CHEMICALS MEETING THE CRITIERIA FOR LISTING AS DEVELOPMENTAL AND REPRODUCTIVE TOXICANTS (DARTs) VIA THE AUTHORITATIVE BODIES MECHANISM: 4 CHEMICALS IDENTIFIED BY U.S. EPA

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The four chemicals listed in the table below meet the criteria for listing under Proposition 65 via the authoritative bodies listing mechanism. The regulatory guidance for listing by this mechanism is set forth in Title 22, California Code of Regulations (CCR), Section 12306. For example, the regulations include provisions covering the criteria for evaluating the documentation and scientific findings by the authoritative body to determine whether listing under Proposition 65 is required.

The U.S. Environmental Protection Agency (U.S. EPA) has been identified as an authoritative body for purposes of Proposition 65 (22 CCR Section 12306(l)) and has identified the chemicals in the table below as causing developmental or reproductive toxicity. This was done by that Agency in implementing its Toxic Release Inventory (TRI) program (*i.e.*, Section 313 of the Emergency Planning and Community Right-to-Know Act of 1986 (EPCRA)). On the basis of identifying chemicals which caused reproductive, developmental and/or other toxicities the U.S. EPA added a number of chemicals to the TRI list. The U.S. EPA published its toxicity findings in the *Federal Register* (**59:**1788-1859, 1994 and **59:**61432-61485, 1994). In proposing specific chemicals for addition to the TRI list, the Agency stated that a hazard assessment was performed for each candidate, "…in accordance with relevant EPA guidelines for each adverse human health or environmental effect…" (*Federal Register* **59:**1790).

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

OEHHA also finds that the criteria for "as causing reproductive toxicity" given in regulation (22 CCR 12306[g]) have been satisfied for the chemicals in the table below. In making this evaluation, OEHHA relied upon the documents and reports cited by U.S. EPA in making their finding that the specified chemicals cause reproductive toxicity. In some cases, OEHHA consulted additional sources of information on the specific studies cited by U.S. EPA. This was done only where necessary to affirm or clarify details of results and study design for studies cited by U.S. EPA; OEHHA did not review additional studies not relied on by U.S. EPA.

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

Chemical	**CAS No.**	**Endpoints**	**Pesticide status or usage**
Avermectin B1 (abamectin) [Avermectin B1A] [Avermectin B1B]	71751-41-2 65195-55-3 65195-56-4	developmental toxicity	Registered in CA
delta-8, 9-isomer of Avermectin B1	None available	developmental toxicity	Plant photo-degradate of avermectin B1
Imazalil	35554-44-0	developmental toxicity	Registered in CA
N-methyl-pyrrolidone (NMP)	872-50-4	developmental toxicity male reproductive toxicity female reproductive toxicity	Solvent

Studies cited by U.S. EPA in making findings with regard to reproductive toxicity are briefly described below. The statements in bold reflect data and conclusions which appear to satisfy the criteria for sufficiency of evidence for reproductive toxicity in regulation (22 CCR 123069g)). 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.

Avermectin B1 (CAS No. 71751-41-2 [65195-55-3, 65195-56-4]) and its delta-8, 9-isomer

Developmental toxicity **has been manifested as malformations in experimental animals.**

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

Supporting documentation (U.S. EPA, 1993a) for the TRI listing states, "A peer review evaluation of the developmental and reproductive toxicity of abamectin concluded that this compound induces developmental toxicity in several species with the mouse being the most sensitive species (74 [U.S. EPA, 1993e]). Increased retinal folds in weanlings, decreased viability and lactation indices, decreased body weight, increased number of dead pups at birth (LEL was 0.4 mg/kg/day; NOEL was 0.12 mg/kg/day) were noted in a 2-generation rat reproduction study (74 [U.S. EPA, 1993e]). Based on the NOEL, an RfD of 0.0004 mg/kg/day was derived (74 [U.S. EPA, 1993e])."

U.S. EPA (1996) published a final rule establishing a tolerance for combined residues of the insecticide avermectin B1 and its delta-8, 9-isomer in or on the raw agricultural commodities cucurbit group. Additional details of the Agency's evaluation of the data on these compounds are presented in tolerance notices for other commodities (U.S. EPA, 1989a and 1989b).

In setting the residue tolerance, U.S. EPA (1996) states, "The Agency used a two-generation rat reproduction study with an uncertainty factor of 300 to establish a Reference Dose (RfD). The 300-fold uncertainty factor was utilized for (1) inter- and intraspecies differences, (2) the extremely serious nature (pup death) [of the effect] observed in the reproduction study, (3) maternal toxicity (lethality) no-observable-effect level (NOEL) (0.05 mg/kg body weight (bwt)/day), and (4) cleft palate in the mouse developmental toxicity study with isomer (NOEL = 0.06 mg/kg bwt/day). Thus based on a NOEL of 0.12 mg/kg bwt/day from the two-generation rat reproduction (sic) and an uncertainty factor of 300, the RfD is 0.0004 mg/kg/day." The document goes on to state, "Because of the developmental effects seen in animal studies, the Agency used the mouse teratology study (with a NOEL of 0.06 mg/kg/day for developmental toxicity for the delta-8,9 isomer) to assess acute dietary exposure and determine a margin of exposure (MOE) for the overall U.S. population and certain subgroups. Since the toxicological end-point pertains to developmental toxicity, the population group of interest for this analysis is women aged 13 years and above, the subgroup which most closely approximates women of child-bearing age."

In the final rule document establishing TRI additions (U.S. EPA 1994b), the Agency notes, "One commenter, Merck, states that primates are less sensitive to the acute effects of abamectin and its analog, ivermectin, than rodents. The commenter implies that because humans are primates, abamectin should be less toxic in humans than in rodents.

The commenter further contends that ivermectin and abamectin have been used safely in animals and humans. Abamectin interferes with gamma-aminobutyric acid (GABA) transmission and, as such, produces neurotoxic clinical signs such as tremors, ataxia, convulsions, or coma that are more severe in rodents and dogs than primates. EPA agrees that the available studies indicate that the sensitivity as well as doses required to produce neurotoxic effects vary from rodents to primates by a 20-fold factor. However, abamectin was proposed for addition to the EPCRA section 313 list based on developmental effects rather than neurotoxicity. There are no developmental studies with abamectin in primates. Therefore, EPA believes that the rodent studies cited in the proposed rule provide sufficient evidence that abamectin can reasonably be anticipated to cause developmental toxicity in humans. When administered in therapeutic doses, the Agency does not dispute the animal and human safety and efficacy of ivermectin and abamectin, but the safety of a 0.2 to 0.3 mg/kg single therapeutic dose does not diminish the findings of the developmental, reproductive, neurotoxic, chronic, and carcinogenic animal studies with abamectin which in some cases demonstrate compound-related effects at higher than therapeutic doses in all species tested."

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

1. **Adequacy of the experimental design:** All studies listed below were discussed in U.S. EPA's peer review of the developmental and reproductive toxicity of avermectin (U.S. EPA, 1993e), and all were considered in the Agency's weight-of-evidence determination. OEHHA notes that the effects on postnatal growth and pup death observed in a 2-generation reproductive toxicity study conducted in rats (study "n" below) appear to have been the result of exposure to avermectin during the postnatal period. As current interpretation of the Proposition 65 statute precludes consideration of adverse developmental effects resulting solely from postnatal exposures, OEHHA has not incorporated these specific effects in determining whether the criteria in 22 CCR 12306(g) have been met.
   Study a) developmental toxicity study in rats (tech grade avermectin B1),
   Study b) developmental toxicity study in rabbits ("MK-0936 avermectin B1; approximately 94% pure"),
   Study c) range-finding developmental toxicity study in rats (avermectin B1a),
   Study d) one-generation reproduction toxicity study in rats (Avermectin B1a),
   Study e) one-generation reproduction toxicity study in rats (avermectin B1),
   Study f) developmental toxicity study in mice,
   Study g, a & b) a pair of replicated developmental toxicity studies which were analyzed in combination. Both studies rated "core supplementary",
   Study h) developmental toxicity study in rats (delta 8,9-isomer of avermectin),
   Study i) one-generation reproductive toxicity study in rats (avermectin B1)
   Study j) maternotoxicity study in mice (avermectin B1)
   Study k) maternotoxicity study in mice (8,9-isomer of avermectin B1)

Study l) developmental toxicity study in mice (8,9-isomer of avermectin B1) - inadequate study, as doses were too low to demonstrate any maternal or fetal effects,
Study m) developmental toxicity study in mice ("isomer of avermectin B1")
Study n) reproductive toxicity study in rats (avermectin B1)
Study o) developmental toxicity study in mice (22,23-dihydro-avermectin B1a),
Study p) developmental toxicity study in mice (22,23-dihydro-avermectin B1a),
Study q) developmental toxicity study in mice (ivermectin),
Study r) developmental toxicity study in rats (ivermectin),
Study s) developmental toxicity study in rabbits (ivermectin),
Study t) developmental toxicity study in dogs (ivermectin),
Study u) developmental toxicity study in mice (form not identified).

2. **Route of administration:**

Study a) oral, presumed gavage,
Study b) oral, presumed gavage,
Study c) oral, presumed gavage,
Study d) oral, presumed gavage,
Study e) oral, presumed gavage,
Study f) oral, presumed gavage,
Study g, a & b) oral, gavage,
Study h) oral, gavage,
Study i) oral, gavage,
Study j) oral, gavage,
Study k) oral, gavage,
Study l) oral, gavage,
Study m) oral, gavage,
Study n) oral, presumed gavage,
Study o) not stated,
Study p) not stated,
Study q) not stated,
Study r) not stated,
Study s) not stated,
Study t) oral, in sesame oil,
Study u) oral, gavage.

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

Study a) daily on gestation days 6-19,
Study b) daily on gestation days 6-27,
Study c) daily on gestation days 6-15,
Study d) from prior to mating, though gestation and lactation,
Study e) from prior to mating, though gestation and lactation,
Study f) daily on gestation days 6-15,
Study g, a & b) daily on gestation days 6-15,
Study h) daily on gestation days 6-17,
Study i) from prior to mating, though gestation and lactation,
Study j) daily on gestation days 6-15,

Study k) daily on gestation days 6-15,
Study l) daily on gestation days 6-15,
Study m) daily on gestation days 6-15
Study n) from prior to mating, though gestation and lactation, for two generations,
Study o) not stated,
Study p) not stated,
Study q) not stated,
Study r) not stated,
Study s) not stated,
Study t) on each of gestation days 5, 15, 25, and 35; or on each of days 10, 20, 30, and 40,
Study u) daily on gestation days 6-15.

4. **The numbers of test animals:**
Study a) 24-25/dose group,
Study b) not stated,
Study c) 20 mated females per group,
Study d) 15 mated females per group,
Study e) 12 mated females per group,
Study f) 20 mated females per group,
Study g, a & b) 10-15 mated females per group,
Study h) not stated,
Study i) 20 mated females per group,
Study j) 8-13 mated females per group,
Study k) 25 mated females per group,
Study l) 25 mated females per group,
Study m) 23 litters in each of control and high-dose groups (other groups presumably same number, but this is not stated),
Study n) 30 animals/sex/dose,
Study o) 20 per group,
Study p) 35 controls; size of other groups not stated,
Study q) 25 per group,
Study r) 25 per group,
Study s) 16 per group,
Study t) 17-19 per group,
Study u) 10-15 per group.

5. **The choice of species:** Rats, rabbits, dogs, and mice are standard species used in reproductive toxicity studies.

6. **The choice of dosage levels:**
Study a) 0, 0.4, 0.8, 1.6 mg/kg/day,
Study b) 0, 0.5, 1.0, 2.0 mg/kg/day,
Study c) 0, 0.8, 1.6, or 3.2 mg/kg/day,
Study d) 0, 0.1, 0.2, 0.4 mg/kg/day,
Study e) 0, 0.5, 1.0, and 2.0 (reduced to 1.5 mg/kg/day during the course of the study) mg/kg/day,
Study f) 0, 0.1, 0.2, 0.4, 0.8 mg/kg/day,

Study g, a & b) 0, 0.1, 0.2, 0.4, 0.8 mg/kg/day,
Study h) 0, 0.25, 0.5, 1.0 mg/kg/day,
Study i) 0.06, 0.12, 0.40, mg/kg/day,
Study j) 0, 1.5, 3.0, 6.25, 12.5, 25, 50 mg/kg/day,
Study k) 0, 0.05, 0.1, 0.5, 1 mg/kg/day,
Study l) 0, 0.015, 0.03, 0.06 mg/kg/day,
Study m) 0, 0.015, 0.03, 0.1, 0.5 mg/kg/day,
Study n) 0, 0.05, 0.12, 0.40 mg/kg/day,
Study o) 0, 0.4, 0.8, 1.6 mg/kg/day,
Study p) 0, 0.4, 0.8, 1.6 mg/kg/day,
Study q) 0, 0.1, 0.2, 0.4, 0.8 mg/kg/day,
Study r) 0, 2.5, 5, 10 mg/kg/day,
Study s) 0, 1.5, 3, 6 mg/kg/day,
Study t) 0, 0.5 mg/kg/day,
Study u) 0, 0.1, 0.2, 0.4, 0.8 mg/kg/day.

7. **Maternal toxicity:**

Study a) no evidence of maternal toxicity (apparently no dose-related developmental effects either)
Study b) maternal LOEL=2.0 mg/kg/day (decreased body weight gain), NOEL=1.0 mg/kg/day; developmental LOEL=2.0 mg/kg/day (malformations and incomplete ossification), NOEL=1.0 mg/kg/day,
Study c) at high dose: 3 maternal deaths, tremors and ataxia; no clinical signs of toxicity observed in other dose groups, no fetal effects observed.
Study d) maternal NOEL > 0.4 mg/kg/day (hdt); developmental LOEL 0.2 mg/kg/day (increased spastic movements, decreased pup body weights, decreased litter size on lactation day 1), NOEL 0.1 mg/kg/day
Study e) maternal LOEL=1.5-2.0 mg/kg/day (tremors, clinical symptoms, mortality), NOEL 1.0=mg/kg/day; developmental LOEL < 0.5 mg/kg/day (ldt)(decreased pup weight and postnatal survival; decreased mean litter size at 1.5 mg/kg/day on pnd 1).
Study f) maternal NOEL<0.1 mg/kg/day (one maternal death at low dose); developmental LOEL=0.4 mg/kg/day (increased incidence of cleft palate), NOEL=0.2 mg/kg/day,
Study g, a & b) maternal NOEL<0.1 mg/kg/day (one maternal death at low dose); developmental LOEL=0.4 mg/kg/day (increased incidence of cleft palate), NOEL=0.2 mg/kg/day,
Study h) no maternal or developmental effects reported.
Study i) no maternal or developmental effects reported.
Study j) maternal NOEL<1.5 mg/kg/day (one maternal death at low dose); developmental NOEL<1.5 mg/kg/day (increased frequency of cleft palate at low dose)
Study k) maternal NOEL=0.1 mg/kg/day, maternal LOEL=0.5 mg/kg/day; developmental NOEL=0.05 mg/kg/day, LOEL=0.1 mg/kg/day (increased frequency of cleft palate, also exencephaly at higher doses),
Study l) no maternal or developmental toxicity observed,

Study m) maternal NOEL=0.1 mg/kg/day, LOEL=0.5 mg/kg/day (one maternal death; no other adverse maternal effects noted); developmental NOEL=0.03 mg/kg/day, LOEL=0.1 mg/kg/day (increased frequency of cleft palate),
Study n) NOELs for systemic and reproductive toxicity stated to be ≥0.40 mg/kg/day (effects on adult body weights); developmental NOEL=0.12 mg/kg/day, LOEL=0.40 (reduced postnatal viability and growth, retinal abnormalities),
Study o) maternal NOEL=0.2 mg/kg/day, LOEL=0.4 mg/kg/day (maternal death-frequency not stated); developmental NOEL=0.8 mg/kg/day, LOEL=1.6 mg/kg/day (cleft palate),
Study p) maternal NOEL=0.4 mg/kg/day, LOEL=0.8 mg/kg/day (one maternal death each at 0.8 and 1.6 mg/kg/day); developmental NOEL=0.4 mg/kg/day, LOEL 0.8 mg/kg/day (cleft palate),
Study q) maternal NOEL=0.1 mg/kg/day, LOEL=0.2 mg/kg/day (maternal deaths-one at 0.2 mg/kg/day, 3 each at 0.4 and 0.8 mg/kg/day); developmental NOEL=0.2 mg/kg/day, LOEL=0.4 mg/kg/day (cleft palate),
Study r) maternal NOEL=5 mg/kg/day, LOEL=10 mg/kg/day (3 high-dose dams sacrificed moribund); developmental NOEL=5 mg/kg/day, LOEL=10 mg/kg/day (cleft palate),
Study s) maternal NOEL=3 mg/kg/day, LOEL=6 mg/kg/day; developmental NOEL=1.5 mg/kg/day, LOEL=3 mg/kg/day (cleft palate, clubbed forepaw),
Study t) no maternal or developmental effects were noted,
Study u) no maternal NOEL, maternal LOEL=0.1 mg/kg/day (2 maternal deaths); developmental NOEL=0.1 mg/kg/day, LOEL=0.2 mg/kg/day (cleft palate).

Imazalil (CAS No. 35554-44-0)

Developmental toxicity **was evidenced by decreased litter size and increased dead fetuses in rats, and reduced fetal viability in rabbits.**

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

Supporting documentation for the TRI listing (U.S. EPA, 1993a) states, "In a rat teratology study, increased maternal mortality, decreased litter size, and increased number of dead fetuses were observed in animals administered 40 mg/kg/day (LOEL). The NOEL was 10mg/kg/day (11 [U.S. EPA, 1993c]). The study was classified Core Minimum. Stillbirths and altered live birth index were observed in rats orally administered 80 mg/kg/day days 16 through 22 of gestation and 21 days post gestation (9 [RTECS, 1993]). Altered lactation index was observed in rats orally administered 20 mg/kg/day days 16 though 22 of gestation and 21 days post gestation (9 [RTECS, 1993]). Post implantation loss was observed in rabbits orally administered 0.63 mg/kg/day on days 6 through 18 of gestation (9 [RTECS, 1993]). Altered viability index was observed in rabbits orally administered

2.5 mg/kg/day on days 6 through 18 of gestation (9 [RTECS, 1993]). No other studies showing developmental toxicity effects for imazalil are available."

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

1. **Adequacy of the experimental design:**
   Study a) rat developmental toxicity study. Core grade 'minimum' (U.S. EPA, 1993c),
   Study b) rat developmental toxicity study. Data from this study cannot be considered suitable for hazard assessment as: 1) Maternal toxicity at the high dose of 80 mg/kg/day was extreme (25% mortality), confounding interpretation of the increased stillbirth weight observed at that dose, and 2) The only effect documented at the middle dose of 20 mg/kg/day was decreased survival at weaning, an effect which cannot be attributed to prenatal exposure alone (Thienpont et al., 1981).
   Study c) rabbit developmental toxicity study. The number of animals per dose group meets guideline requirements, but there were only two (rather than three) dose groups. Reporting of methods and results is so incomplete as to limit the usefulness of this study for hazard/risk assessment.
2. **Route of administration:**
   Study a) not stated, but presumably oral, due to designation as meeting guideline requirements,
   Study b) oral, diet (Thienpont et al., 1981),
   Study c) oral, gavage (Thienpont et al., 1981).
3. **The frequency and duration of exposure**:
   Study a) not stated explicitly, but Agency designation as 'core grade minimum' (sufficient for risk assessment) indicates that the study came close to, or met, test guideline requirements of daily treatment on each of gestation days 6-15 (U.S. EPA, 1983a).
   Study b) gestation days 16-22, and 21 days postnatally (Thienpont et al., 1981),
   Study c) gestation days 6-18 (Thienpont et al., 1981).
4. **The numbers of test animals:**
   Study a) not stated explicitly, but Agency designation as 'core grade minimum' (sufficient for risk assessment) indicates that the study came close to, or met, test guideline requirements of 20 pregnant animals per dose group (U.S. EPA, 1983a).,
   Study b) 20 animals per group (Thienpont et al., 1981),
   Study c) 20 animals per group (Thienpont et al., 1981).
5. **The choice of species:**
   Rats and rabbits are species typically used in toxicity testing.
6. **The choice of dosage levels:**
   Study a) 0, 10, 40 mg/kg/day (and possibly one more dose level as well, as required by U.S. EPA test guidelines).
   Study b) 0, 5, 20, and 80 mg/kg/day (Thienpont et al., 1981),

Study c) 0, 0.63, 2.5 mg/kg/day (Thienpont et al., 1981).

7. **Maternal toxicity:**

Study a) LEL=40 mg/kg/day, NOEL=10 mg/kg/day (based on increased maternal mortality and decreased food consumption). These values are identical to those determined for developmental toxicity, which are based on decreased litter size and increased number of dead fetuses.

Study b) There was 25 % maternal mortality in the high-dose group given 80 mg/kg/day. Food consumption during the treatment period was also significantly reduced at this dose (Thienpont et al., 1981).

Study c) Reduced body weight gain was observed at the low dose of 0.63 mg/kg/day, and body weight loss was observed at the high dose of 2.5 mg/kg/day.

N-methylpyrrolidone (NMP) (CAS No. 872-50-4)

Male reproductive toxicity **has been manifested as reductions in the male fertility index in a multigeneration study in rats.**
Female reproductive toxicity **has been manifested as reductions in the female fecundity index in a multigeneration study in rats.**
Developmental toxicity **has been manifested as resorptions, malformations, reduced litter size, reduced postnatal survival and reduced pup body weight in experimental animals.**

The U.S. Environmental Protection Agency (U.S. EPA, 1994a and 1994b) concluded that, "...there is sufficient evidence for listing N-methylpyrrolidone 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 (U.S. EPA, 1993b) states, "In a two-generation reproductive study, there was evidence of reproductive [toxicity] in the F1 generation [in rats] after exposure to 50 mg/kg/day (LOAEL; no NOAEL was established). In addition, exposure to 500 mg/kg/day resulted in an increased incidence of dams with decreased corpora lutea. There was also evidence of developmental toxicity in both generations after exposure to 500 mg/kg/day as demonstrated by reduced litter size, reduced postnatal survival, and reduced pup weight."

"Maternal toxicity (significant reduction in mean body weight gain) was observed in rabbits receiving 175 mg/kg by gavage on days 6 through 18 of gestation (the NOAEL was 55 mg/kg/day). Exposure to 540 mg/kg/day (LOAEL) resulted in developmental toxicity as demonstrated by a significant increase in resorptions, and malformations (misshapen skull bone and cardiovascular malformations). The NOAEL for developmental toxicity was 175 mg/kg/day."

The Agency assessment cited by the TRI supporting documentation (U.S. EPA, 1993d) concluded that, "Reproductive and developmental studies in animals exposed to NMP

showed effects including reduced fertility and reduced mean offspring body weight at birth and throughout lactation. These effects in animals suggest that similar effects may occur in humans. … Exposure to 540 mg/kg resulted in developmental toxicity as demonstrated by a significant increase in resorptions, and malformations (misshapen skull bone and cardiovascular malformations). … There was evidence of reproductive toxicity in the F1 generation after exposure to doses as low as 50 mg/kg, the lowest dose tested. Exposure to 50 mg/kg or more resulted in significant reductions in the male fertility index and the female fecundity index. In addition, exposure to 500 mg/kg resulted in an increased incidence of dams with decreased corpora lutea. There was also an increased incidence of males with atrophied testes, but it is not clear whether the number affected was statistically significant. There was also evidence of developmental toxicity in both generations after exposure to 500 mg/kg as demonstrated by reduced litter size, reduced survival, and reduced pup body weight."

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

1. **Adequacy of the experimental design**:
   Study a) rabbit teratology study,
   Study b) rat multigeneration study. In responding to comments on the TRI proposed rule, U.S. EPA (1994b) concluded, "The review of the 2-generation rat reproductive study by an independent reviewer did not find fault with the entire study but stated that it should not be used for risk assessment purposes. EPA agrees with this judgment but is not using this study for risk assessment purposes, but rather *as an indication of human health hazard* [emphasis added] … The Agency believes that despite the flaws in the study, the data described above clearly show evidence of developmental toxicity. In addition, EPA believes that the body of evidence supports the finding that NMP is uniquely toxic to the developing fetus…".
2. **Route of administration:**
   Study a) oral, gavage
   Study b) oral, diet.
3. **The frequency and duration of exposure**:
   Study a) rabbit gavage teratology study- daily exposure, days 6-18 gestation.
   Study b) rat multigeneration feeding study- 10 days prior to mating and continuing throughout mating, gestation and lactation for both generations.
4. **The numbers of test animals**:
   Study a) 15-20/group.
   Study b) 30/sex/group.
5. **The choice of species**:
   Rabbits are standard test species for developmental toxicology studies and rats are a standard species for reproductive toxicology studies.
6. **The choice of dosage levels**:
   Study a) 0, 55, 175, or 540 mg NMP/kg bw/day.

Study b) 0, 50, 160, 500 mg NMP/kg diet.

7. **Maternal toxicity:**

Study a) maternal toxicity was reported as decreased food intake during dosing and decreased weight gain during dosing at 175 and 540 mg NMP/kg bw/day.

Study b) maternal toxicity was reported as reduced food intake, body weight and/or body weight gain in the F0 and F1 generations at the 500 mg NMP/kg diet dose.

References

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

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