CHEMICALS UNDER CONSIDERATION FOR POSSIBLE LISTING VIA THE AUTHORITATIVE BODIES MECHANISM 15 CHEMICALS IDENTIFIED BY US EPA

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The 15 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 which 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-One-Liner" database maintained by US EPA's Office of Pesticide Programs. 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 used by US EPA to indicate the extent to which a study conformed to published test guidelines (US EPA 1983a and 1983b). For example, a "core grade guideline" study was considered to meet all guideline requirements, and a "core grade minimum" study was considered sufficient for risk assessment.

Chemical	Chemical Abstracts No.	DART Endpoints	Pesticide status or usage
Chinomethionat (Oxythioquinox)	2439-01-2	Developmental toxicity	Registered in CA
Cycloate	1134-23-2	Developmental toxicity	Registered in CA
Cyclohexanol	108-93-0	Male reproductive toxicity	Non-pesticidal solvent with a variety of uses
Diclofop Methyl	51338-27-3	Developmental toxicity	Registered in CA
Fenoxaprop Ethyl	66441-23-4	Developmental toxicity	Registered in CA
Fluazifop butyl	69806-50-4	Developmental toxicity	Registered in CA
Fluvalinate	69409-94-5	Developmental toxicity	Registered in CA
Hydramethylnon (Amdro)	67485-29-4	Developmental toxicity, male reproductive toxicity	Registered in CA
Molinate	2212-67-1	Developmental toxicity, male reproductive toxicity, female reproductive toxicity	Registered in CA
Myclobutanil	88671-89-0	Developmental toxicity, male reproductive toxicity	Registered in CA
Oxydemeton methyl	301-12-2	Female reproductive toxicity, male reproductive toxicity	Registered in CA
Propachlor	1918-16-7	Developmental toxicity	Pesticide, not currently registered in CA
Resmethrin	10453-86-8	Developmental toxicity	Registered in CA
Sodium fluoroacetate	62-74-8	Male reproductive toxicity	Registered in CA
Sodium nitrite	7632-00-0	Developmental toxicity	Meat preservative

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. Where NOELs (no-observed-effect-level), LOELs (lowest-observed-effect-level), or LELs (lowest-effect-level) are included in this document, they are quoted directly from the cited references.

Chinomethionat (Oxythioquinox; CAS No. 2439-01-2)

***Developmental toxicity* has been manifested as increased resorptions, decreased fetal weights, and morphological defects.**

The US Environmental Protection Agency (US EPA, 1994a and 1994b) concluded that: "...there is sufficient evidence for listing chinomethionat on 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:

> "In a developmental toxicity study in rats, increased resorption and decreased fetal weight were reported at 37.5 mg/kg/day (the highest dose tested). The NOEL was 12.5 mg/kg/day. No details regarding frequency and duration of treatment were reported. The study was classified as Core Minimum. In another developmental study in rats given 30 mg/kg/day in carboxy methyl cellulose by gavage from gestation day 6 to 20, cleft palate, anasarca and micrognathia was observed."

The TRI listing is based on US EPA's Tox-One-Liner Database for Morestan (chinomethionat) (US EPA, 1986).

For the first rat teratology study, US EPA (1986) stated that the doses tested were 0, 100, 250, 750 ppm (equivalent to 0, 5, 12.5, 37.5 mg/kg/day). The fetotoxic NOEL and LEL were 250 and 750 ppm, respectively, based on decreased fetal weight and growth. The reproductive NOEL and LEL were also 250 and 750 ppm, respectively, based on increased resorptions. The maternal NOEL and LEL were 100 and 250 ppm, respectively, based on ruffed fur and poor food consumption.

In the second rat teratology study, US EPA (1986) stated that the "levels tested by gavage in Charles River COBS CD strain [rats were] 0, 10, 30, and 90 mg/kg/day". The developmental NOEL and LEL were 10 and 30 mg/kg/day, based on "multiple malformations occurring at the top dose [including]: cleft palate, small mouth and jaws; also vertebral anomalies; bent clavicles, scapulae, ilia, and bent limb bones. Some of the malformations also appear at mid dose. No malformations at low dose or in controls." In addition, embryolethality and increased post-implantation loss occurred at the highest dose and the sex ratio was somewhat reduced at all doses. The maternal NOEL and LEL were 30 and 90 mg/kg/day, respectively, based on reduced maternal body weight and feed consumption.

With regards 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 CFR 12306, and notes the following:

1. **Adequacy of the experimental design:**
   Study a) rat teratology study #1- Core Grade Minimum,
   Study b) rat teratology study #2 - Core Grade Guideline.
2. **Route of administration:**
   Study a) rat teratology study #1 - unspecified,
   Study b) rat teratology study #2 - oral gavage.
3. **The frequency and duration of exposure:**
   Details are not explicitly stated. However, both of these studies were considered to meet guideline specifications, which require daily treatment of pregnant rats during gestation days 6-15.
4. **The numbers of test animals:**
   Details are not explicitly stated. However, both of these studies were considered to meet guideline specifications, which require a minimum of 20 pregnant rats per dose group.
5. **The choice of species:**
   The rat is a standard test species.
6. **The choice of dosage levels:**
   Study a) rat teratology study #1 - 0, 100, 250, 750 ppm (equivalent to 0, 5, 12.5, 37.5 mg/kg/day),
   Study b) rat teratology study #2 - 0, 10, 30, 90 mg/kg/day.
7. **Maternal toxicity:**
   Study a) rat teratology study #1 - the maternal toxicity NOEL and LEL (100 and 250 ppm, respectively) were based on ruffed fur and poor food consumption. These are lower than the NOEL and LEL for developmental toxicity (250 and 750 ppm, respectively), which were based on growth deficits and increased resorptions,
   Study b) rat teratology study #2 - Developmental toxicity (NOEL 10 mg/kg/day; LEL 30 mg/kg/day) was observed at doses lower than those that produced maternal toxicity (NOEL 30 mg/kg/day; LEL 90 mg/kg/day).

Cycloate (CAS No. 1134-23-2)

***Developmental toxicity* has been manifested as decreased pup weight and survival in rat studies.**

The US Environmental Protection Agency (US EPA, 1994a and 1994b) concluded that "...there is sufficient evidence for listing cycloate on 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:

> "Decreased weight and survival were observed in the offspring of rats orally administered 24 mg/kg/day (LOEL) and 72 mg/kg/day of cycloate, respectively (duration and frequency not reported). The reproductive NOEL was 8 mg/kg/day. Decreased pup weight was observed at 20 mg/kg/day and decreased pup survival was observed at 50 mg/kg/day in a 2-generation rat reproduction study. The NOEL values for these endpoints were 2.5 mg/kg/day and 20 mg/kg/day, respectively. Other studies which tested doses up to 400 mg/kg/day failed to find any reproductive or developmental effects."

Details of the studies cited by US EPA in support of the TRI listing were obtained from the California Department of Pesticide Regulations' Summary of Toxicology Data on Cycloate (CDPR, 1994). The CDPR (1994) and US EPA (1993a) report the same developmental NOEL and LOEL for each of the studies.

With regards 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 CFR12306, and notes the following:

1. **Adequacy of the experimental design:**
   Both studies appear to be acceptable under FIFRA. US EPA (1993a) stated that the 2-generation rat reproduction study was rated "supplementary" because the test compound was not identified in the report.
2. **Route of administration:**
   Oral, in diet for both studies.
3. **The frequency and duration of exposure:**
   Continuous, in diet.
4. **The numbers of test animals:**
   Study a) 3-generation rat reproduction study: 15 males, 30 females per generation,
   Study b) 2-generation rat reproduction study: 25 per sex per group.
5. **The choice of species:**
   The rat is a standard test species.
6. **The choice of dosage levels:**
   Study a) 3-generation rat reproduction study: 0, 8, 24, 72 mg/kg/day,
   Study b) 2-generation rat reproduction study: 0, 50, 400, 1000 ppm (approximately equivalent to 0, 2.5, 20, 50 mg/kg/day).
7. **Maternal toxicity:**
   In both reproduction studies, parental and developmental toxicity occurred at the same doses. For both rat reproduction studies, parental toxicity consisted of decreased body weight at the 2 highest doses (CDPR, 1994). In addition, F0 and F1 breeding adults in the 2-generation study had mineralization of the brain and biliary hyperplasia at the highest dose, and thoracic and sacral spinal cord degeneration at the two highest doses

(females only). In the TRI final rule document (US EPA, 1994a), the Agency states with specific reference to cycloate: "As described in unit IV.E. of this preamble, developmental effects seen in developing organisms are considered to be adverse whether or not they occur at doses that are also maternally toxic."

Cyclohexanol (CAS No. 108-93-0)

Male reproductive toxicity **has been manifested as decreased fertility, testicular atrophy, sperm abnormalities and biochemical changes in the testes.**

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

Supporting documentation for the TRI listing (US EPA, 1993b) states:

> "In male rats or gerbils exposed to 15 mg/kg for 21-37 days, reproductive effects observed included testicular atrophy, loss of Type A spermatogonia, spermatocytes and spermatozoa, 'shrinkage' of seminiferous tubules and Leydig cells, reductions in RNA protein, sialic acid, and glycogen in testes, epididymis and seminal vesicles and increased testicular cholesterol and alkaline phosphatase. These changes were associated with 'an antifertility state,' and occurred at exposure levels which had no effect on the liver or kidney or any general metabolic activities (HSDB, 1993)."

The primary study on which the TRI listing for cyclohexanol is based has been previously published in the literature (Tyagi et al., 1979) and summarized by US EPA (1985).

> In both gerbils and rats, Tyagi et al. (1979) states that, "Cyclohexanol administration did not cause loss in body weight, whereas a significant reduction was noticed in the weights of testes, epididymides, seminal vesicles and ventral prostate. The thyroid and adrenal gland did not change." In addition, it was stated that the "seminiferous tubule presented marked degenerative changes in both the animal species. The changes consisted of loss of type A spermatogonia, spermatocytes, spermatids and spermatozoa." Leydig and Sertoli cell degeneration was also observed. Other changes in both species included significant decreases in total protein, RNA and sialic acid contents of the testes, epididymides and seminal vesicles and increased cholesterol content and phosphatase activity in testes.

With regards 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 CFR12306, and notes the following:

1. **Adequacy of the experimental design:**
   In its Final Rule, US EPA (1994a) states that, "...the overall reproductive toxicity of this chemical, based on a weight-of-evidence, supports the addition of cyclohexanol to the EPCRA section 313 list."
2. **Route of administration:**
   Subcutaneous for both species.
3. **The frequency and duration of exposure:**
   Rats - injected once per day for 37 days; gerbils - injected once per day for 21 days.
4. **The numbers of test animals:**
   For both rats and gerbils, 20 males per group.
5. **The choice of species:**
   Rat and gerbil
6. **The choice of dosage levels:**
   For both rats and gerbils, 0 and 15 mg/kg/day.
7. **Maternal toxicity:**
   Not relevant. Tyagi et al. (1979) specifically mention the absence of evidence for systemic toxicity at doses affecting reproductive endpoints in adult males.

<u>Diclofop Methyl (CAS No. 51338-27-3)</u>

***Developmental toxicity* has been manifested as increased resorptions and pup mortality, reduced body weights, and effects on the kidneys.**

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

Supporting documentation for the TRI listing (US EPA, 1993a) states, "In a rat teratology study, increased resorptions, reduced body weights, and dilation of the renal pelvis or distention of the ureter in offspring were reported in rats fed 1.6 mg/kg/day (LOEL). The NOEL was 0.5 mg/kg/day. Increased pup mortality was observed at 5 mg/kg/day (LOEL) in a 3-generation rat reproduction study. The NOEL was 1.5 mg/kg/day."

The TRI listing is based on the description of the two primary studies by the US EPA (1993d) Tox-One-Liner for diclofop methyl. The 1986 Summary of Toxicology Data for Diclofop-Methyl by the California Department of Food and Agriculture summarizes the same studies.

The US EPA Final Rule (1994b) reaffirmed that there is sufficient evidence for listing diclofop methyl based on the available developmental . . . toxicity data. The Final Rule also noted that in the rat teratology study, the Agency erred in interpreting gavage doses

as diet concentrations (ppm) in the TRI listing (US EPA, 1993b). The actual doses for the developmental NOEL and LOEL are 10 and 32 mg/kg/day, respectively.

With regards 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 CFR 12306, and notes the following:

1. **Adequacy of the experimental design:**
   Both studies were rated as Core Grade Minimum.
2. **Route of administration:**
   Study a) rat teratology study - oral gavage,
   Study b) 3-generation rat 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) 3-generation rat reproduction study - continuous, in diet.
4. **The numbers of test animals:**
   Study a) rat teratology study - 20 per group,
   Study b) 3-generation rat reproduction study - 10 males and 15 females per group; 3 generations, 2 litters per generation.
5. **The choice of species:**
   The rat is a standard test species.
6. **The choice of dosage levels:**
   Study a) rat teratology study - 0, 10, 32, 100 mg/kg/day,
   Study b) 3-generation rat reproduction study - 0, 10, 30, 100 ppm (equivalent to 0, 0.5, 1.5, 5 mg/kg/day).
7. **Maternal toxicity:**
   Study a) rat teratology study - the maternal LOEL of 10 mg/kg/day (lowest dose tested) is based on increased liver weights,
   Study b) 3-generation rat reproduction study - no maternal toxicity apparent.

<u>Fenoxaprop Ethyl (CAS No. 66441-23-4)</u>

***Developmental toxicity* has been manifested as decreased viability, impaired growth and delayed ossification.**

The US Environmental Protection Agency (US EPA, 1994a and 1994b) concluded that: ". . . there is sufficient evidence for listing fenoxaprop ethyl on 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:

> "In a developmental toxicity study, fetotoxic effects (slightly impaired growth and delayed ossification) were reported at 100 mg/kg/day. The NOEL was 32 mg/kg/day. These effects were observed at doses that were also toxic to maternal

animals. In a two-generation reproductive toxicity feeding study in rats, decreased survival, decreased body weight at study termination, and significant changes in kidney and liver weights were reported in the F2a and F2b litters. The fetotoxic LOEL in this study was 5 ppm (0.25 mg/kg/day, the lowest dose tested). The LOEL and NOEL for maternal toxicity (increased kidney and liver weights) were 80 ppm [180 ppm, see below] (4 mg/kg/day) and 30 ppm (1.5 mg/kg/day), respectively. Thus, the fetotoxic effects were observed at doses lower than those that produced maternal toxicity."

The TRI listing is based on the evaluation of the two primary studies by US EPA (1993a) in its Tox-One-Liner Database for fenoxaprop ethyl. However, a discrepancy was observed in the Tox-One-Liner obtained by OEHHA (US EPA, 1989) concerning the highest dose tested in the two-generation rat study. The Tox-One-Liner (US EPA, 1989) lists the highest dose as 180 ppm and the maternal LEL (highest dose tested) as 80 ppm. The difference appears to be due to a typographical error in the Tox-One-Liner, listing the maternal LEL as 80 ppm rather than the true dose of 180 ppm, that was carried over into the TRI document (US EPA, 1993a). Correction of this error would result in a change of the LEL, but not the NOEL, for maternal toxicity.

For the rat teratology study, US EPA (1989) noted that the doses tested were 0, 10, 32, 100 mg/kg by gavage in Wistar rats. The fetotoxic NOEL and LEL were 32 and 100 mg/kg, respectively, based on slightly impaired growth and delayed ossification. The maternal NOEL and LEL were also 32 and 100 mg/kg, respectively, based on reduced body weight gain.

In the two-generation rat reproduction study, US EPA (1989) noted that the dose levels tested were 0, 5, 30, and 180 ppm. No NOEL was identified for fetotoxicity, as the lowest concentration tested (5 ppm) was associated with decreased survival and terminal body weights, and significant changes in kidney and liver weights for F2a and F2b generations. The maternal NOEL and LEL were 30 and [180] ppm, respectively, based on increased liver and kidney weight.

US EPA (1989) lists a "replacement" two-generation rat reproduction study that has the same dose levels, but different toxic endpoints than the two-generation rat reproduction study listed in the TRI document (US EPA, 1993a). The "replacement" study lists an offspring NOEL and LEL of 5 and 30 ppm, based on decreased body weight at day 21 post-partum. The 5 ppm NOEL was most recently restated by US EPA (1991a) and was considered as support of the tolerances for fenoxaprop ethyl.

With regards 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 CFR 12306, and notes the following:

1. **Adequacy of the experimental design:**
   Both studies are listed as Core Grade Minimum.

2. **Route of administration:**
   Study a) rat teratology study - oral gavage,
   Study b) 2-generation rat reproduction study - oral, in diet.
3. **The frequency and duration of exposure:**
   Study a) rat teratology study - not stated directly, but the study was designated "core grade minimum", indicating it was considered to satisfy guideline specifications which require treatment daily on gestation days 6-15,
   Study b) 2-generation rat reproduction study - not stated, but guideline requirements specify treatment continuously from before mating of parental generation; throughout mating, gestation and lactation; and continued into the 2d generation.
4. **The numbers of test animals:**
   Not stated directly for either study, but guidelines specify a minimum of 20 pregnant rats per dose group.
5. **The choice of species:**
   The rat is a standard test species.
6. **The choice of dosage levels:**
   Study a) rat teratology study - 0, 10, 32, 100 mg/kg/day,
   Study b) 2-generation rat reproduction study - 0, 5, 30, 180 ppm (equivalent to approximately 0, 0.25, 1.5, 9 mg/kg/day).
7. **Maternal toxicity:**
   Study a) rat teratology study - maternal and developmental toxicity occurred at the same doses (NOEL 32 mg/kg/day; LEL 100 mg/kg/day),
   Study b) 2-generation rat reproduction study - Fetotoxic effects were observed at concentrations (5 ppm) lower than those which produced maternal toxicity (NOEL 30 ppm; LEL 180 ppm).

Fluazifop butyl (CAS No. 69806-50-4)

***Developmental toxicity* has been manifested as reduced viability and morphological abnormalities.**

The US Environmental Protection Agency (US EPA, 1994a and 1994b) concluded that: ". . . there is sufficient evidence for listing fluazifop butyl on 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) describes the results of developmental toxicity studies in rats and rabbits, and a two-generation reproductive toxicity study in rats. In a developmental toxicity study conducted in rats, "delayed ossification and an increased incidence of hydroureter were observed in fetuses (fetotoxic LOEL 5 mg/kg/day and NOEL 1 mg/kg/day)". An increased incidence of diaphragmatic hernia was observed in the same study with a LOEL of 200 mg/kg/day and a NOEL of 10 mg/kg/day. "Fetotoxicity (delayed ossification and lens opacities) was also demonstrated

in New Zealand White Rabbits (LOEL 30 mg/kg/day; the NOEL was 10 mg/kg/day) (24 [US EPA, 1993d])." "In a 2-generation reproductive toxicity dietary study in Wistar rats, the reproductive LOEL of 250 ppm (12.5 mg/kg/day; the NOEL was 80 ppm or 4 mg/kg/day) was based on reduced litter sizes, reduced viability, reduced testis and epididymis weights and tubular atrophy in offspring (24 [US EPA, 1993d])." Details of the study protocols were obtained from US EPA's Tox-One-Liner database (US EPA, 1993d).

With regards 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 CFR 12306, and notes the following:

1. **Adequacy of the experimental design:**
   Study a) rat developmental toxicity study,
   Study b) rabbit developmental toxicity study,
   Study c) rat reproductive toxicity study: All 3 studies were rated Core Grade Minimum.
2. **Route of administration:**
   Study a) oral, gavage,
   Study b) not stated,
   Study c) oral, diet.
3. **The frequency and duration of exposure:**
   Study a) not stated, but the study was considered to meet guideline specifications which require daily treatment on gestation days 6-15,
   Study b) not stated, but the study was considered to meet guideline specifications which require daily treatment on gestation days 6-18,
   Study c) not stated, but the study was considered to meet guideline specifications which require continuous exposure from prior to mating of the parental generation, throughout mating, gestation, lactation, and maturation of subsequent generations.
4. **The numbers of test animals:**
   Study a) not stated, but the study was considered to meet guideline specifications which require a minimum of 20 pregnant rats per dose group,
   Study b) not stated, but the study was considered to meet guideline specifications which require a minimum of 12 pregnant rabbits per dose group,
   Study c) not stated, but the study was considered to meet guideline specifications which require a minimum of 20 pregnant rats per dose group.
5. **The choice of species:**
   Rats and rabbits are standard test species.
6. **The choice of dosage levels:**
   Study a) 0, 1, 5, 10, 200 mg/kg/day,
   Study b) 0, 10, 30, 90 mg/kg/day,

Study c) 0, 10, 80, 250 ppm.

7. **Maternal toxicity:**

Study a) reduced body weight gain was observed at a LOEL of 200 mg/kg/day, with a NOEL of 10 mg/kg/day,

Study b) the maternal NOEL was stated to be 30 mg/kg/day, with an LEL of 90 mg/kg/day. The endpoint on which this determination was based is stated to have been an increased rate of spontaneous abortions, which is usually considered to be an endpoint of developmental or reproductive toxicity - rather than of maternal toxicity,

Study c) not relevant.

Fluvalinate (CAS No. 69409-94-5)

***Developmental toxicity* has been manifested as delayed ossification and decreased weight and length of fetuses.**

The US Environmental Protection Agency (US EPA, 1994a and 1994b) concluded that: ". . . there is sufficient evidence for listing fluvalinate on 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, "Delayed ossification and decreased weight and length of fetuses were observed in offspring of rats orally administered 50 mg/kg/day (LOEL) on days 6-15 of gestation. The NOEL was 10 mg/kg/day. These effects were observed at doses that produced maternal toxicity. Curved tibia and fibula were observed in the offspring of rabbits orally administered 125 mg/kg/day (LOEL). The NOEL was 25 mg/kg/day. In a 2-generation reproduction study, a decrease in pup weight and growth were observed in offspring of rats orally administered 5 mg/kg/day (LOEL). The NOEL was 1 mg/kg/day. Significantly decreased weight and survival were observed in offspring of rats orally administered 25 mg/kg/day".

The TRI listing is based on descriptions of the primary studies provided by US EPA (1993d) Tox-One-Liners for fluvalinate. Additional details of the studies cited by US EPA in support of the TRI listing were obtained from the California Department of Food and Agriculture's Summary of Toxicology Data for Fluvalinate (CDFA, 1988) and IRIS (US EPA, 1996). IRIS apparently cited an incorrect dose level of 20 mg/kg/day for the developmental NOEL in the rabbit teratology study. The actual dose level appears to have been 25 mg/kg/day.

With regards 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 CFR 12306, and notes the following:

1. **Adequacy of the experimental design:**
   Study a) rat teratology study - Core Grade Minimum,
   Study b) rabbit teratology study - Core Grade Guideline,
   Study c) 2-generation rat reproduction study - Core Grade Guideline.
2. **Route of administration:**
   Study a) rat teratology study - oral gavage,
   Study b) rabbit teratology study - not stated, but likely oral gavage,
   Study c) 2-generation rat 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) rabbit teratology study - not stated,
   Study c) 2-generation rat reproduction study - continuous, in diet.
4. **The numbers of test animals:**
   Study a) rat teratology study - not stated, but US EPA (1983) test guidelines require a minimum of 20 pregnant rats per dose group,
   Study b) rabbit teratology study - not stated, but US EPA (1983) test guidelines require a minimum of 12 pregnant rabbits per dose group,
   Study c) 2-generation rat reproduction study - 150 rats per sex assigned to one control and five treatment groups. US EPA test guidelines (1983) require enough animals to ensure at least 20 pregnant females per dose group at, or near, term.
5. **The choice of species:**
   The rat and rabbit are standard test species.
6. **The choice of dosage levels:**
   Study a) rat teratology study - 0, 2, 10, 50 mg/kg/day,
   Study b) rabbit teratology study - 0, 5, 25, 125 mg/kg/day,
   Study c) 2-generation rat reproduction study - 0, 20, 100, 250, 500, 1000 ppm (equivalent to 0, 1, 5, 12.5, 25, 50 mg/kg/day) (250 and 1000 ppm groups part of pilot study only).
7. **Maternal toxicity:**
   Study a) rat teratology study - the maternal NOEL and LEL were 2 and 10 mg/kg/day, respectively, due to decreased body weight gain. Maternal toxicity was observed at a dose below that observed for fetotoxicity,
   Study b) rabbit teratology study - maternal NOEL and LEL were 25 and 125 mg/kg/day, respectively, due to anorexia and general depression. Maternal and fetal toxicity occurred at the same dose level,
   Study c) 2-generation rat reproduction study - maternal and paternal NOEL and LEL were 20 and 100 ppm, respectively, due to skin lesions (both generations), decreased body weight in females and maternal body weight decreased during gestation and lactation for F2a generation. Maternal and fetal toxicity occurred at the same dose level.

Hydramethylnon (CAS No. 67485-29-4)

***Developmental toxicity* has been manifested as decreased fetal body weights, increased post-implantation loss and vertebral abnormalities. *Male reproductive toxicity* has been manifested as testicular atrophy and infertility.**

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

For reproductive toxicity, supporting documentation for the TRI listing (US EPA, 1993a) states, "In a 90-day dog feeding study, testicular atrophy was observed at 6 mg/kg/day (LOEL). The NOEL was 3 mg/kg/day. In a 90-day rat study, dietary administration of 5 mg/kg/day (LOEL) produced testicular atrophy. The NOEL was 2.5 mg/kg/day. Dietary administration of 6.5 mg/kg/day for 18 months produced testicular lesions in mice. The NOEL was 2.75 mg/kg/day. In a 2-year rat study, dietary administration of 5 mg/kg/day produced decreased testicular weight and testicular atrophy. The NOEL was 2.5 mg/kg/day. In a 3-generation rat reproduction study, oral administration of 5 mg/kg/day produced male infertility. The NOEL was 2.5 mg/kg/day." For developmental toxicity, supporting documentation for the TRI listing (US EPA, 1993a) states, "Decreased fetal weight was observed in the offspring of rats administered 30 mg/kg/day (LOEL). The NOEL was 10 mg/kg/day. Increased post-implantation loss and decreased fetal viability were observed in the offspring of rabbits administered 15 mg/kg/day (LOEL). The NOEL was 5 mg/kg/day. Vertebral anomalies were seen in the offspring of rabbits administered 10 mg/kg/day (LOEL). The NOEL was 5 mg/kg/day."

The TRI listing is based on evaluations of 7 studies summarized in IRIS (US EPA, 1993c) and in the US EPA Tox-One-Liner for hydramethylnon (US EPA, 1993d). In lieu of being able to obtain the US EPA one-liner for the chemical, IRIS (US EPA, 1992c) and the California Department of Pesticide Regulation's Summary of Toxicology Data on Hydramethylnon (CDPR, 1993) were referred to for their largely complete summaries of all studies supporting the TRI listing.

With regards 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 CFR 12306, and notes the following:

1. **Adequacy of the experimental design:**
   All 7 studies were rated Core Grade Minimum
2. **Route of administration:**
   Study a) 90-day dog feeding study - oral, in gelatin capsules,
   Study b) 90-day rat feeding study - oral,
   Study c) 18-month mouse feeding study - oral, in diet,

Study d) 2-year rat feeding study - oral, in diet,
Study e) 3-generation rat reproduction study - oral, in diet,
Study f) rat teratology study - oral gavage,
Study g) rabbit teratology study - oral gavage.

3. **The frequency and duration of exposure:**
   Study a) 90-day dog feeding study - dosed once per day,
   Study b) 90-day rat feeding study - unspecified, probably continuous in diet for 90 days,
   Study c) 18-month mouse feeding study - continuous, in diet,
   Study d) 2-year rat feeding study - continuous, in diet,
   Study e) 3-generation rat reproduction study - continuous, in diet. The two highest dose groups were discontinued after F0 generation parents had been evaluated in a recovery experiment,
   Study f) rat teratology study - each of gestation days 6-15,
   Study g) rabbit teratology study - each of gestation days 6-18.
4. **The numbers of test animals:**
   Study a) 90-day dog feeding study - unspecified,
   Study b) 90-day rat feeding study - unspecified,
   Study c) 18-month mouse feeding study - unspecified,
   Study d) 2-year rat feeding study - 50 per sex per dose,
   Study e) 3-generation rat reproduction study - 12 males and 24 females per treatment group,
   Study f) rat teratology study - 26 per group,
   Study g) rabbit teratology study - 16 per group.
5. **The choice of species:**
   Rats, rabbits, mice and dogs are standard test species.
6. **The choice of dosage levels:**
   Study a) 90-day dog feeding study - 0, 3, 6, 12 mg/kg/day,
   Study b) 90-day rat feeding study - total dose levels unspecified, at least 0, 50, 100 ppm (equivalent to 0, 2.5, 5 mg/kg/day),
   Study c) 18-month mouse feeding study - 0, 25, 50, 100, 200 ppm (equivalent to 0, 2.75, 3.75 mg/kg/day, for control group and two lowest treatment groups, respectively. Equivalent mg/kg/day at two highest doses is not known),
   Study d) 2-year rat feeding study - 0, 25, 50, 100, 200 ppm (equivalent to 0, 1.25, 2.5, 5, 10 mg/kg/day),
   Study e) 3-generation rat reproduction study - 0, 25, 50, 100, 200 ppm (equivalent to 0, 1.25, 2.5, 5, 10 mg/kg/day),
   Study f) rat teratology study - 0, 3, 10, 30 mg/kg/day,
   Study g) rabbit teratology study - 0, 5, 10, 20 mg/kg/day.
7. **Maternal toxicity:**
   Study a) not relevant,
   Study b) not relevant,
   Study c) not relevant,
   Study d) not relevant,

Study e) 3-generation rat reproduction study - Maternal and reproductive toxicity occurred at the same doses. The maternal NOEL and LEL were 50 and 100 ppm, respectively, based on decreased food consumption and body weight gain,

Study f) rat teratology study - maternal toxicity occurred at a dose below that which caused developmental toxicity. The maternal NOEL and LEL were 3 and 10 mg/kg/day, respectively, based on decreased mean body weight gain and discoloration of body fat,

Study g) rabbit teratology study - maternal toxicity occurred at a dose below that which caused developmental toxicity. The maternal LEL (lowest dose tested) was 5 mg/kg/day, respectively, based on decreased body weight gain. It should be noted that gestational weight gain in rabbits is known to be highly variable, and is therefore not generally considered an accurate indication of maternal toxicity (US EPA, 1991b).

Molinate (CAS No. 2212-67-1)

***Developmental toxicity* has been manifested as reduced viability, reduced body weights, and an increased frequency of morphological variations. *Male reproductive toxicity* has been manifested as reduced fertility, testicular degeneration, and sperm abnormalities. *Female reproductive toxicity* has been manifested as reduced fertility and fecundity, and abnormal histopathology of ovarian tissues.**

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

Supporting documentation for the TRI listing (US EPA, 1993a) discusses data on developmental toxicity, and male and female reproductive toxicity:

> "In a rat developmental toxicity study, adverse effects observed at 35 mg/kg/day (LOEL) included increased post-implantation loss, lower fetal body weight, increased incidence of runts, and external/soft tissue/skeletal variants . . . In a rabbit developmental study, adverse effects such as an increase in the number of abortions, and a decrease in the number of does with live fetuses were noted at 200 mg/kg/day."
>
> "In a rat fertility test, reductions in fertility, dose-related altered sperm morphology, and a reduction in the number of viable fetuses were observed . . . In

a 90-day study in male rats, the lowest toxic oral dose of 324 mg/kg[1] produced adverse effects on spermatogenesis, male fertility, and viability index (9 [RTECS, 1993]). The 20-day inhalation male rat TCLo is 0.0006 mg/L. At this exposure level adverse effects on spermatogenesis and male fertility index were reported (9 [RTECS, 1993]) . . . In a 3-month rat inhalation study, testicular degeneration and abnormal spermatozoa were observed at 0.002 mg/L (LOEL). No NOEL was determined (71 [RTECS, 1993])."

"In a 2-generation rat reproduction study, the reproductive NOEL was 0.3 mg/kg/day and the LOEL was 2.5 mg/kg/day based on reduced fecundity, and increased incidence of ovarian vacuolation/hypertrophy (71 [US EPA, 1992a])."

In the final rule document (US EPA, 1994b), the Agency responded to comments from Zeneca Inc. which argued against including molinate as a reportable compound under TRI. The specifics of these comments and the Agency's response were:

"Zeneca Incorporated contends that the observations attributed to the 35 mg/kg/day dose level in the rat developmental toxicity study 'in fact occurred at 140 mg/kg/day, the highest dose tested and were thus a consequence of maternal toxicity.' The commentor states that the NOEL for that study was 35 mg/kg/day. The Agency does not agree that the NOEL for this study was 35 mg/kg/day. The NOEL for developmental toxicity was 2.2 mg/kg/day based on an increase in runting at the next highest doses, 35 and 140 mg/kg/day . . . The NOEL for maternal toxicity was 35 mg/kg/day and that the effects on the pups (runting) occurred at a dose level lower than the dose level found to be maternally toxic."

The same commentor stated that the evidence for the reproductive toxicity of molinate rests solely on studies in rodents, and that studies in other species "have shown 'conclusively that the effects seen in rodents is [sic] not relevant to man.'" The Agency countered that "data on the rabbit and dog do not support the commentor's contention that the effects seen in rodents are specific only to rodents. For example, in each of the fertility studies in rabbits, both an increase in pre-implantation loss and abnormal sperm were observed. These two consistent [reproducible] observations are suggestive of fertility effects, are two of the same observations found in rats and although not as dramatic as observed in rats, cannot be negated. In the chronic dog study, lesions in male reproduction organs and effects on sperm were observed, which demonstrated that, at least in the males, the gonads are target organs for molinate . . . Since molinate is reaching the gonads in all species, not only in rodents as the commentor claims, molinate can reasonably be anticipated to cause fertility/reproductive effects in humans. Further, animals are accepted as surrogates for toxicity testing to predict potential

[1] This appears to be a verbatim citation of RTECS. RTECS expresses oral doses as summed over the entire treatment period. Hence 324 mg/kg was the total given over a period of 90 days, and the daily dose would actually have been 3.6 mg/kg.

hazard to humans, except in a few rare cases where effects have been determined to be species-specific [e.g., $\alpha 2\mu$-globulin]."

With regards 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 CFR 12306, and notes the following:

1. **Adequacy of the experimental design:**
   Study a) rat developmental toxicity study was classified as acceptable by the California Department of Pesticide Regulation (CDPR, 1997),
   Study b) rabbit developmental toxicity study was classified as acceptable by CDPR (1997),
   Study c) rat fertility study - study was rated as core grade supplementary. This study was used as the principal study in calculating the oral RfD for molinate. For this purpose, the study was considered to be of fair quality and was given a medium confidence rating,
   Study d) 90-day rat study - not a standard reproductive toxicity protocol. Original study report in Russian language,
   Study e) 20-day inhalation rat study - not a standard reproductive toxicity protocol,
   Study f) 2-generation rat reproduction study - females only treated. This study was considered to be acceptable as a supplemental study by CDPR (1997),
   Study g) 3-month rat inhalation study.
2. **Route of administration:**
   Study a) gavage,
   Study b) gavage,
   Study c) gavage,
   Study d) oral,
   Study e) inhalation,
   Study f) oral - feed,
   Study g) inhalation.
3. **The frequency and duration of exposure:**
   Study a) daily on gestation days 6-15,
   Study b) not stated, but guidelines specify treatment on each of gestation days 6 - 18,
   Study c) 0, 12, or 30 mg/kg/day for 30 days or; 0, 0.2, 4, 12, or 30 mg/kg/day for 5 or 10 weeks,
   Study d) 0, 3.6, or 18 mg/kg/day for 90 days,
   Study e) 0, 0.1, 0.6, 1.8, 4.0 mg/m3, 6 hrs/day, 5 days/week for 13 weeks or; 0, 0.07, 0.16, 0.30, or 1.6 mg/m3, 6 hrs/day, 5 days/week for 4 weeks,
   Study f) prior to mating and continuously throughout gestation, lactation, and weaning of their offspring for 2 generations,
   Study g) duration of 3 months.

4. **The numbers of test animals:**
   Study a) 26 pregnant females per dose group,
   Study b) not specifically stated, but study was generally considered to be of acceptable quality,
   Study c) not stated,
   Study d) not known,
   Study e) not stated,
   Study f) 25 females per dose group,
   Study g) not stated.
5. **The choice of species:**
   The rat and rabbit are standard species in toxicity testing.
6. **The choice of dosage levels:**
   Study a) 0, 2.2, 35, 140 mg/kg/day,
   Study b) 0, 2, 20, 200 mg/kg/day,
   Study c) 0, 0.2, 4, 12, 30, and 60 mg/kg/day,
   Study d) 0, 6, 50, and 450 ppm in the feed,
   Study e) 0, 0.1, 0.6, 1.8, 4.0 mg/m^3, 6 hrs/day, 5 days/week for 13 weeks or; 0, 0.07, 0.16, 0.30, or 1.6 mg/m^3, 6 hrs/day, 5 days/week for 4 weeks,
   Study f) 0, 6, 50, 450 ppm,
   Study g) 0, 2, 10, 50 mg/m^3.
7. **Maternal toxicity:**
   Study a) The NOEL for maternal toxicity was 35 mg/kg/day, the NOEL for developmental toxicity was 2.2 mg/kg/day,
   Study b) Maternal NOEL = 20 mg/kg/day, developmental NOEL = 20 mg/kg/day,
   Study c) not relevant,
   Study d) not relevant,
   Study e) not relevant,
   Study f) adult female systemic toxicity NOEL = 6 ppm (0.3 mg/kg); reproductive toxicity NOEL = 6 ppm (0.3 mg/kg/day),
   Study g) not relevant.

Myclobutanil (CAS No. 88671-89-0)

***Male reproductive toxicity* has been manifested as testicular atrophy and abnormal histopathology of the seminiferous tubules. *Developmental toxicity* has been manifested as reduced viability.**

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

Supporting documentation for the TRI listing (US EPA, 1993a) states that, "Testicular atrophy (the LOEL was 9.84 mg/kg/day, the NOEL was 2.49 mg/kg/day) was observed in a 2-year chronic feeding study in rats (11 [US EPA 1993c]). The seminiferous tubules were frequently devoid of spermatid formation and germinal epithelial cells. . . Testicular atrophy (the LEL was 46.4 mg/kg/day, the NOEL was 9.28 mg/kg/day) was also noted in a 2-generation reproduction study (Core Guideline) (11 [US EPA 1993c])." The TRI supporting documentation also discusses developmental toxicity studies in rats and rabbits: "In a developmental toxicity study in rats, increased resorption and decreased viability were observed at 93.8 mg/kg/day (LOEL). The NOEL was 31.3 mg/kg/day (24 [US EPA, 1993d]). In a developmental toxicity study in rabbits, an increased number of resorptions per litter, reduced viability index, and reduced litter size were observed at 200 mg/kg/day (LOEL). The NOEL was 60 mg/kg/day."

With regards 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 CFR 12306, and notes the following:

1. **Adequacy of the experimental design:**
   Study a) 2-year chronic feeding study in rats - used as critical study for oral RfD, study is stated to be of good quality and was given a high confidence rating,
   Study b) 2-generation reproductive toxicity study in rats - rated as core-grade guideline,
   Study c) developmental toxicity study in rats - rated as core-grade minimum,
   Study d) developmental toxicity study in rabbits - study rated as core-grade minimum.
2. **Route of administration:**
   Oral for all 4 studies.
3. **The frequency and duration of exposure:**
   Study a) daily for 24 months,
   Study b) not stated, but guidelines specify daily prior to mating and throughout mating, gestation, and lactation for the parental generation; and continuously for subsequent generations until the end of the study,
   Study c) treatment on each of gestation days 6 - 15,
   Study d) not stated, but guidelines specify treatment on each of gestation days 6 - 18.
4. **The numbers of test animals:**
   Study a) 27-28 animals of each sex per dose group,
   Study b) not stated, but guidelines specify a minimum of 20 males per dose group, and sufficient females to ensure a minimum of 20 pregnant at or near term,
   Study c) not stated, but guidelines specify a minimum of 20 animals per dose group,
   Study d) not stated, but guidelines specify a minimum of 12 animals per dose group.

5. **The choice of species:**
   Rats and rabbits are standard test species for toxicity studies.
6. **The choice of dosage levels:**
   Study a) The overall mean daily consumption for males was 0, 2.49, 9.84, or 39.21 mg/kg bw/day,
   Study b) 0, 2.32, 9.28, 46.4 mg/kg bw/day,
   Study c) 0, 31.26, 93.77, 312.58, and 468.9 mg/kg/day,
   Study d) 0, 20, 60, and 200 mg/kg/day.
7. **Maternal toxicity:**
   Study a & b) not relevant,
   Study c) maternal: NOEL 312.6 mg/kg/day, LEL 468.9 mg/kg/day; developmental: NOEL 31.3 mg/kg/day, LEL 93.8 mg/kg/day,
   Study d) maternal: NOEL 20 mg/kg/day, LEL 60 mg/kg/day; developmental: NOEL 60 mg/kg/day, LEL 200 mg/kg/day,

Oxydemeton methyl (CAS No. 301-12-2)

Female and male reproductive toxicity **have been manifested as decreased litter size and fetal viability; decreased ovarian weights; and decreased testicular weights and increased epididymal vacuolation.**

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

Supporting documentation for the TRI listing (US EPA, 1993a) states that, "The peer review Committee (PRC) for developmental and reproductive toxicity for oxydemeton methyl concluded that oxydemeton methyl causes reproductive effects in rats (72 [US EPA, 1992b]). . . . These effects include decreased litter size and viability, decreased weight of the testes and ovaries, and increased epididymal vacuolation."

The memorandum cited by the supporting documentation for the TRI listing (US EPA, 1992b) states:

> "The Committee concluded that oxydemeton-methyl causes reproductive effects in rats. The lowest NOEL for reproductive toxicity in the rat multigeneration reproduction studies is 0.38 mg/kg/day based upon effects on epididymal vacuolation, decreased testicular and ovarian weight and fertility. A NOEL of 0.9 mg/kg/day was found for reproductive toxicity in a short-term (5-day) study in the rat. It is recommended that this study be used for the assessment of occupational risk because worker exposure is of similar short duration. Although developmental toxicity was not demonstrated in an acceptable study in the rat, retesting is recommended in the rabbit."

An additional US EPA document (US EPA, 1987), entitled "Guidance for the Reregistration of Pesticide Products Containing Oxydemeton-Methyl as the Active Ingredient" also discusses the reproductive toxicity of this pesticide. This document was not cited by the TRI listing notice, but shares its conclusions:

> "The Agency reviewed data from two studies that raised substantial concerns regarding potential reproductive effects resulting from exposure to oxydemeton-methyl. The data, submitted by Mobay Chemical Corporation, include a two-generation rat reproduction study and interim progress reports of an on-going male rat reproduction system toxicity study. Oxydemeton-methyl has the potential to adversely affect reproduction, as shown by rats with histopathologic changes in the epididymis, alterations in sperm morphology and motility, and decreases in the fertility index, testicular weight, litter size, pup weight, and pup survivability."

With regards 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 CFR 12306, and notes the following:

1. **Adequacy of the experimental design:**
   Two multigeneration reproductive toxicity studies performed in rats were evaluated. US EPA's Peer Review Committee (US EPA, 1992b) concluded that, "Taken together, the two reproduction studies satisfy the requirement for a multigeneration reproduction study." The Peer Review Committee also concluded that an additional study, a "dominant lethal plus" study, "which measures male reproductive function after an exposure period of 5 days, is the most appropriate study for the assessment of worker risk."
2. **Route of administration:**
   Oral - oxydemeton methyl was administered in the feed in all three of the relevant studies.
3. **The frequency and duration of exposure:**
   In the two multigeneration reproductive toxicity studies, oxydemeton methyl was administered in the feed from the time the parental animals were 6-7 weeks old, throughout mating, gestation, lactation, and maturation of the of the F1 generation. Treatment was continued throughout mating, gestation, and lactation, as the F2 generation was produced.
4. **The numbers of test animals:**
   Study a) 20 females and 10 males per dose group,
   Study b) 35 animals per sex per dose group,
   Study c) 20 male breeder rats per dose group, and 105 satellite male rats per dose group (sacrificed at different time points for auxiliary studies).
5. **The choice of species:**
   Rats are a standard test species for toxicity studies.
6. **The choice of dosage levels:**

Study a) 0, 0.05, 0.5, 2.5 mg/kg/day,
Study b) 0, 0.043, 0.13, 0.38, 2.1 mg/kg/day,
Study c) 0, 0.15, 0.90, 5.0 mg/kg/day.

7. **Maternal toxicity:**
   Not relevant.

Propachlor (CAS No. 1918-16-7)

***Developmental toxicity* was manifested as decreased fetal viability.**

The US Environmental Protection Agency (US EPA, 1994a and 1994b) concluded that: ". . . there is sufficient evidence for listing Propachlor 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, 1993a) states that, "No evidence of maternal toxicity was seen in rabbits administered propachlor by gavage at 0, 5, 15, or 50 mg/kg/day on days 7- 19 of gestation (11 [US EPA, 1993c]). Statistically significant increases in mean implantation loss with corresponding decreases in the mean number of viable fetuses were reported at 15 and 50 mg/kg/day when compared to controls." An additional oral study, performed in rats, found no evidence of maternal or developmental toxicity. The TRI supporting documentation also cites a 10-day health advisory for propachlor, which is based upon the rabbit developmental toxicity data (US EPA, 1988b).

With regards 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 CFR 12306, and notes the following:

1. **Adequacy of the experimental design:**
   Study a) Rabbit: details of study design appear to meet FIFRA test guideline requirements,
   Study b) Rat: stated to meet US EPA core-grade minimum requirements.
2. **Route of administration:**
   Oral for both studies.
3. **The frequency and duration of exposure:**
   Study a) Rabbit: daily on gestation days 7-19,
   Study b) Rats: not stated, but as the study was stated to meet FIFRA requirements, exposure would have been daily on each of gestation days 6-15 in rats.
4. **The numbers of test animals:**
   Study a) Rabbit: 16 animals per dose group,
   Study b) Rat: not stated, but as the study was stated to meet FIFRA requirements, would have been a minimum of 20 animals per dose groups.
5. **The choice of species:**
   Rabbits and rats are standard test species for toxicity studies.

6. **The choice of dosage levels:**
   Study a) Rabbit: 0, 5, 15, 50 mg/kg/day,
   Study b) Rat: 0, 20, 60, or 200 mg/kg/day.
7. **Maternal toxicity:**
   Study a) Rabbit: It is specifically stated that developmental toxicity was observed at doses lower than those causing maternal toxicity,
   Study b) It is specifically stated that no maternal or developmental toxicity was observed.

Resmethrin (CAS No. 10453-86-8)

***Developmental toxicity* was manifested as reduced viability of offspring, and reduced body weights among survivors.**

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

Supporting documentation for the TRI listing (US EPA, 1993a) discusses the results of two reproductive toxicity studies on resmethrin, both of which reported reduced viability of offspring and reduced pup weights among survivors. A one-generation reproductive toxicity study conducted in rats found an increased number of stillborn pups with exposure to 25 mg/kg bw/day in the diet (US EPA, 1993c). Increased stillbirths and reduced pup weights among survivors was observed at a higher dose of 125 mg/kg bw/day. No NOAEL was identified in this study. In a three-generation reproductive toxicity study also conducted in rats, dietary administration giving a daily dose of 25 mg/kg bw produced an increase in the number of pups born dead, and a decrease in the body weight of surviving pups (US EPA, 1993c). No NOAEL was identified for this study. It should be noted that the effects cited by US EPA in support of their action were evidence of developmental toxicity, but were reported from multigeneration studies of reproductive toxicity. For that reason, US EPA cites reproductive toxicity as the basis for addition to the TRI list, while developmental toxicity is the appropriate basis for addition to the Proposition 65 list.

With regards 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 CFR 12306, and notes the following:

1. **Adequacy of the experimental design:**
   Study a) The one-generation study is stated to be core grade supplementary (US EPA, 1993c), as US EPA test guidelines (1983) require a minimum of two generations for a reproductive toxicity study,

Study b) The three-generation study is stated to be core grade guideline, and was used to set the oral RfD for resmethrin (US EPA, 1993c).

2. **Route of administration:**
   Oral, dietary, for both studies.
3. **The frequency and duration of exposure:**
   Daily, from prior to mating of parental generation, through subsequent generations until sacrifice for evaluation.
4. **The numbers of test animals:**
   Study a) Not stated,
   Study b) Stated to be 20 males and 20 females for each dose group.
5. **The choice of species:**
   Rats are standard test species for toxicity studies.
6. **The choice of dosage levels:**
   Study a) 0, 25, 125 mg/kg/day. It is not clearly stated whether other doses were tested, but 25 mg/kg/day was a LOAEL, and no NOAEL was identified (so presumably no lower doses were tested),
   Study b) Stated to have been 0, 25, 40, and 62.5 mg/kg/day.
7. **Maternal toxicity:**
   Study a) Not discussed,.
   Study b) Not specifically discussed, but reproductive toxicity (as demonstrated by increased stillbirths and reduced pup weights) was considered to be the critical effect in determining the RfD. No other endpoints of toxicity were mentioned.

Sodium fluoroacetate (CAS No. 62-74-8)

***Male reproductive toxicity* was evidenced by decreased testes weight and altered spermatogenesis.**

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

Supporting documentation for the TRI listing (US EPA, 1993b) states that, "In a 13-week oral study in rats, gavage administration of 0.02 mg/kg/day resulted in decreased testis weight and altered spermatogenesis in males (IRIS, 1993 [US EPA, 1993c]); the NOEL = 0.05 mg/kg/day." IRIS (US EPA, 1993c) used this study as the principal study in determining the oral RfD for sodium fluoroacetate; decreased testes weights and altered spermatogenesis were the critical effects in males.

The study described above, as well as an additional oral study in male rats, are discussed in a Pesticide Reregistration Eligibility Document (US EPA, 1995). Similar adverse effects on male reproductive endpoints were demonstrated in both studies.

With regards 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 CFR 12306, and notes the following:

1. **Adequacy of the experimental design:**
   The study design was a 13-week subchronic toxicity protocol. The study was used by US EPA in considering sodium fluoroacetate for reregistration (US EPA, 1995), as well as serving as the critical study in establishing the RfD for this pesticide (US EPA, 1993c and 1995). Thus, it seems reasonable to assume that the experimental design was considered adequate by FIFRA standards.
2. **Route of administration:**
   Oral, gavage.
3. **The frequency and duration of exposure:**
   Daily for 13 weeks.
4. **The numbers of test animals:**
   20 animals per dose group.
5. **The choice of species:**
   Rats are a standard test species for toxicity studies.
6. **The choice of dosage levels:**
   0, 0.05, 0.20, and 0.50 mg/kg/day.
7. **Maternal toxicity:**
   Not relevant to consideration of male reproductive toxicity.

<u>Sodium nitrite (CAS No. 7632-00-0)</u>

***Developmental toxicity* has been manifested as reduced viability and adverse effects on growth, including biochemical and/or metabolic changes.**

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

The US Environmental Protection Agency (US EPA, 1994a) stated that,

> "Fetotoxicity (fetal death) was reported following oral exposures of pregnant rats to sodium nitrite (30 mg/kg/day) during gestation days 1 through 22. In mice, exposed orally to 80 mg/kg/day during gestation days 6 to 15 there was increased preimplantation loss and fetal death, and in mice exposed to a lower dose (20 mg/kg/day) during gestation days 1 to 14, abnormalities of the blood or lymphatic system were reported in offspring. In offspring of rats orally exposed to 26 to 256 mg/kg/day during pregnancy (gestation days 1 through 22) and/or lactation (20 to

21 days after birth), effects on growth including biochemical and/or metabolic changes were noted".

Information such as species and number of animals used; doses, route, and days of treatment; and details of toxicological findings was provided, or obtained from the original studies cited (Globus and Samuel, 1978; Roth *et al.,* 1987; Shuval and Gruener, 1972) .

It was also noted in the US EPA proposed rule document (US EPA, 1994a) that sodium nitrite causes methemoglobinemia. Newborn infants are known to be particularly susceptible to this effect, in part because of the continued presence of fetal hemoglobins in their erythrocytes. The rate of nitrate-induced oxidation of fetal hemoglobin to methemoglobin is approximately twice that found for adult hemoglobin. As fetuses are dependent on fetal hemoglobins to carry oxygen to their tissues, it is expected that fetuses would also be particularly sensitive to any sodium nitrate reaching their bloodstream.

With regards 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 CFR 12306, and notes the following:

1. **Adequacy of the experimental design:**
   All of the studies, with the exception of study d, a Japanese developmental study in mice exposed to sodium nitrite on gestational days 6-15, were reviewed in the original publications. All of the studies reviewed appeared to be adequately designed and conducted.
2. **Route of Administration**
   Oral in all studies.
3. **The frequency and duration of exposure:**
   Study a) Rat - gestation days 1-22,
   Study b) Rat - gestation days 1-22 and lactation days 1-20,
   Study c) Mouse - gestation days 1-14,
   Study d) Mouse - gestation days 6-15,
4. **The numbers of test animals:**
   Study a) 7-12 animals/group,
   Study b) 5-8 animals/group,
   Study c) 4, 9, 12 or 23 animals/group,
   Study d) not known.
5. **The choice of species:**
   The rat and mouse are standard test species.
6. **The choice of dosage levels:**
   Study a) 30 mg/kg/d,
   Study b) 26-256 mg/kg/d,
   Study c) 20 mg/kg/d,
   Study d) 80 mg/kg/d.
7. **Maternal toxicity:**

Minimal maternal toxicity (reduced fluid intake in late gestation) was reported in study b. No parameters related to possible maternal toxicity were reported in the other studies reviewed.

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