CHEMICALS UNDER CONSIDERATION FOR POSSIBLE LISTING VIA THE AUTHORITATIVE BODIES MECHANISM 11 CHEMICALS IDENTIFIED BY US EPA

PACKAGE 11A.1
January 29, 1999

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

The 11 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 (DART). This was done by that Agency in implementing its Toxics Release Inventory (TRI) program (*i.e.*, Section 313 of the Emergency Planning and Community Right-to-Know Act of 1986 [EPCRA]). On the basis of identifying chemicals that caused reproductive, developmental and/or other toxicities the US EPA added a number of chemicals to the TRI list. The US EPA published its toxicity findings in the *Federal Register* (**59:**1788-1859, 1994 and **59:**61432-61485, 1994). In proposing specific chemicals for addition to the TRI list, the Agency stated that a hazard assessment was performed for each candidate, "…in accordance with relevant EPA guidelines for each adverse human health or environmental effect…" (*Federal Register* **59:**1790).

OEHHA has found that the chemicals in the table below have been "formally identified" as causing reproductive toxicity according to the regulations covering this issue (22 CCR 12306[d]) because the chemicals have "been identified as causing … reproductive toxicity by the authoritative body" (*i.e.*, US EPA) "in a document that indicates that such identification is a final action" (*e.g.*, the TRI *Final Rule* [*Federal Register* **59:**61432]) and have "been included on a list of chemicals causing … reproductive toxicity issued by the authoritative body" "and the document specifically and accurately identifies the chemical" and has been "published by the authoritative body in a publication, such as, but not limited to the federal register…"

OEHHA also finds that the criteria for "as causing reproductive toxicity" given in regulation (22 CCR 12306[g]) appear to have been satisfied for the chemicals in the table

below. In making this evaluation, OEHHA relied upon the documents and reports cited by US EPA in making their finding that the specified chemicals cause reproductive toxicity. In some cases, OEHHA consulted additional sources of information on the specific studies cited by US EPA. This was done only where necessary to affirm or clarify details of results and study design for studies cited by US EPA; OEHHA did not review additional studies not relied on by US EPA.

A major source of information used by the US EPA was the "Tox-Oneliner" database maintained by US EPA's Office of Pesticide Programs (OPP). This database consists of brief summaries of (usually unpublished) data submitted to the Agency in compliance with regulatory requirements. Many database entries include a notation of "core grade" – a system formerly used by US EPA to indicate the extent to which a study conformed to published test guidelines (US EPA 1983a and 1983b). Under this scheme, a "core grade guideline" study was considered to meet all guideline requirements; a "core grade minimum" study was considered sufficient for risk assessment; and a "core grade supplementary study" was considered to provide useful supplementary information, but not to be suitable for risk assessment on its own.

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 the study descriptions below, they are quoted directly from the cited references.

Chemical	CAS No.	Endpoints	Pesticide status or usage
Amitraz	33089-61-1	developmental toxicity	Registered in CA
Disodium cyano-dithiomidocarbo-nate	138-93-2	developmental toxicity	Registered in CA
Fenbutatin oxide	13356-08-6	developmental toxicity	Registered in CA
Metiram	9006-42-2	developmental toxicity	Registered in CA
Metribuzin	21087-64-9	developmental toxicity	Registered in CA
Nabam	142-59-6	developmental toxicity	Registered in CA
Nitrapyrin	1929-82-4	developmental toxicity	Registered in CA
Potassium dimethyl-dithiocarbamate	128-03-0	developmental toxicity	Registered in CA

Chemical	CAS No.	Endpoints	Pesticide status or usage
Sodium dimethyl-dithiocarbamate	128-04-1	developmental toxicity	Registered in CA
Triadimefon	43121-43-3	developmental toxicity male reproductive toxicity Female reproductive toxicity	Registered in CA
Triphenyltin hydroxide	76-87-9	Developmental toxicity	Not currently registered in CA

Studies cited by US EPA in making findings with regard to reproductive toxicity are briefly described below. The statements in bold reflect data and conclusions which appear to satisfy the criteria for sufficiency of evidence for reproductive toxicity in regulation (22 CCR 12306[g]). Where a notation of "not stated" has been made, OEHHA staff were unable to find an explicit statement of a particular detail such as the number of animals in each dose group.

Amitraz (CAS No. 33089-61-1)

***Developmental toxicity* has been manifested as decreased fetal viability and an increased frequency of morphological abnormalities.**

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

Supporting documentation for the TRI listing (US EPA, 1993a) states, "A three-generation reproduction study in rats demonstrated increased mortality during suckling and decreased litter size. The fetotoxic LOAEL in this study was 5 mg/kg/day and the NOAEL was 1.6 mg/kg/day. In a teratology study in rabbits, a fetotoxicity LOAEL of 5 mg/kg/day, and NOAEL of 1 mg/kg/day was based on the incidence of cleft palate and meningocoele associated with small ears and displaced toe. Data from OPP's Tox-Oneliner database support these findings."

In the TRI final rule document (US EPA, 1994b) the agency responded to extensive comments on these studies by the regulated community. Both studies were reanalyzed, and the agency's original conclusions (US EPA, 1994a) reaffirmed. With regard to the multigeneration reproductive toxicity study, US EPA (1994b) concluded, "EPA's reanalysis of this data indicates that there was a decrease in litter size and pup survival at 5 mg/kg/day in all 3 generations and a slight reduction in pup weight in the F_1 and F_2 generations. Thus there was direct evidence of fetotoxicity." With regard to the rabbit

teratology study, the agency concluded (US EPA, 1994b), "Upon reanalysis of the rabbit teratology study, EPA determined that although this study does not fully satisfy the guidelines for study conduct under FIFRA [*Federal Insecticide, Fungicide, Rodenticide Act*], it is sufficient for the purposes of hazard assessment, with a NOEL and LOEL for maternal and developmental toxicity of 5 and 25 mg/kg/day, respectively."

With regard to the studies cited as supporting US EPA's action in adding a chemical to the EPCRA-TRI list, OEHHA finds that the evidence for DART effects appears to meet the criteria of 22 CCR 12306, and notes the following:

1. **Adequacy of the experimental design:**
   Study a) rat 3-generation reproductive toxicity study. Study rated as core grade minimum (US EPA, 1997b).
   Study b) rabbit teratology study. No core grade reported (US EPA, 1997b). According to the Final Rule document for additions to the TRI list (US EPA, 1994b), "…EPA determined that although this study does not fully satisfy the guidelines for study conduct under FIFRA, it is sufficient for the purposes of hazard assessment…" .
2. **Route of administration:**
   Study a) oral, diet.
   Study b) oral, gavage (CDPR, 1994).
3. **The frequency and duration of exposure:**
   Study a) daily from prior to mating of parental generation, throughout maturation and reproduction of subsequent generations.
   Study b) daily on each of gestation days 6 - 18.
4. **The numbers of test animals:**
   Study a) 20-24 females per group (CDPR, 1994).
   Study b) 8 - 10 pregnant animals per group (CDPR, 1994).
5. **The choice of species:**
   Rats and rabbits are standard species for use in toxicological studies.
6. **The choice of dosage levels:**
   Study a) 0, 15 (1.6 mg/kg), 50 (5.0 mg/kg), and 200 ppm.
   Study b) 0, 1, 5, 25 mg/kg/day.
7. **Maternal toxicity:**
   Study a) none noted in consulted documentation.
   Study b) The US EPA Tox-Oneliner on Amitraz (US EPA, 1990) states that a maternal LEL of 25 mg/kg was based on the frequency of abortion of entire litters. The NOEL for this endpoint was stated to be 5 mg/kg. However, in the absence of other indications of serious systemic toxicity in the dam, this endpoint is generally considered a manifestation of developmental toxicity.

Disodium cyanodithiomidocarbonate (CAS No. 138-93-2)

***Developmental toxicity* was manifested as increased skeletal variations and increased resorptions.**

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

Supporting documentation for the TRI listing (US EPA, 1993b) states, “Rats administered disodium cyanodithiomidocarbonate by gavage on gestation days 6 to 15 demonstrated increased skeletal variations in offspring. The NOEL is 6 mg/kg, LEL is 18 mg/kg. In a rabbit teratology study, increased resorptions were observed in rabbits administered the compound by gavage on gestation days 6 - 18. The NOEL is 3 mg/kg, LEL is 10 mg/kg."

Stakeholder comments on the TRI proposed-listing document (US EPA, 1994a) contended that the skeletal variations and increased resorptions observed with disodium cyanodithiocarbonate exposure should not be considered as evidence of developmental toxicity. The Agency disagreed with these comments, and reaffirmed their previous conclusion (US EPA, 1994b).

With regard to the studies cited as supporting US EPA’s action in adding a chemical to the EPCRA-TRI list, OEHHA finds that the evidence for DART effects appears to meet the criteria of 22 CCR12306, and notes the following:

1. **Adequacy of the experimental design:**
   Study a) rat developmental toxicity study. Data are described as 'adequate' (US EPA, 1994d).
   Study b) rabbit developmental toxicity study. Data are described as 'adequate' (US EPA, 1994d).
2. **Route of Administration:**
   Study a) oral, gavage.
   Study b) oral, gavage.
3. **The frequency and duration of exposure:**
   Study a) daily on gestation days 6 - 15.
   Study b) daily on gestation days 6 - 18.
4. **The numbers of test animals:**
   Not stated for either study. However, numbers were considered sufficient for a designation of 'adequate' in the Reregistration Eligibility Document (US EPA, 1994d). US EPA test guidelines (1983a) require a minimum of 20 rats or 12 rabbits per dose group
5. **The choice of species:**
   The rat and rabbit are standard species used in toxicology testing.

6. **The choice of dosage levels:**
   Study a) 0, 2, 6, 18 mg/kg/day.
   Study b) 0, 3, 10, or 30 mg/kg/day
7. **Maternal toxicity:**
   Study a) both maternal and developmental toxicity had a LOEL of 18 mg/kg/day and a NOEL of 6 mg/kg/day (US EPA, 1994d).
   Study b) both maternal and developmental toxicity had a LOEL of 10 mg/kg/day and a NOEL of 3 mg/kg/day (US EPA, 1994d).

Fenbutatin oxide (CAS No. 13356-08-6)

Developmental toxicity **has been manifested as intrauterine lethality and decreased viability.**

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

Supporting documentation for the TRI listing (US EPA, 1993b) states, "In a rat teratology study, the LOEL for developmental toxicity (toxic to zygote) was 60 mg/kg/day and the NOEL was 30 mg/kg/day…. In a rabbit teratology study, oral administration of 5 mg/kg/day produced intrauterine lethality and was also toxic to maternal animals. The NOEL was 1 mg/kg/day…. In a 3-generation rat reproduction study, administration of 15 mg/kg/day (LOEL) produced [a] decreased viability index. The NOEL was 5 mg/kg/day."

With regard to the studies cited as supporting US EPA's action in adding a chemical to the EPCRA-TRI list, OEHHA finds that the evidence for DART effects appears to meet the criteria of 22 CCR 12306, and notes the following:

1. **Adequacy of the experimental design:**
   Study a) rat teratology study, classified core minimum.
   Study b) rabbit teratology study, classified core minimum.
   Study c) 3-generation rat reproduction study, not rated, but appears to meet FIFRA guidelines.
2. **Route of administration:**
   Study a) not stated, but US EPA (1983a) test guidelines specify the oral route of exposure.
   Study b) oral.
   Study c) not stated, but US EPA (1983b) specify the oral route as standard.

3. **The frequency and duration of exposure:**
   Study a) not stated, but US EPA (1983a) test guidelines specify exposure daily, on each of gestation days 6 -15 for rats.
   Study b) daily, on gestations days 6 - 18 (US EPA, 1994c).
   Study c) not stated, but US EPA test guidelines for reproductive toxicity studies (US EPA, 1983b) require at least one generation to be exposed continuously from the prenatal period through sexual maturation and a round of reproduction.
4. **The numbers of test animals:**
   Study a) not stated, but US EPA (1983a) guidelines specify at least 20 pregnant rats per dose group.
   Study b) not stated, but US EPA (1983a) guidelines specify at least 12 pregnant rabbits per dose group.
   Study c) not stated, but US EPA (1983b) guidelines specify the use of sufficient animals to ensure at least 20 pregnant females per dose group.
5. **The choice of species:**
   Rats and rabbits are standard species for use in toxicological studies.
6. **The choice of dosage levels:**
   Study a) the only doses stated are the LOEL of 60 mg/kg/day and the NOEL of 30 mg/kg/day. In order to meet guideline standards (US EPA, 1983a), there must have also been an untreated control group, and at least one additional dose group.
   Study b) 0, 1, 5, and 10 mg/kg/day (US EPA, 1994c).
   Study c) the only doses stated are the LOEL of 15 mg/kg/day and the NOEL of 5 mg/kg/day. In order to meet guideline standards (US EPA, 1983b) there would have to have been at least an untreated control group, and one additional dose level.
7. **Maternal toxicity:**
   Study a) not mentioned.
   Study b) there was evidence of both maternal and developmental toxicity at the same dose level of 5 mg/kg/day. 1 mg/kg/day was a NOEL for both maternal and developmental toxicity.
   Study c) not mentioned.

<u>Metiram (CAS No. 9006-42-2)</u>

***Developmental toxicity* was evidenced by delayed ossification of the parietal bone in rat pups prenatally exposed to ethylene thiourea, a metabolite of metiram.**

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

Supporting documentation for the TRI listing (US EPA, 1993a) states, "Metiram is an ethylenebisthiocarbamate fungicide. Evidence suggests that ethylenebisthiocarbamate fungicides and ethylenethiourea (a common contaminant, metabolite, and degradation product of these fungicides) cause adverse developmental toxicity in experimental animals. … A NOAEL of 5 mg/kg has been reported for ethylenethiourea, based on results from a rat developmental toxicity study. Ethylenethiourea caused delayed ossification or hardening of the parietal bone in pups." According to the US EPA Special Review Document on EBDCs (US EPA, 1989a), "Animal metabolism of the EBDCs is rapid and ETU and ethylene bisdiisothiocyanate sulfide (EBIS) are major metabolites."

In the final notice of intent to deny applications for registration of EBDC fungicides, US EPA (1992b) states, "The no-observable-adverse-effect level (NOAEL) for developmental toxicity resulting from exposure to ETU is equal to or less than 5.0 mg/kg/day based on a rat study … ETU was shown to be developmentally toxic at dose levels lower than those that produced no apparent maternal toxicity. At 5.0 mg/kg/day, which was the lowest dose tested, developmental toxicity was observed in the form of delayed ossification or hardening of the parietal bone (in the skull). Delayed ossification was clearly dose-related at higher rates than in control and appears to be a sensitive indicator of exposure to ETU … The results of the NTP study conducted on rats and mice indicated that ETU affected thyroid function in both species. However, a mouse study showed no developmental toxicity at very high doses (800 mg/kg/day by gavage). Therefore, simple inhibition of the thyroid gland may not necessarily be the mechanism by which developmental effects are manifested in rats. Preliminary evidence in the literature indicates developmental effects in rabbits." These studies appear to be the same as those referred to in the TRI documentation.

With regard to the studies cited as supporting US EPA's action in adding a chemical to the EPCRA-TRI list, OEHHA finds that the evidence for DART effects appears to meet the criteria of 22 CCR 12306, and notes the following:

1. **Adequacy of the experimental design:**
   US EPA (1989a) used these studies in the Agency's 'Special Review' process for evaluating the risks posed to humans and the environment by EBDCs and ethylenethiourea. The Agency considered the data suitable for this purpose.
2. **Route of administration:**
   Study a) rat developmental toxicity study – oral.
   Study b) mouse developmental toxicity study - oral gavage.
   Study c) rabbit developmental toxicity study - not stated.

3. **The frequency and duration of exposure:**
   Study a) daily from prior to pregnancy through gestation day 15, or daily on gestation days 6 through 15.
   Study b) not stated.
   Study c) not stated.
4. **The numbers of test animals:**
   Not stated for any study.
5. **The choice of species:**
   Rats, mice, and rabbits are all standard species for developmental and reproductive toxicity testing.
6. **The choice of dosage levels:**
   Study a) 5.0 mg/kg/day was the lowest dose tested.
   Study b) 0, 200, 400, 800 mg/kg/day.
   Study c) not stated.
7. **Maternal toxicity:**
   Study a) US EPA (1992b) states, "ETU was shown to be developmentally toxic at dose levels lower than those that produced no apparent maternal toxicity."
   Study b) not relevant as the study was considered to be negative.
   Study c) not stated.

Metribuzin (CAS No. 21087-64-9)

***Developmental toxicity* was manifested as growth retardation and minor skeletal abnormalities.**

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

Supporting documentation for the TRI listing (US EPA, 1993b) states, "In a rabbit teratology study, the NOEL for maternal and fetotoxicity was 15 mg/kg/day, and the LOEL was 45 mg/kg/day… In a[nother] rabbit teratology study, developmental effects including irregular spinus process and decreased pup body weight were observed in rats treated with metribuzin (Sencor) during gestation day 7-19 at 85 mg/kg/day. The NOEL for developmental toxicity was 30 mg/kg/day."

With regard to the studies cited as supporting US EPA's action in adding a chemical to the EPCRA-TRI list, OEHHA finds that the evidence for DART effects appears to meet the criteria of 22 CCR 12306, and notes the following:

1. **Adequacy of the experimental design:**
   Study a) core grade guideline (US EPA, 1986),
   Study b) core grade minimum.
2. **Route of administration:**
   Not stated for either study, but US EPA test guidelines for developmental toxicity studies (US EPA, 1983a) specify the gavage route of exposure. As both of these studies received acceptable grades, it is presumed that guideline requirements were met.
3. **The frequency and duration of exposure:**
   Study a) not stated, but US EPA test guidelines for developmental toxicity studies (US EPA, 1983a) specify daily dosing on each of gestation days 6 - 18 for rabbits. As the study was considered to meet guideline requirements, it is presumed that this requirement was met.
   Study b) stated to have been daily on gestation days 7 - 19.
4. **The numbers of test animals:**
   Not stated for either study, but US EPA test guidelines for developmental toxicity studies (US EPA, 1983a) specify a minimum of 12 rabbits per dose group. As both of these studies received acceptable grades, it is presumed that guideline requirements were met.
5. **The choice of species:**
   The rabbit is a standard species for use in toxicological studies.
6. **The choice of dosage levels:**
   Study a) 0, 15, 45, 135 mg/kg/day.
   Study b) 0, 10, 30, 85 mg/kg/day.
7. **Maternal toxicity:**
   Study a) LEL = 45 mg/kg/day, NOEL = 15 mg/kg/day.
   Study b) LOEL = 30 mg/kg/day, NOEL = 10 mg/kg/day.

<u>Nabam (CAS No. 142-59-6)</u>

***Developmental toxicity* was evidenced by delayed ossification of the parietal bone in rat pups prenatally exposed to ethylene thiourea, a metabolite of nabam.**

The US Environmental Protection Agency (US EPA, 1994a and 1994b) concluded that "… there is sufficient evidence for listing nabam on EPCRA section 313 pursuant to EPCRA section 313(d)(2)(B) based on the … developmental toxicity data for ethylenethiourea, a metabolite and degradation product of nabam."
Supporting documentation for the TRI listing (US EPA, 1993a) states, "Nabam is an ethylenebisthiocarbamate fungicide. Evidence suggests that ethylenebisthiocarbamate fungicides and ethylenethiourea (a common contaminant, metabolite, and degradation product of these fungicides) cause adverse developmental toxicity in experimental animals… A NOAEL of 5 mg/kg has been reported for ethylenethiourea, based on results from a rat developmental toxicity study. Ethylenethiourea caused delayed ossification or

hardening of the parietal bone in pups." According to the US EPA Special Review Document on EBDCs (US EPA, 1989a), "Animal metabolism of the EBDCs is rapid and ETU and ethylene bisdiisothiocyanate sulfide (EBIS) are major metabolites."

In the final notice of intent to deny applications for registration of EBDC fungicides, US EPA (1992b) states, "The no-observable-adverse-effect level (NOAEL) for developmental toxicity resulting from exposure to ETU is equal to or less than 5.0 mg/kg/day based on a rat study… ETU was shown to be developmentally toxic at dose levels lower than those that produced no apparent maternal toxicity. At 5.0 mg/kg/day, which was the lowest dose tested, developmental toxicity was observed in the form of delayed ossification or hardening of the parietal bone (in the skull). Delayed ossification was clearly dose-related at higher rates than in control and appears to be a sensitive indicator of exposure to ETU… The results of the NTP study conducted on rats and mice indicated that ETU affected thyroid function in both species. However, a mouse study showed no developmental toxicity at very high doses (800 mg/kg/day by gavage). Therefore, simple inhibition of the thyroid gland may not necessarily be the mechanism by which developmental effects are manifested in rats. Preliminary evidence in the literature indicates developmental effects in rabbits." These studies appear to be the same as those referred to by the TRI documentation.

With regard to the studies cited as supporting US EPA's action in adding a chemical to the EPCRA-TRI list, OEHHA finds that the evidence for DART effects appears to meet the criteria of 22 CCR 12306, and notes the following:

1. **Adequacy of the experimental design:**
   US EPA (1989a) used these studies in the Agency's 'Special Review' process for evaluating the risks posed to humans and the environment by EBDCs and ethylenethiourea. The Agency considered the data suitable for this purpose.
2. **Route of administration:**
   Study a) rat developmental toxicity study - oral.
   Study b) mouse developmental toxicity study - oral gavage.
   Study c) rabbit developmental toxicity study - not stated.
3. **The frequency and duration of exposure:**
   Study a) daily from prior to pregnancy through gestation day 15, or daily on gestation days 6 through 15.
   Study b) not stated.
   Study c) not stated.
4. **The numbers of test animals:**
   Not stated for any study.
5. **The choice of species:**
   Rats, mice, and rabbits are all standard species for developmental and reproductive toxicity testing.
6. **The choice of dosage levels:**
   Study a) 5.0 mg/kg/day was the lowest dose tested.

Study b) 0, 200, 400, 800 mg/kg/day.
Study c) not stated.

7. **Maternal toxicity:**
   Study a) US EPA (1992b) states, "ETU was shown to be developmentally toxic at dose levels lower than those that produced no apparent maternal toxicity."
   Study b) not relevant as the study was considered to be negative.
   Study c) not stated.

Nitrapyrin (CAS No. 1929-82-4)

***Developmental toxicity* was evidenced by an increased frequency of crooked hyoid bones seen in rabbits exposed *in utero*.**

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

Supporting documentation (US EPA, 1993a) for the TRI listing states, "Increased incidence of crooked hyoid bones was observed in the offspring of rabbits orally administered 30 mg/kg/day (LOEL) on days 6 through 18 of gestation. The NOEL was 10 mg/kg/day (67 [US EPA, 1992a]). Craniofacial abnormalities were seen in the offspring of rabbits orally administered 30 mg/kg/day on days 6 through 18 of gestation (9 [RTECS, 1993]). Decreased weight and hypertrophy and vacuolization of the liver were observed in offspring of rats dosed with 75 mg/kg/day (67 [US EPA, 1992a])."

As described in by US EPA (1992a), treatment with 30 mg/kg/day nitrapyrin resulted in an increase in the frequency of 'crooked hyoid bone'. This increase was statistically significant as compared to concurrent controls, and exceeded the frequency of this variant among historical controls. It should be noted that there was only one rabbit developmental toxicity study (Berdasco et al., 1988), and that the RTECS reference to 'craniofacial abnormalities' is a description of the 'crooked hyoid bones' observed in that study.

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 developmental toxicity study - study design appears to meet US EPA test guideline standards (Berdasco et al., 1988; US EPA, 1992a).
   Study b) reproductive toxicity study in rats - study considered by US EPA in evaluating the developmental and reproductive toxicity of nitrapyrin (US EPA, 1992a).
2. **Route of administration:**
   Study a) oral, gavage
   Study b) not stated.
3. **The frequency and duration of exposure:**
   Study a) daily on each of gestation days 6 - 18
   Study b) daily for ten weeks prior to mating; it is not stated in the available documentation whether dosing was continued throughout gestation and postnatal development, but it is assumed that this is likely to have been the case.
4. **The numbers of test animals:**
   Study a) 25 pregnant rabbits per dose group
   Study b) not stated
5. **The choice of species:**
   Rats and rabbits are standard test species used in developmental and reproductive toxicity testing.
6. **The choice of dosage levels:**
   Study a) 0, 3, 10, 30 mg/kg/day,
   Study b) 0, 5, 20, and 75 mg/kg/day.
7. **Maternal toxicity:**
   Study a) decreased body weight gain, and increased absolute and relative liver weights were observed in dams given 30 mg nitrapyrin/kg bw. 10 mg/kg/day was the NOEL for maternal toxicity. The same doses were determined to be the LOEL and NOEL, respectively, for developmental toxicity,
   Study b) systemic toxicity was observed at 20 mg/kg/day nitrapyrin, in the form of increased absolute and relative kidney and liver weights in F_0 males. The NOEL for this endpoint was 5 mg/kg/day. Adverse effects on offspring were seen at 75 mg/kg/day, with a NOEL of 20 mg/kg/day.

<u>Potassium dimethyldithiocarbamate (CAS No. 128-03-0)</u>

***Developmental toxicity* was manifested as skeletal abnormalities, increased postimplantation loss, and decreased fetal weights in rabbits exposed prenatally.**

The US Environmental Protection Agency (US EPA, 1994a and 1994b) concluded that "… there is sufficient evidence for listing potassium dimethyldithiocarbamate on EPCRA

section 313 pursuant to EPCRA section 313(d)(2)(B) based on the available developmental toxicity data for this chemical."

It should be noted that the statement in the final rule document (US EPA 1994b) which cites 'neurological toxicity' as the basis for listing was an editing error (US EPA, 1997a). The concluding statement should have read 'developmental toxicity'.

Supporting documentation for the TRI listing (US EPA, 1993b) states, "New Zealand White rabbits given 38 mg/kg/day by gavage on days 6 to 18 of gestation exhibited malalignment of sternebrae, total postimplantation loss ($p<0.01$) and fetal weight decrement. Also at this dose level various possible malformations including adactyly, gastroschisis, short tail, anal atresia, spina bifida, atelectasis, costal cartilage anomaly, vertebral anomaly with/without rib, caudal vertebrae anomaly, and severe sternebrae malalignment in 6/52 fetuses from 5/11 litters. At the 77 mg/kg/day dose level, there was severe fetal/embryo lethality. The NOEL was 12.8 mg/kg/day."

With regard to the studies cited as supporting US EPA's action in adding a chemical to the EPCRA-TRI list, OEHHA finds that the evidence for DART effects appears to meet the criteria of 22 CFR 12306, and notes the following:

1. **Adequacy of the experimental design:**
   The rabbit developmental toxicity study was considered to be core minimum (US EPA, 1989b).
2. **Route of administration:**
   Oral, gavage.
3. **The frequency and duration of exposure:**
   Daily, on gestation days 6 - 18.
4. **The numbers of test animals:**
   20 pregnant rabbits per group.
5. **The choice of species:**
   Rabbits are a standard species in toxicological testing.
6. **The choice of dosage levels:**
   0, 12.8, 38, or 77 mg active ingredient/kg bw.
7. **Maternal toxicity:**
   NOEL: 12.8 mg active ingredient/kg bw. LEL: 38 mg active ingredient/kg/day for clinical signs, and at the HTD (highest tolerated dose) [77 mg/kg/day] body weight-gain decrement and reduced food consumption. Possible increased maternal death and abortions at 38 mg active ingredient/kg/day and above.

<u>Sodium dimethyldithiocarbamate (CAS No. 128-04-1)</u>

Developmental toxicity **was manifested as skeletal abnormalities, increased postimplantation loss, and decreased fetal weights in rabbits exposed prenatally to**

potassium dimethyldithiocarbamate. In solution, the active component, *i.e.*, the dimethyldithiocarbamate ion, is present for both the sodium and potassium salts.

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

Supporting documentation for the TRI listing (US EPA, 1993b) states, "New Zealand White rabbits given 38 mg/kg/day by gavage on days 6 to 18 of gestation exhibited malalignment of sternebrae, total postimplantation loss ($p<0.01$) and fetal weight decrement. Also at this dose level various possible malformations including adactyly, gastroschisis, short tail, anal atresia, spina bifida, atelectasis, costal cartilage anomaly, vertebral anomaly with/without rib, caudal vertebrae anomaly, and severe sternebrae malalignment in 6/52 fetuses from 5/11 litters. At the 77 mg/kg/day dose level, there was severe fetal/embryo lethality. The NOEL was 12.8 mg/kg/day."

With regard to the studies cited as supporting US EPA's action in adding a chemical to the EPCRA-TRI list, OEHHA finds that the evidence for DART effects appears to meet the criteria of 22 CCR 12306, and notes the following:

1. **Adequacy of the experimental design:**
   The rabbit developmental toxicity study was considered to be core grade minimum (US EPA 1989b).
2. **Route of administration:**
   Oral, gavage.
3. **The frequency and duration of exposure:**
   Daily, on gestation days 6 - 18.
4. **The numbers of test animals:**
   20 pregnant rabbits per group.
5. **The choice of species:**
   Rabbits are a standard species in toxicological testing.
6. **The choice of dosage levels:**
   0, 12.8, 38, or 77 mg active ingredient/kg bw.
7. **Maternal toxicity:**
   NOEL: 12.8 mg active ingredient/kg bw. LEL: 38 mg active ingredient/kg/day for clinical signs, and at the HTD (highest tolerated dose) [77 mg/kg/day] body weight-gain decrement and reduced food consumption. Possible increased maternal death and abortions at 38 mg active ingredient/kg/day and above.

Triadimefon (CAS No. 43121-43-3)

The *developmental toxicity* of triadimefon was manifested as fetal resorptions, malformations, and skeletal alterations in the offspring of treated experimental animals. *Male and female reproductive toxicity* were manifested as decreased fertility, decreased litter size, and decreased pup viability.

The US Environmental Protection Agency (US EPA, 1994a and 1994b) concluded that "…there is sufficient evidence for listing triadimefon 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, 1993b) states, "Cleft palates were observed in the offspring of rats orally administered 75 mg/kg/day (LOEL) for an unspecified duration. The NOEL was 30 mg/kg/day…(24 [US EPA, 1997c]). Increased incidence of abnormal ribs, extra ribs, and distended urinary bladders were observed in the offspring of rats orally administered 90 mg/kg/day (LOEL). The NOEL was 30 mg/kg/day…(24 [US EPA, 1997c]). Increases in fetal resorptions were observed in rabbits given 100 mg/kg/day by gavage (LOEL). The NOEL was 30 mg/kg/day… (24 [US EPA, 1997c]). Increased incidence of incomplete ossification of pelvic pubes and phalanges, and irregular spinous processes were observed in the offspring of rabbits orally administered 50 mg/kg/day (LOEL) on days 6 through 18 of gestation. The NOEL was 20 mg/kg/day…(24 [US EPA, 1997c]). In a 3-generation rat reproduction study, decreased fertility and decreased litter size were observed at 90 mg/kg/day (LOEL). The NOEL was 15 mg/kg/day…(24 [US EPA, 1997c]). In a 2-generation reproduction study in rats, decreased pup weights, decreased litter size, and decreased pup viability were observed at 90 mg/kg/day (LOEL). The NOEL was 2.5 mg/kg/day… (24 [US EPA, 1997c])."

With regard to the studies cited as supporting US EPA's action in adding a chemical to the EPCRA-TRI list, OEHHA finds that the evidence for DART effects appears to meet the criteria of 22 CFR 12306, and notes the following:

1. **Adequacy of the experimental design:**
   Study a) rat developmental toxicity study - core grade minimum,
   Study b) rat developmental toxicity study - core grade minimum,
   Study c) rabbit developmental toxicity study - core grade supplementary,
   Study d) rat reproductive toxicity study - core grade minimum,
   Study e) rat reproductive toxicity study - core grade supplementary (due to insufficient number of doses tested, and incomplete reporting of clinical and necropsy data.
2. **Route of administration:**
   Study a) appears to have been oral, gavage,
   Study b) oral, gavage,
   Study c) oral, gavage,

Study d) not stated. Probably oral in drinking water or feed, but possibly inhalation,

Study e) not stated. Probably oral in drinking water or feed, but possibly inhalation.

3. **The frequency and duration of exposure:**

Study a) not stated, but as the study was considered to have minimally met US EPA test guidelines for developmental toxicity studies in rats (US EPA, 1983a), treatment must have been given once daily on each of gestation days 6 - 15,

Study b) not stated, but as the study was considered to have minimally met US EPA test guidelines for developmental toxicity studies in rats (US EPA, 1983a), treatment must have been given once daily on each of gestation days 6 - 15,

Study c) not stated, but as the study was considered to have minimally met US EPA test guidelines for developmental toxicity studies in rabbits (US EPA, 1983a), treatment must have been given once daily on each of gestation days 6 - 18,

Study d) daily, from prior to mating of parental generation through maturation and reproduction of F_2 animals,

Study e) daily, from prior to mating of parental generation through maturation and reproduction of F_1 animals.

4. **The numbers of test animals:**

Study a) not stated, but as the study was considered to have minimally met US EPA test guidelines for developmental toxicity (US EPA, 1983a), there must have been a minimum of 20 pregnant rats per dose group.

Study b) not stated, but as the study was considered to have minimally met US EPA test guidelines for developmental toxicity (US EPA, 1983a), there must have been a minimum of 20 pregnant rats per dose group.

Study c) not stated, but as the study was considered to have minimally met US EPA test guidelines for developmental toxicity (US EPA, 1983a), there must have been a minimum of 12 pregnant rabbits per dose group.

Study d) not stated, but as the study was considered to have minimally met US EPA test guidelines for reproductive toxicity (US EPA, 1983b), there must have been a minimum of 20 pregnant rats per dose group.

Study e) not stated. However, an insufficient number of animals per dose group was not listed among this study's deficiencies. Thus it would seem that US EPA test guidelines for reproductive toxicity (US EPA, 1983b) were met for this variable, indicating that there must have been a minimum of 20 pregnant rats per dose group.

5. **The choice of species:**

Study a) rat,

Study b) rat,

Study c) rabbit,
Study d) rat,
Study e) rat.

6. **The choice of dosage levels:**
   Study a) 0, 10, 75, 100 mg/kg/day,
   Study b) 0, 10, 30, 90 mg/kg/day,
   Study c) 0, 10, 30, 100 mg/kg/day,
   Study d) 0, 50, 300, 1800 ppm,
   Study e) 0, 50, 1800 ppm.
7. **Maternal toxicity:**
   Study a) maternal NOEL = 10 mg/kg/day; maternal LEL = 30 mg/kg/day (decreased weight gain). Teratogenic NOEL = 50 mg/kg/day; teratogenic LEL = 75 mg/kg/day (cleft palate),
   Study b) maternal NOEL = 30 mg/kg/day; maternal LEL = 90 mg/kg/day (decreased maternal weight gain during treatment). Developmental NOEL = 30 mg/kg/day; developmental LEL = 90 mg/kg/day (morphological abnormalities),
   Study c) maternal NOEL = 10 mg/kg/day; maternal LEL = 30 mg/kg/day (decreased weight gain). Developmental NOEL = 30 mg/kg/day; developmental LEL = 100 mg/kg/day (increased resorptions),
   Study d) maternal NOEL = 300 ppm; maternal LEL = 1800 ppm (decreased body weight gain, decreased lactation performance). Fetotoxic NOEL = 50 ppm; fetotoxic LEL = 300 ppm (decreased pup weight gain). Reproductive NOEL = 300 ppm; LEL = 1800 ppm (decreased fertility, decreased litter size),
   Study e) reproductive NOEL = 50 ppm; LEL = 1800 ppm (reduced birth and pup weights, reduced litter size, reduced viability).

<u>Triphenyltin hydroxide (CAS No. 76-87-9)</u>

The *developmental toxicity* of triphenyltin hydroxide was manifested as decreased embryo/fetal viability in rats.

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

Supporting documentation for the TRI listing (US EPA, 1993a) states, "In a teratogenicity study in rats, oral doses of 15 mg/kg during gestation days 1 - 7 prevented implantation (HSDB 1993); when administered from day 8 and onwards, the compound was fetolethal. Data from OPP's one-liner database support these findings."

The original paper (Winek et al., 1979) was retrieved in order to supply the study details provided below.

With regard to the studies cited as supporting US EPA's action in adding a chemical to the EPCRA-TRI list, OEHHA finds that the evidence for DART effects appears to meet the criteria of 22 CFR 12306, and notes the following:

1. **Adequacy of the experimental design:**
   Insufficient numbers of doses and animals per dose group for risk assessment purposes. Data are, however, sufficient as an indication of potential hazard.
2. **Route of administration:**
   Oral, gavage.
3. **The frequency and duration of exposure:**
   Daily on gestation days 1 - 7; or daily on gestation days 8 - 14; or daily on gestation days 14 - 20.
4. **The numbers of test animals:**
   Each dose/time group was treated as a separate experiment with 6 test animals and 2 controls.
5. **The choice of species:**
   Rats
6. **The choice of dosage levels:**
   Animals treated on days 1 - 7 received 20 mg/kg/day; those treated on days 8 - 14 or 14 - 20 were given 15 mg/kg.
7. **Maternal toxicity:**
   Not mentioned, but all maternal animals survived until sacrifice and necropsy on gestation day 20.

References

Berdasco, N.M., Lomax, L.G., Zimmer, M.A., and T.R. Hanley, Jr. (1988) Teratologic evaluation of orally administered nitrapyrin in rats and rabbits. *Fund. & Appl. Toxicol*. **11**: 464-471.

California Department of Pesticide Regulation (CDPR, 1994). *Summary of Toxicology Data. Amitraz.* California Environmental Protection Agency, CDPR, Medical Toxicology Branch.

Hazardous Substances Data Bank (HSDB, 1993). Triphenyltin hydroxide.

Registry of Toxic Effects of Chemical Substances (RTECS, 1993). National Institute for Occupational Safety and Health, National Library of Medicine, Bethesda, MD.

US Environmental Protection Agency (US EPA, 1983a). *Health Effects Test Guidelines; Teratogenicity Study*. Office of Toxic Substances, Office of Pesticides and Toxic Substances.

US Environmental Protection Agency (US EPA, 1983b). *Health Effects Test Guidelines; Reproduction and Fertility Effects.* Office of Toxic Substances, Office of Pesticides and Toxic Substances.

US Environmental Protection Agency (US EPA, 1986). *Tox-Oneliner Database (sanitized version)*, Office of Pesticide Programs, Arlington, VA.

US Environmental Protection Agency (US EPA, 1989a). Ethylene bisdithiocarbamates (EBDCs); Notice of Intent to Cancel; Conclusion of Special Review. *Federal Register* **57:**7484.

US Environmental Protection Agency (US EPA, 1989b). *Tox-Oneliner Database (sanitized version)*, Office of Pesticide Programs, Arlington, VA.

US Environmental Protection Agency (US EPA, 1990). *Tox-Oneliner Database (sanitized version)*, Office of Pesticide Programs, Arlington, VA.

US Environmental Protection Agency (US EPA, 1992a). *Carcinogenicity Peer Review of Nitrapyrin.* Memorandum from the Carcinogenicity Peer Review Committee, Health Effects Division. US EPA, Washington DC.

US Environmental Protection Agency (US EPA, 1992b). *Ethylene bisdithiocarbamates (EBDCs); Notice of final determination; Notice of Intent to Cancel; Conclusion of Special Review.* Federal Register **57**:7484.

US Environmental Protection Agency (US EPA, 1993a). *Support Document for the Health and Ecological Toxicity Review of TRI Expansion Chemicals.* US EPA Office of Pesticide Programs, Washington, DC.

US Environmental Protection Agency (US EPA, 1993b). *Support Document for the Addition of Chemicals from Federal Insecticide, Fungicide, Rodenticide Act (FIFRA) Active Ingredients to EPCRA Section 313.* US EPA Office of Pesticide Programs, Washington, DC.

US Environmental Protection Agency (US EPA, 1994a). Proposed Rule: Addition of Certain Chemicals; Toxic Chemical Release Reporting; Community Right to Know. *Federal Register* **59**: 1788.

US Environmental Protection Agency (US EPA, 1994b). Final Rule: Addition of Certain Chemicals; Toxic Chemical Release Reporting; Community Right to Know. *Federal Register* **59**(229): 61432.

US Environmental Protection Agency (US EPA, 1994c). *Reregistration Eligibility Decision (RED): Fenbutatin-oxide.* US EPA, OPPTS. Washington D.C. 20460.

US Environmental Protection Agency (US EPA, 1994d). *Reregistration Eligibility Decision (RED): Disodium cyanodithiomidocarbonate (DCDIC).* US EPA Office of Pesticide Programs and Toxic Substances, Washington, DC.

US Environmental Protection Agency (US EPA, 1997a). Letter from Dr. Maria Doa, Chief, Toxics Release Inventory Branch, OPPTS, US EPA, to Dr. James Donald, Reproductive and Cancer Hazard Assessment Section, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, dated May 22, 1997.

US Environmental Protection Agency (US EPA, 1997b). *Integrated Risk Information System.* U.S. EPA, Washington DC.

US Environmental Protection Agency (US EPA, 1997c). *Tox-Oneliner Database (sanitized version)*, Office of Pesticide Programs, Arlington, VA.

Winek, C.L., Marks, M.J. Jr., Shanor, S.P., Davis, E.R. (1979) Acute and subacute toxicology and safety evaluation of triphenyl tin hydroxide (Vancide KS). *Toxicology Annual.* **3**:281-296.