978; Barnett et al., 1980). The three studies appear to have been

produced by the same research group, and employed the same basic treatment protocol. In each study, the animals were given daily doses of 0, 0.18, or 9.00 mg/kg/day of diazinon throughout gestation.

Cranmer et al., (1978) reported significant effects of prenatal exposure to diazinon on postnatal plasma corticosterone levels and adrenal weights. Barnett et al. (1980) found no change in litter size or birthweight of mouse pups exposed to diazinon during gestation. Postnatal viability of exposed pups was significantly reduced among the high-dose group. There were also significant and lasting effects on certain immunological parameters. Spyker and Avery (1977) found that prenatal diazinon exposure depressed postnatal growth, and caused significant delays in attainment of behavioral and physiological developmental landmarks. While exposure of maternal animals was restricted to the duration of gestation, the possibility that diazinon was secreted in the dams' milk, and hence that lactational exposures occurred, cannot be ruled out.

With regard to the studies cited as supporting US 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) rat developmental toxicity study (Dobbins, 1967): the extremely low number of animals per dose group (1-8) makes this study unsuitable for quantitative risk assessment purposes.
 - Study b, c, & d) mouse developmental toxicity studies (Barnett et al., 1980; Cranmer et al., 1978; Spyker and Avery, 1977). All 3 studies used only 2 dose-groups plus a control group. Although none would fully meet US EPA test guideline standards for registration (1983a), they appear adequate for hazard identification purposes.
2. **Route of administration:**
 - Study a) oral, gavage.
 - Study b, c & d) oral, in a dietary supplement of peanut butter or homogenized peanuts.
3. **The frequency and duration of exposure:**
 - Study a) once per day on each of gestation days 8-12 or 12-15, or single-day dosings on day 9 or 10.
 - Study b, c & d) daily, throughout gestation.
4. **The numbers of test animals:**
 - Study a) most groups had 1 or 2 animals per group, the largest group had 8 animals.
 - Study b) 19-22 pregnant animals per group.
 - Study c) 43 controls, 21 and 19 in the two dose groups.
 - Study d) not clearly stated.
5. **The choice of species:**
 - The rat and mouse are standard test species.
6. **The choice of dosage levels:**

Study a) 0, 6.6, 9.0, 16.5, 17.3, 52.6, 63.5, 63.8, 70.6, 89.9, 95.2 mg/kg/day, RTECS (1993) reports repeated dosings as summed over the days of treatment.

Study b, c & d) 0, 0.18, 9.00 mg/kg/day. RTECS (1993) reports these doses as summed over the full exposure period.

7. Maternal toxicity:

Study a) none reported at the lower doses. Maternal deaths were observed with exposure to 95.2 (3/8 animals) or 89.9 mg/kg (1/3 animals) on gestation day 9, or with 17.3 mg/kg/day (1/2 animals) on each of gestation days 12-15.

Study b) maternal weight gain was significantly decreased in the dosed groups, as compared to controls. However, this effect was not dose-related.

Study c, d) not mentioned.

Dichlorophene (CAS No. 97-23-4)

Developmental toxicity was evidenced by an increased incidence of microphthalmia, delayed ossification, reductions in body weight and length, and increased resorption frequency.

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

Supporting documentation for the TRI listing (US EPA, 1993b) states, "Increased incidence of microphthalmia was observed in the offspring of rats administered 25 mg/kg/day (teratogenic LOEL). The NOEL was 5.0 mg/kg/day. A dose of 75 mg/kg/day (fetotoxic LOEL) produced delayed ossification of vertebral centra and sternaebra, reduced body weight and length, and increased resorptions in rat fetuses. The fetotoxic NOEL was 5.0 mg/kg/day. The study was classified core minimum..." Further details of the study were obtained from the tox one-liner database (US EPA, 1984), as cited in the TRI supporting documentation (US EPA, 1993b).

With regard to the studies cited as supporting US EPA's action in adding a chemical to the EPCRA-TRI list, OEHHHA 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 rated core minimum
- 2. Route of administration:**
Oral, gavage (US EPA, 1984)
- 3. The frequency and duration of exposure:**

Not stated. However, as this study was rated "core grade minimum" it would have met US EPA test guidelines (US EPA, 1983a) which require treatment on each of gestation days 6 - 15.

4. The numbers of test animals:

Not stated. However, as this study was rated "core grade minimum" it would have met US EPA test guidelines (US EPA, 1983a) which require a minimum of 20 animals per dose group.

5. The choice of species:

The rat is a standard test species.

6. The choice of dosage levels:

0, 5, 25, 75 mg/kg/day.

7. Maternal toxicity:

Maternal toxicity was evidenced by reduced body weight gain and food consumption. The LEL for these effects was 25 mg/kg/day, and the NOEL was 5.0 mg/kg/day.

2,4-DP (dichloroprop) (CAS No. 120-36-5)

Developmental toxicity following prenatal exposure to 2,4-DP has been manifested as reduced viability in fetal rats, and musculoskeletal abnormalities and fetotoxicity in fetal mice.

The US Environmental Protection Agency (US EPA, 1994a and 1994b) concluded that "...there is sufficient evidence for listing 2,4-DP 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 (US EPA, 1993a) states, "Developmental toxicity has been reported in rats and mice (RTECS, 1993) administered oral doses as low as 20 mg/kg 2,4-DP during gestation days 4-18, with behavioral and/or physical effects in newborn rats, and, in mice, increased postimplantation loss. Exposure of mice to higher doses (3000 and 4000 mg/kg) for shorter durations [sic] (i.e. gestation days 6-15) caused musculoskeletal abnormalities and fetotoxicity (RTECS, 1993). Data from OPP's 'Tox Oneliner' database support these findings."

OEHHA has retrieved and reviewed the original articles cited in RTECS (1993). 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. Of the references cited by RTECS, only one (Roll and Matthiaschk, 1983) was reported in sufficient detail for risk assessment. Roll and Matthiaschk (1983) found adverse effects on fetal weight in mice exposed to doses of 300 mg/kg and above, and skeletal anomalies following prenatal exposure to doses of 400 mg/kg and above.

Of the studies summarized by US EPA's tox one-liner database (US EPA, 1993c), only the rat multi-generation reproduction study reported an adverse effect on exposed offspring. The fetotoxic LEL for this study was stated to be 2000 ppm, based upon findings of an increased number of small litters, and increased mortality. The corresponding NOEL was 1000 ppm.

With regard to the studies cited as supporting US 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) Developmental toxicity studies in rats and mice (Buschmann et al., 1986a). The study is reported in abstract form only, so the adequacy cannot be determined.

Study b) Behavioral developmental toxicity study in rats (Buschmann, et al., 1986b). The study is reported in abstract form only, so the adequacy cannot be determined.

Study c) Developmental toxicity in mice (Roll and Matthiaschk, 1983). The basic protocol and evaluation methods correspond to standard techniques.

Study d) Developmental toxicity study in rats. Range finding study, rated 'core grade guideline' (US EPA, 1993c).

Study e) Developmental toxicity study in rats. Rated 'invalid' (US EPA, 1993c) due to excessive deficiencies.

Study f) Developmental toxicity study in rabbits. Range finding study, rated 'core grade minimum' (US EPA, 1993c).

Study g) 3-generation reproductive toxicity study in rats. Rated 'core grade minimum' (US EPA, 1993c).

2. Route of administration:

Study a) Oral, gavage.

Study b) Oral, gavage.

Study c) Oral, gavage.

Study d) Not stated, but US EPA test guidelines for developmental toxicity studies (US EPA, 1983a) specify the gavage route of exposure. As the study received an acceptable grade, it is presumed that guideline requirements were met.

Study e) Not stated,

Study f) Not stated, but US EPA test guidelines for developmental toxicity studies (US EPA, 1983a) specify the gavage route of exposure. As the study received an acceptable grade, it is presumed that guideline requirements were met.

Study g) Oral, diet.

3. The frequency and duration of exposure:

Study a) Once on each of 'p.c.' ['p.c.' is not defined, presumably refers to 'post conception] days 4, 10, 13, and 18.

Study b) Once on each of 'p.c.' days 4, 10, 13, and 18.

Study c) Daily on each of gestation days 6-15.

Study d) Not stated, but US EPA test guidelines for developmental toxicity studies (US EPA, 1983a) specify treatment to cover the organogenesis phase of prenatal development, generally days 6-15 for rats. As the study received an acceptable grade, it is presumed that guideline requirements were met.

Study e) Not stated.

Study f) Not stated, but US EPA test guidelines for developmental toxicity studies (US EPA, 1983a) specify treatment to cover the organogenesis phase of prenatal development, generally days 6-18 for rabbits. As the study received an acceptable grade, it is presumed that guideline requirements were met.

Study g) Not stated, but US EPA test guidelines for reproductive toxicity studies (US EPA, 1983b) specify continuous exposure from prior to mating of the parental generation, throughout gestation and lactation, and continuing through postnatal development and reproduction of the F1 generation to produce the F2. As the study was considered to meet guideline requirements, it is presumed that this dosing schedule was adhered to.

4. The numbers of test animals:

Study a) Not stated.

Study b) Not stated.

Study c) 21-38 litters per dose group, except for the highest dose group, which had 12 pregnant females.

Study d) Not stated, but US EPA test guidelines for developmental toxicity studies (US EPA, 1983a) specify a minimum of 20 pregnant rats per dose group. As the study received an acceptable grade, it is presumed that guideline requirements were met.

Study e) Not stated.

Study f) Not stated, but US EPA test guidelines for developmental toxicity studies (US EPA, 1983a) specify a minimum of 12 pregnant rabbits per dose group. As the study received an acceptable grade, it is presumed that guideline requirements were met.

Study g) Not stated, but US EPA test guidelines for reproductive toxicity studies (US EPA, 1983b) specify a minimum of 20 pregnant animals per dose group. As the study received an acceptable grade, it is presumed that guideline requirements were met.

5. The choice of species:

Rats, rabbits, and mice are standard species used in toxicology testing.

6. The choice of dosage levels:

Study a) Rats: 0, 5, 30, 100, 200 mg/kg. Mice: 0, 5, 30, 100, and 150 mg/kg.

Study b) 0, 5, 30, 100, and 200 mg/kg.

Study c) 0, 100, 200, 300, 400, 500 mg/kg/day.

Study d) 0, 25, 100 mg/kg.

Study e) 0, 10, 30, 100 mg/kg.

Study f) 0, 25, 100 mg/kg.
Study g) 0, 1000, 2000 ppm

7. Maternal toxicity:

Study a) Not discussed.
Study b) Not discussed.
Study c) Significant decrease in maternal gestational weight gain at the high dose of 500 mg/kg/day.
Study d) Not discussed.
Study e) Not discussed.
Study f) Not discussed.
Study g) Maternal NOEL=1000 ppm. Maternal LEL=2000 ppm for reduced body weight, and increase in number of small litters.

Dimethoate (CAS No. 60-51-5)

Developmental toxicity has been manifested as musculoskeletal abnormalities and increased mortality.

The US Environmental Protection Agency (US EPA, 1994a and 1994b) concluded that, "...there is sufficient evidence for listing dimethoate 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 (US EPA, 1993a) states, "The NOEL for developmental effects (in rats) was 6 mg/kg/day. At a LOEL of 12 mg/kg/day an increase in the incidence of wavy ribs was observed in the fetuses (HSDB, 1993). In a five generation chronic feeding study (actual doses were 9.5-10.5 mg/kg/day) in male and female CD-1 mice, an increase in mortality of the pups occurred (HSDB, 1993). At 12 mg/kg/day [reported in RTECS as 120 mg/kg, over days 6-15 of gestation], musculoskeletal abnormalities were observed in the rat offspring (RTECS, 1993)."

The two primary studies on which the TRI listing is based for dimethoate, the rat developmental and the mouse five-generation reproduction study, have been previously published in the literature. Both studies are summarized by US EPA (1993c) and report essentially the same adverse effects on development.

For the rat teratology study, Khera et al. (1979) states, "Dimethoate treatment at the 12 and 24 mg/kg doses was associated with a statistically significant increase in the numbers of anomalous litters (each having at least one anomalous fetus), and wavy-ribbed fetuses. Other anomalies in the dimethoate-treated fetuses, although statistically not significant on their own, were extra ribs, fused sternbrae, runted fetuses, hydroureter and dilated urinary bladder."

For the mouse 5-generation reproduction study, Budreau and Singh (1973) reported that the survival rate of total pups and litters was significantly reduced by dimethoate treatment in generations I, III, IV, and V. The authors also stated, "Growth rate of the dimethoate pups was consistently lower than that for controls, although comparison of the mean weights showed a statistically significant difference in only one instance." Parental effects included reduced mating success and longer reproduction time.

US EPA (1995) has recently evaluated other reproductive and developmental toxicity data in support of a proposed tolerance for dimethoate. These include: a). a two-generation reproduction study in rats fed diets containing 0, 1, 15, or 65 ppm (equivalent to 0/0, 0.08/0.09, 1.2/1.3, or 5.46/6.04 mg/kg/day for males/females). A tentative reproductive NOEL of 15 ppm was based on decreased fertility in the F1b, F2a, and F2b matings. Other effects seen at this concentration were: decreased pup weight during the lactation period for both sexes and both generations, and decreased live births in the F2b litters, b). a developmental toxicity study in rats (0, 3, 6, or 18 mg/kg/day via gavage) with no developmental toxicity observed, and a NOEL for maternal toxicity established at 6 mg/kg/day due to hypersensitivity, tremors, and unsteady gait, and c). a developmental toxicity study in rabbits (0, 10, 20, or 40 mg/kg/day via gavage) with a NOEL of 20 mg/kg/day based on significant reductions in fetal weights, and a maternal NOEL of 10 mg/kg/day based on body weight decrement.

With regard to the studies cited as supporting US 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 22CCR 12306, and notes the following:

1. **Adequacy of the experimental design:**
Study a) rat teratology study - rated core grade supplementary, due primarily to insufficient numbers of pregnant dams per dose group,
Study b) mouse 5-generation reproduction study - rated core grade supplementary, due primarily to an insufficient number of dose groups.
2. **Route of administration:**
Study a) oral gavage,
Study b) oral, in drinking water.
3. **The frequency and duration of exposure:**
Study a) each of gestation days 6-15,
Study b) continuous, in drinking water.
4. **The numbers of test animals:**
Study a) 15-17 pregnant dams per group,
Study b) 14 females and 10 males per generation.
5. **The choice of species:**
The rat and mouse are standard test species.
6. **The choice of dosage levels:**
Study a) 3, 6, 12, and 24 mg/kg/day,
Study b) 0 and 60 ppm (0 and 9.5-10.5 mg/kg/day).
7. **Maternal toxicity:**

- Study a) decreased maternal body weight, neurotoxicity (clonic spasms and muscular tremors), and one death at the highest dose (24 mg/kg/day), with developmental effects reported at both 24 and 12 mg/kg/day;
- Study b) no maternal effects other than the parental effects of reduced mating success and longer reproduction time.

Diuron (CAS No. 330-54-1)

Developmental toxicity has been manifested as skeletal anomalies and decreased body weights.

The US Environmental Protection Agency (US EPA, 1994a and 1994b) concluded that "...there is sufficient evidence for listing diuron 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 (US EPA, 1993a) states, "Offspring of Wistar rats fed diuron during gestation days 6-15 demonstrated an increase in fetotoxic effects including wavy ribs, extra ribs, and delayed ossification. The developmental LOAEL in this study was 100 mg/kg/day; no NOEL was determined. Maternal and fetal body weights decreased at 400 mg/kg/day (IRIS; US EPA, 1993d). In a three-generation reproduction study in rats fed 6.25 mg/kg/day, decreased body weights were reported in the F_{2b} and F_{3a} litters (IRIS; US EPA 1993d); however, only one dose was tested."

The two primary studies on which the TRI listing is based for diuron, the rat teratology and the rat three-generation reproduction study, have been described in the published literature (Khera et al., 1979; Hodge et al., 1967).

In the rat teratology study (Khera et al., 1979), there were significant decreases in maternal and fetal weights at the high dose of 500 mg diuron/kg bw/day, given by gavage on gestation days 6 - 15. The frequency of wavy ribs was increased over controls in all three diuron-treated groups; the increases were statistically significant at the mid and high dose. Delayed ossification of the calvarium was observed in all groups, with a statistically significant increase over controls at the low dose of 125 mg diuron/kg bw/day. US EPA (1988), determined a LOAEL of 125 mg diuron/kg bw/day, based upon the ossification effects observed at that dose. As this was the lowest dose tested, no NOAEL was established.

For the three-generation rat reproduction study (Hodge et al., 1967), animals were given food which contained diuron at concentrations of either 0 or 125 ppm. Neither the fertility index nor the average number of pups per litter was altered by exposure to diuron. There was some evidence for adverse effects on postnatal growth of the F_{2b} and F_{3a} generations, but this finding was not repeated when the study was replicated.

With regard to the studies cited as supporting US 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 CCR12306, and notes the following:

1. **Adequacy of the experimental design:**
 - Study a) rat teratology study - IRIS (US EPA, 1993d) states that this study is core grade supplementary. This grade was probably given due to the numbers of animals per dose group, which is slightly lower than that specified by US EPA testing guidelines (US EPA, 1983a). However, the use of this study as the basis for the 10-day Health Advisory for Diuron in drinking water (US EPA, 1988), indicates that the Agency determined the data were suitable for risk assessment.
 - Study b) rat 3-generation reproduction study - IRIS (US EPA, 1993d) states that no core grade was given for this study.
2. **Route of Administration:**
 - Study a) rat teratology study - oral gavage.
 - Study b) rat 3-generation reproduction study - oral, in diet.
3. **The frequency and duration of exposure:**
 - Study a) rat teratology study - each of gestation days 6-15.
 - Study b) rat 3-generation reproduction study - continuous, in diet.
4. **The numbers of test animals:**
 - Study a) rat teratology study - 14-19 pregnant dams per dose group.
 - Study b) rat 3-generation reproduction study - 8 males and 16 females per group, study repeated once with the same numbers of animals.
5. **The choice of species:**
 - The rat is a standard test species.
6. **The choice of dosage levels:**
 - Study a) rat teratology study - 0, 125, 250, 500 mg/kg/day; when corrected for 80% active ingredient, the dose levels were 0, 100, 200, 400 mg/kg/day (US EPA, 1993d).
 - Study b) rat 3-generation reproduction study - 0 and 125 ppm (0 and 6.25 mg/kg/day, US EPA, 1993d).
7. **Maternal toxicity:**
 - Study a) rat teratology study - maternal body weight was decreased at the highest dose tested (500 mg/kg/day).
 - Study b) rat 3-generation reproduction study - no maternal toxicity reported.

Naled (CAS No. 300-76-5)

Female reproductive toxicity was evidenced by decreased litter size in a two-generation reproductive toxicity study in rats.

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

Supporting documentation for the TRI listing (US EPA, 1993a) states, "In a 2-generation [rat] reproduction study, the NOEL was 6 mg/kg/day. At 18 mg/kg/day, decreased litter size, survival, and pup body weight were observed (IRIS [US EPA], 1993[d]). No other reproductive toxicity studies were available."

With regard to the studies cited as supporting US 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:**
The 2-generation rat reproductive toxicity study was rated core grade minimum (US EPA, 1993d).
2. **Route of administration:**
Not stated, but US EPA test guidelines for reproductive toxicity studies (US EPA, 1983b) specify the oral route of exposure. As the study received an acceptable grade, it is presumed that guideline requirements were met.
3. **The frequency and duration of exposure:**
Not stated, but US EPA test guidelines for reproductive toxicity studies (US EPA, 1983b) specify continuous exposure from prior to mating of the parental generation, throughout gestation and lactation, and continuing through postnatal development and reproduction of the F1 generation to produce the F2. As the study was considered to meet guideline requirements, it is presumed that this dosing schedule was adhered to.
4. **The numbers of test animals:**
Not stated, but US EPA test guidelines for reproductive toxicity studies (US EPA 1983b) specify sufficient animals to ensure a minimum of 20 pregnant animals per dose group. As the study received an acceptable grade, it is presumed that guideline requirements were met.
5. **The choice of species:**
Rats are a standard test species for reproductive toxicity studies.
6. **The choice of dosage levels:**
0, 6, 18 mg/kg/day. As the study rated 'core grade minimum' (US EPA, 1993d), there was presumably at least one additional dose level, which would have been required to meet US EPA test guideline standards for a reproductive toxicity study (US EPA, 1983b).
7. **Maternal toxicity:**
Maternal toxicity was not mentioned. The LEL for parental toxicity of 18 mg/kg/day, was based on decreased body weight in males (US EPA, 1993d). The NOEL for this effect was 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 US Environmental Protection Agency (US 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 (US 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 [US 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 [US EPA, 1993c]). Both of these developmental toxicity studies were classified as Core Minimum."

With regard to the studies cited as supporting US 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 (US EPA, 1993c).

Study b) rat developmental toxicity study, core grade minimum (US EPA, 1993c).

2. Route of administration:

Not stated for either study, but US EPA test guidelines for developmental toxicity studies (US EPA, 1983a) specify the gavage route of exposure. As both of these studies received acceptable grades, it is presumed that guideline requirements were met.

3. The frequency and duration of exposure:

Not stated for either study, but US EPA test guidelines for developmental toxicity studies (US 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 these requirements were met.

4. The numbers of test animals:

Not stated for either study, but US EPA test guidelines for developmental toxicity studies (US 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 guideline requirements were met.

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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