CHEMICALS MEETING THE CRITERIA FOR LISTING VIA THE AUTHORITATIVE BODIES MECHANISM

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

The 7 chemicals listed in the table below meet the criteria for listing under Proposition 65 via the authoritative bodies listing mechanism. A notice announcing the Office of Environmental Health Hazard Assessment's intent to list these chemicals as known to cause reproductive toxicity was published in the *California Regulatory Notice Register* on September 4, 1998. These 7 chemicals represent a subset of the 15 chemicals under consideration for listing that were announced in a public notice published in the *California Regulatory Notice Register* (*Register* 98, No. 15-Z) on April 10, 1998. A document providing the supporting information for listing the 15 chemicals was also released on April 10, 1998 in a document entitled, "Chemicals Under Consideration for Possible Listing Via the Authoritative Bodies Mechanism -- 15 Chemicals Identified by US EPA". Both the notice and supporting document were posted on the Office of Environmental Health Hazard Assessment Home Page at www.calepa.cahwnet.gov/oehha/.

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 the 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 toxicity's 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 the document specifically and accurately identifies the chemical" and has been "published

by the authoritative body in a publication, such as, but not limited to the federal register…"

OEHHA also finds that the criteria for "as causing reproductive toxicity" given in regulation (22 CCR 12306[g]) have been satisfied for the chemicals in the table below. In making this evaluation, OEHHA relied upon the documents and reports cited by 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. A major source of information used by the US EPA was the "Tox Oneliner" 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 of the database entries include a notation of "core grade" – a system intended to reflect the extent to which a study met applicable US EPA toxicity testing guidelines.

Chemical	CAS No.	Toxicological Endpoints	Reference
Chinomethionat (Oxythioquinox)	2439-01-2	Developmental toxicity	US EPA (1994a, b)
Cyclohexanol	108-93-0	Male reproductive toxicity	US EPA (1994a, b)
Fluazifop butyl	69806-50-4	Developmental toxicity	US EPA (1994a, b)
Fluvalinate	69409-94-5	Developmental toxicity	US EPA (1994a, b)
Oxydemeton methyl	301-12-2	Female reproductive toxicity, male reproductive toxicity	US EPA (1987; 1994a, b)
Resmethrin	10453-86-8	Developmental toxicity	US EPA (1994a, b)
Sodium fluoroacetate	62-74-8	Male reproductive toxicity	US EPA (1994a, b; 1995)

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.

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 CCR 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).

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.

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 CCR 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 CCR 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 (1983b) test guidelines require a minimum of 20 pregnant rats per dose group,
   Study b) rabbit teratology study - not stated, but US EPA (1983b) 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 (1983a) 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.

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, 1992]). . . . 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, 1992) 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 CCR 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, 1992) 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 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.

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 CCR 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 (1983a) 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 CCR 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 can be assumed 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.

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