CHEMICALS UNDER CONSIDERATION FOR POSSIBLE LISTING AS CAUSING DEVELOPMENTAL AND REPRODUCTIVE TOXICITY VIA THE AUTHORITATIVE BODIES MECHANISM: 6 CHEMICALS IDENTIFIED BY US EPA

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The 6 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…" Five of the six chemicals in the table below were additions to the TRI list in 1994. The sixth chemical, the delta-8,9-isomer of avermectin B1 (along with its parent compound, Avermectin B1 or Abamectin) was formally

identified by US EPA as causing developmental toxicity in a *Federal Register* notice establishing a pesticide tolerance (US EPA, 1996).

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

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 This database consists of brief summaries of (usually unpublished) data submitted to the Agency in compliance with regulatory requirements.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

Chemical	**CAS No.**	**Endpoints**	**Pesticide status or usage**
Avermectin B1 (abamectin)	71751-41-2 65195-55-3 65195-56-3	Developmental toxicity	Registered in CA
delta-8, 9-isomer of Avermectin B1	None available	Developmental toxicity	Plant photo-degredate of avermectin B1
Nitrapyrin	1929-82-4	Developmental toxicity	Registered in CA
Thiabendazole	148-79-9	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

Note: CAS Nos. for Avermectin pertain specifically to Avermectin B1A, Avermectin B1B, and Avermectin B1 (the mixture of these two components). There is no CAS No. for the delta-8, 9-isomer of avermectin.

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.

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

Developmental toxicity **has been manifested as pup death and cleft palate in experimental animals.**

The US Environmental Protection Agency (US 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 (US EPA, 1993b) 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 [US EPA, 1993d]). Increased retinal folds in weanlings, decreased viability and 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). Based on the NOEL, an RfD of 0.0004 mg/kg/day was derived (74)."

In the final rule document establishing TRI additions (US 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."

US 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. This regulation was established in response to a petition submitted by the Merck Research Laboratories. Scientific data submitted in the petition, along with other relevant material, were evaluated by the Agency.

In the *Federal Register* notice establishing the tolerance (US EPA, 1996), it is stated that, "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 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 . . . to assess acute dietary exposure and determine a margin of exposure (MOE) for the overall US 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."

Additional details of the experimental data are discussed in the Final Rule documents setting Avermectin B1 tolerances for other commodities (US EPA, 1989a and b).

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. US EPA noted that the compound induces developmental toxicity in several species with the mouse being the most sensitive species (74 [US EPA, 1993d]). With respect to the 2-generation rat study described in US EPA (1993), OEHHA notes the following:

1. **Adequacy of the experimental design:** 2-generation rat reproductive toxicity study. Considered adequate for risk assessment purposes by US EPA's Health Effects Peer Review Committee for Developmental and Reproductive Toxicity (US EPA, 1993d).
2. **Route of administration:** oral, gavage**.**
3. **The frequency and duration of exposure:** daily, from pre-mating period of parental generation, for 2 generations.
4. **The numbers of test animals:** 30 rats/sex/dose group.
5. **The choice of species:** Rats are a standard species used in reproductive toxicity studies.
6. **The choice of dosage levels:** 0. 0.05, 0.12, and 0.040 mg/kg/day.
7. **Maternal toxicity:** Significantly reduced adult weights in the high dose group at some time points.

Nitrapyrin (CAS No. 1929-82-4)

***Developmental toxicity* was evidenced by morphological variations and abnormalities 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, 1992]). 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, 1992])."

As described in by US EPA (1992), 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.

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, 1992).
   Study b) reproductive toxicity study in rats - study considered by US EPA in evaluating the developmental and reproductive toxicity of nitrapyrin (US EPA, 1992).
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.
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.

Thiabendazole (CAS No. 148-79-8)

The *developmental toxicity* of thiabendazole has been manifested as decreased fetal weights and increased malformations in mice exposed *in utero*, and decreased offspring viability in rats during the course of a multigeneration reproductive toxicity study.

The US Environmental Protection Agency (US EPA, 1994a and 1994b) concluded that "…there is sufficient evidence for listing thiabendazole 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, 1993b) for the TRI listing states, "Oral administration of 600 mg/kg/day (LEL) to rats on days 6 through 15 of gestation produced cleft palate and open eyes (9 [RTECS, 1993]). Musculoskeletal abnormalities were observed in the offspring of mice orally administered 240 mg/kg on day 9 of gestation (9). Musculoskeletal abnormalities were also observed in the offspring of rats orally administered 296 mg/kg/day on days 8 through 15 of gestation (9). Decreased litter size, and skin abnormalities were observed in the offspring of rats orally administered 667 mg/kg/day on days 8 through 15 of gestation (9). Oral administration of 1,300 mg/kg/day produced musculoskeletal abnormalities and fetal death in the offspring of mice (9). Oral administration of 2,400 mg/kg/day on day 11 of gestation produced craniofacial abnormalities in the offspring of mice (9). The RTECS data cannot be evaluated because of the lack of data.

Decreased male fertility index was observed at 240 mg/kg/day in a 6-week rat oral study (9). Changes in testes weights were observed in male rats orally administered 150 mg/kg/day for 13 weeks (9). In a 3-generation rat reproduction study, decreased viability

index was seen in the offspring of rats administered 40 mg/kg/day (LOEL). The NOEL was 20 mg/kg/day. The study was not classified (24 [US EPA, 1993c])."

Because of EPA's statement concerning their inability to evaluate data as reported by RTECS, OEHHA attempted to retrieve the original articles as cited by RTECS. Only one of these articles could be obtained (Ogata et al., 1984), and details of that study are 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:**
   Study a) the original study was reviewed by OEHHA staff, and found to be comparable to the "core grade minimal" standard formerly used by US EPA.
   Study b) not graded.
2. **Route of administration:**
   Study a) oral, gavage,
   Study b) not specified, probably oral – in the diet.
3. **The frequency and duration of exposure:**
   Study a) daily on each of gestation days 7 - 15; or once on gestation day 9,
   Study b) continuously for 3-generations.
4. **The numbers of test animals:**
   Study a) 20 - 34 pregnant animals per group, per experiment (some doses were replicated, resulting in up to 86 pregnant animals per dose),
   Study b) not stated.
5. **The choice of species:**
   Study a) mouse,
   Study b) rat.
6. **The choice of dosage levels:**
   Study a) 0, 700, 1300, 2400 mg/kg on each of gestation days 7 - 15; or, 0, 30, 60, 62, 120, 129, 240, 269, 480, 558, 670, 804, 965, 1157, 1389, 1667, 2000, 2400 mg/kg on day 9 only,
   Study b) 0, 20, 40, 80 mg/kg/day.
7. **Maternal toxicity:**
   Study a) maternal deaths at highest doses: 61% at 2400 mg/kg, and 13% at 1300 mg/kg on days 6 - 15; 22% at 2400, 10% at 2000, and 6% at 1667 mg/kg on gestation day 9. Dams treated on gestation days 6 - 15 were said to have had lower gestational weight-gains, and higher organ weights than untreated controls, but no data were presented. Dams treated only on gestation day 9 with a dose of 2400, 2000, 1667, or 1389 mg/kg were said to have had higher organ weights (heart, liver, kidney) than did untreated controls. Reductions in fetal weights, and increases in malformation frequency, were seen at doses lower than those causing maternal toxicity.

Study b) not stated.

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, 1997]). 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, 1997]). 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, 1997]). 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, 1997]). 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, 1997]). 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, 1997])."

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.

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