CHEMICALS PRIORITIZED FOR CONSIDERATION FOR DEVELOPMENTAL/REPRODUCTIVE TOXICITY EVALUATION
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency
December 26, 1997

[Note: These are the data summaries referred to in the December 26, 1997 California Regulatory Notice Register notice, "Availability of Final Data Summaries and Priorities for Chemicals With Respect to Their Potential to Cause Birth Defects or Other Reproductive Harm"].

OEHHA prioritizes chemicals for consideration by the Developmental and Reproductive Toxicant (DART) Identification Committee of OEHHA's Science Advisory Board using the process described in the document entitled "Procedure for Prioritizing Candidate Chemicals for Consideration Under Proposition 65 by the State's Qualified Experts". The process involves selecting from chemicals proposed for evaluation by the DART Identification Committee and evaluating the potential levels of developmental/reproductive toxicity concern through review of information available from secondary sources. Secondary sources consulted include: databases such as Reprotox™, Reprotext®, Shepard's Catalog of Teratogenic Agents and RTECS®; publications by bodies such as USEPA, ATSDR, IPCS; and standard texts such as *Reproductive Hazards Of Industrial Chemicals,* and *Chemically Induced Birth Defects*. Data summaries, which provide an overview of the data available in secondary sources, were prepared for each of these chemicals, and each chemical was assigned a draft level of developmental/reproductive toxicological concern. The draft data summaries were released for public comment on September 12, 1997. The priority status for chemicals in this group for which no comments were received have been finalized, as shown below. The priority status for the remaining chemicals in this group will remain draft until the submissions received have been evaluated. At that time, an ammended list of final priorities and data summaries will be released.

CHEMICAL	CASRN	FINAL PRIORITY	FINAL EXPOSURE CONCERN	PAGE
Progesterone	57-83-0	High	Medium	3
Carbamazepine	298-46-4	High	Low	12
Chromium (hexavalent form)	--	Medium	High	19
Formamide	75-12-7	Medium	Low	23
Methyl butyl ketone	591-78-6	Medium	Low	26
1,2-Dichloropropane	78-87-5	Low	Medium	28
Beryllium	--	Insufficient data	Medium	33
Toluene-2,4-diisocyanate	584-84-9	Insufficient data	Medium	36

CASRN = Chemical Abstracts Service Registration Number

PROGESTERONE:
DEVELOPMENTAL/REPRODUCTIVE TOXICITY DATA SUMMARY

Progesterone (CAS No. 57-83-0) was formerly used to treat bleeding during pregnancy, for infertility and for habitual abortion. Birth control pills use synthetic progestins, rather than progesterone. Use of progesterone, along with estrogen, for premenstrual and postmenopausal therapy is a recent development. It is also used as a veterinary drug. Progesterone is on the Proposition 65 list as a carcinogen.

Overview of Developmental/Reproductive Toxicity Concern

There is a **HIGH** level of developmental/reproductive toxicity concern over progesterone due to effects on male and female reproductive toxicity endpoints. Progesterone has been reported to cause effects on female fertility that are consistent with therapeutic use as a contraceptive. Other studies report pregnancy loss in females, reproductive organ toxicity in males, and effects on development of the external genitalia in offspring. These effects have been demonstrated in laboratory animals with supportive data in humans. Progesterone does not appear to produce malformations in laboratory animals when administered during embryogenesis, although some suggestive data for this toxic effect have been produced in human studies.

Developmental toxicity

Concern has been raised in human studies about an association between progestin use in pregnancy and incidence of hypospadia in males and masculinization of the external genitalia in females. Detailed review of the studies would be necessary to determine if progesterone, rather than synthetic progestins, was implicated in the effect and whether confounding factors were controlled. Several large scale studies have failed to find a more general association between progestin use in pregnancy and birth malformations. In rats and guinea pigs, progesterone administration during pregnancy has been reported to cause abnormalities of the urogenital system.

Female reproductive toxicity

Progesterone has a contraceptive effect that can be used therapeutically for birth control. When exposures occur outside of the context of contraceptive therapy, these effects are equivalent to female reproductive toxicity. RTECS cites 40 studies in animals in which progesterone was administered prior to mating; in 28 of these adverse effects on fertility were reported, and in the other 12 adverse effects on reproductive organs or the menstrual cycle were reported. In 15 studies progesterone was administered during pregnancy and adverse effects on fertility, parturition, or postpartum effects were reported. Test species include mice, rats, rabbits, monkeys, pigs, dogs, horses, and sheep/goats. RTECS also cites 7 human studies in which progesterone was administered prior to mating, and effects were reported on fertility, menstrual cycle and reproductive organs.

Male reproductive toxicity

In two studies, progesterone was administered by injection (i.m.) to men. Impotence, breast development and effects on spermatogenesis were reported. In 8 animal studies (including rats, mice, rabbits, guinea pigs, cattle and monkeys) progesterone administered by injection, oral, dermal, or inhalation routes was reported to have toxic effects on the reproductive tract and, in some studies, on spermatogenesis and mating performance. No evaluations of fertility were identified.

Overview of Exposure Concern

There is a **MEDIUM** level of concern over the extent of exposure to progesterone. Progesterone was formerly used therapeutically for bleeding during pregnancy, infertility, habitual abortion and birth control. Currently, birth control

pills use synthetic progestins, rather than progesterone. A recent PDR reported that one IUD uses progesterone. However, progesterone is available for purchase in numerous commercial products that are not sold or regulated as drugs, such as a dermal patch intended for use for menopausal symptoms. The medical literature also reports progesterone use for premenstrual symptoms. FDA allows use of progesterone in cosmetics in amounts not exceeding 5 mg/oz. There is considerable uncertainty concerning the extent of exposure from commercial products. No quantitative data on exposure were located. No production data after 1979 was available from secondary sources.

Data on developmental and reproductive toxicity

NOTE: Unless otherwise indicated, all information, including the citation, is obtained from secondary sources. Full citations of all studies are not provided here. A large number of animal studies were performed in the 1950's and 60's in connection with contraceptive development. These studies were found primarily in RTECS and are described below with text modified from the RTECS entries.

Developmental toxicity in humans

1. Author not provided, as cited in RTECS®.
   Women were exposed via a parenteral route to 600 µg/kg on 67-71d of pregnancy. Toxic effects included: Specific Developmental Abnormalities- urogenital system. Reference: Mayo Clinic Proceedings 33:200, 1958.
2. Author not provided, as cited in RTECS®.
   Women were exposed via an unreported route to 386 mg/kg on weeks 18-34 of pregnancy. Toxic effects included: Specific Developmental Abnormalities- urogenital system. Reference: AMA Journal of Diseases of Children 95:9, 1958.
3. Author not provided, as cited in RTECS®.
   Women were exposed orally to 113 mg/kg in weeks 6-32 of pregnancy. Toxic effects included: Specific Developmental Abnormalities- urogenital system. Reference: Journal of Clinical Endocrinology and Metabolism 19:1369, 1959.
4. Check *et al*. (1986), as cited in Reprotox ™.
   No increase in birth defects was seen in progesterone exposed pregnancies.
5. Hayles and Nolan (1957), as cited in Shepard's Catalog of Teratogenic Agents.
   Two cases were reported of masculinized female infants whose mothers received progesterone (10 mg by injection for 3 days, and up to 60 mg orally).
6. Heinonen *et al.* (1977), as cited in Reprotox ™
   In more than 500 pregnancies with progesterone exposure, no relationship was shown with birth defects in offspring.
7. Kallen *et al*. (1992), as cited in Reprotox ™.
   No increase in birth defects was seen in progesterone exposed pregnancies.
8. Michaelis *et al*. (1983), as cited in Reprotox ™.
   In 186 progesterone exposed pregnancies, no increase in birth defects could be identified.
9. Reessiguie *et al*. (1985), as cited in Reprotox ™.
   No increase in birth defects was seen in progesterone exposed pregnancies.
10. Rock *et al*. (1985), as cited in Shepard's Catalog of Teratogenic Agents, HSDB.
    In 42 pregnancies treated with progesterone suppositories (average total dose 2236), 28% abortions but no malformations were found. In 45 pregnancies treated with i.m. progesterone (average total dose 1009 mg), 5.8% spontaneous abortions and 2 malformations (a unilateral undescended testes and a meningomyelocele) were reported.

Developmental toxicity in animals

1. Adams *et al*. (1961), as cited in IARC.
   Rabbits were given 1 mg via injection on gd 1-4. there were no discernible effects on 6.5 day old blastocysts.

2. Author not provided, as cited in RTECS®.
   Hamsters were exposed via subcutaneous injection to 80 mg/kg on gd 1 . Toxic effects included: Maternal Effects- Parturition; Effects On Newborn- Live birth index. Reference: Biology of Reproduction 6:281, 1972.
3. Author not provided, as cited in RTECS®.
   Mice were exposed via subcutaneous injection to 240 mg/kg on gd 14-16 . Toxic effects included: Effects On Newborn- Biochemical and metabolic; - Delayed effects; Effects On Newborn. Reference: Developmental Pharmacology and Therapeutics 10:385, 1987.
4. Author not provided, as cited in RTECS®.
   Rabbits were exposed via an unreported route to 120 µg /kg on gd 6-29 . Toxic effects included: Effects On Newborn- Weaning or lactation index. Reference: Contraception 17:489, 1978.
5. Author not provided, as cited in RTECS®.
   Rats were exposed via intramuscular injection to 110 mg/kg on gd 1-22. Toxic effects included: - Delayed effects. Effects On Newborn. Reference: Journal of Clinical Investigation 41:710, 1962.
6. Author not provided, as cited in RTECS®.
   Rats were exposed via intramuscular injection to 30 mg/kg on gd 1-6. Toxic effects included: Effects On Embryo Or Fetus- Fetotoxicity. Reference: Folia Biologica 16:343, 1968.
7. Author not provided, as cited in RTECS®.
   Rats were exposed via intramuscular injection to 35 mg/kg on gd 4-20. Toxic effects included: Effects On Embryo Or Fetus- Extra embryonic structures. Reference: Folia Biologica 16:343, 1968.
8. Author not provided, as cited in RTECS®.
   Rats were exposed via parenteral route to 36,300 µg /kg on gd 7-17. Toxic effects included: Specific Developmental Abnormalities- Central nervous system; Effects On Newborn- Biochemical and metabolic. Reference: Brain Research 170:194, 1979.
9. Author not provided, as cited in RTECS®.
   Rats were exposed via a parenteral route to 60 µg /kg on gd 16-19. Toxic effects included: Specific Developmental Abnormalities- Blood and lymphatic systems (including spleen and marrow). Reference: Bulletin of Experimental Biology and Medicine 82:1561, 1976.
10. Author not provided, as cited in RTECS®.
    Rats were exposed via subcutaneous injection to 1 mg/kg on gd 9. Toxic effects included: Effects On Newborn- Behavioral. Reference: Bulletin of Experimental Biology and Medicine 74:1255, 1972.
11. Author not provided, as cited in RTECS®.
    Rats were exposed via subcutaneous injection to 4 mg/kg on gd 9. Toxic effects included: Specific Developmental Abnormalities- Central nervous system. Reference: Bulletin of Experimental Biology and Medicine 74:1255, 1972.
12. Author not provided, as cited in RTECS®.
    Rats were exposed via subcutaneous injection to 420 mg/kg on gd 15-17. Toxic effects included: Effects On Embryo Or Fetus- Fetal death. Reference: Endocrinology 75:145, 1964.
13. Author not provided, as cited in RTECS®.
    Rats were exposed via subcutaneous injection to 9 mg/kg on gd 15-20. Toxic effects included: Specific Developmental Abnormalities- Urogenital system. Reference: Journal of Reproduction and Fertility 5:331, 1963.
14. Foote *et al*. (1968), as cited in IARC, RTECS®.
    Female guinea pigs were administered s.c. injections of 1 mg progesterone from day 18 after mating to day 60. No masculinization was reported in fetuses, but abnormalities (undefined) of the urogenital system were reported.
15. Johnstone and Franklin (1964), as cited in Shepard's Catalog of Teratogenic Agents.
    Mice were injected with 0.25 mg from gd 16-19. No effects on female external genitalia were found.
16. Keeler and Binns (1968), as cited in IARC.
    Ewes were given oral doses of 1.3-1.8 mg on gd 14. No toxic or teratogenic effects on the offspring were found.
17. Lerner *et al*. (1962), as cited in IARC.
    Rats were administered 2.5-10 mg on gd 14-19 and no apparent virilizing effects were reported.

18. McCarthy *et al*. (1977), as cited in IARC.
    Rabbits were administered injections of 0.5, 1.0 and 1.0 mg progesterone 2 days before mating, 1 day before mating or on the day of mating (respectively). This led to embryonic deaths by day 4 of gestation.
19. Piotrowski (1969), as cited in IARC.
    Rabbits were administered injections of 30 mg/kg on gd 8-16. Virilization of fetuses (increased anourethral distance in both sexes) and an excess of males were reported.
20. Revesz *et al*. (1960), as cited in Shepard's Catalog of Teratogenic Agents, IARC.
    Rats were exposed to up to 5-200 mg per day on gd 15-20. No abnormalities of the external genitalia of offspring were found.
21. Suchowsky and Junkmann (1961), as cited in Shepard's Catalog of Teratogenic Agents.
    No virilizing effects were found in rat fetuses exposed to progesterone.
22. Wharton and Scott (1964), as cited in IARC.
    Monkeys (rhesus) were given i.m. doses of 50 mg 5 days/week from gd 24-28 to term. No change in duration of pregnancy and no anomalies in the offspring were reported.

Female reproductive toxicity in humans

1. Author not provided, as cited in RTECS®.
   Women were exposed intravaginally to 210 mg/kg on 3W prior to mating. Toxic effects included: Maternal Effects- Menstrual cycle changes or disorders. Reference: American Journal of Obstetrics and Gynecology 76:626, 1958.
2. Author not provided, as cited in RTECS®.
   Women were exposed intravaginally to 475 µg/kg for 1Y prior to mating. Toxic effects included: Maternal Effects- Menstrual cycle changes or disorders; Effects On Fertility - Female fertility index. Reference: Contraception 13:559, 1976.
3. Author not provided, as cited in RTECS®.
   Women were exposed orally to 100 mg/kg on 20D prior to mating. Toxic effects included: Maternal Effects- Uterus, cervix, vagina. Reference: Fertility and Sterility 16:158, 1965.
4. Author not provided, as cited in RTECS®.
   Women were exposed orally to 120 mg/kg on 20D prior to mating. Toxic effects included: Effects On Fertility - Other measures of fertility. Reference: Vitamins and Hormones 17:307, 1959.
5. Author not provided, as cited in RTECS®.
   Women were exposed orally to 120 mg/kg on 20D prior to mating. Toxic effects included: Maternal Effects- Menstrual cycle changes or disorders; Effects On Fertility - Female fertility index; Effects On Fertility - Other measures of fertility. Reference: Acta Endocrinologica, Supplementum 28:18, 1956.
6. Author not provided, as cited in RTECS®.
   Women were exposed orally to 200 mg/kg on 20D prior to mating. Toxic effects included: Maternal Effects- Uterus, cervix, vagina. Reference: American Journal of Obstetrics and Gynecology 85:427, 1963.
7. Author not provided, as cited in RTECS®.
   Women were exposed via a parenteral route to 32 mg/kg on 3W prior to mating. Toxic effects included: Maternal Effects- Menstrual cycle changes or disorders. Reference: American Journal of Obstetrics and Gynecology 76:626, 1958.

Female reproductive toxicity in animals

1. Author not provided, as cited in RTECS®.
   Dogs were exposed via implant to 360 mg/kg on 34W prior to mating. Toxic effects included: Effects On Fertility - Other measures of fertility. Reference: Fertility and Sterility 36:373, 1981.
2. Author not provided, as cited in RTECS®.
   Goats/Sheep were exposed via intramuscular injection to 2545 µg /kg on 7D prior to mating. Toxic effects included: Maternal Effects- Menstrual cycle changes or disorders; Effects On Fertility - Female fertility index. Reference: Journal of Reproduction and Fertility 4:57, 1962.

3. Author not provided, as cited in RTECS®.
   Goats/Sheep were exposed via subcutaneous injection to 1.273 mg/kg for 14 days. Toxic effects included: Maternal Effects: menstrual cycle changes or disorders; Effects On Fertility - Other measures of fertility. Reference: Endocrinology 43:208, 1948.
4. Author not provided, as cited in RTECS®.
   Hamsters were exposed via a parenteral route to 2400 µg /kg on 3D prior to mating. Toxic effects included: Effects On Fertility - Mating Performance. Reference: Journal of Reproduction and Fertility 37:269, 1974.
5. Author not provided, as cited in RTECS®.
   Hamsters were exposed via subcutaneous injection to 240 µg /kg on 1D prior to mating. Toxic effects included: Effects On Fertility - Other measures of fertility. Reference: Proceedings of the Society for Experimental Biology and Medicine 169:189, 1982.
6. Author not provided, as cited in RTECS®.
   Hamsters were exposed via subcutaneous injection to 32 mg/kg on 1D prior to mating. Toxic effects included: Effects On Fertility - Female fertility index. Reference: Journal of Reproduction and Fertility 16:499, 1968.
7. Author not provided, as cited in RTECS®.
   Mice were exposed via subcutaneous injection to 100 mg/kg on 1D of pregnancy. Toxic effects included: Effects On Fertility - Other measures of fertility. Reference: Archives of Toxicology, Supplement 4:248, 1980.
8. Author not provided, as cited in RTECS®.
   Mice were exposed via subcutaneous injection to 20 mg/kg on gd 6-9. Toxic effects included: Effects On Fertility - Post-implantation mortality; Effects On Embryo Or Fetus- Fetotoxicity. Reference: Oyo Yakuri. Pharmacometrics 15:955, 1978.
9. Author not provided, as cited in RTECS®.
   Mice were exposed via an unreported route to 10 mg/kg on 1D prior to mating. Toxic effects included: Effects On Fertility - Other measures of fertility. Reference: Fertility and Sterility 12:346, 1961.
10. Author not provided, as cited in RTECS®.
    Monkeys were exposed via inhalation to 4 µg /kg on 10D prior to mating. Toxic effects included: Effects On Fertility - Other measures of fertility. Reference: Nature 270:532, 1977.
11. Author not provided, as cited in RTECS®.
    Monkeys were exposed via intramuscular injection to 12 mg/kg on 8D prior to mating. Toxic effects included: Effects On Fertility - Other measures of fertility. Reference: Fertility and Sterility 39(Suppl):419, 1983.
12. Author not provided, as cited in RTECS®.
    Monkeys were exposed via subcutaneous injection to 900 µg /kg on 9D prior to mating. Toxic effects included: Effects On Fertility - Other measures of fertility. Reference: Endocrinology 90:257, 1972.
13. Author not provided, as cited in RTECS®.
    Pigs were exposed via subcutaneous injection to 1667 µg /kg on 1D prior to mating. Toxic effects included: Effects On Fertility - Other measures of fertility. Reference: Journal of Reproduction and Fertility 17:227, 1968.
14. Author not provided, as cited in RTECS®.
    Pigs were exposed via subcutaneous injection to 2250 µg /kg on gd 1-5. Toxic effects included: Effects On Fertility - Other measures of fertility. Reference: Journal of Animal Science 18:163, 1959.
15. Author not provided, as cited in RTECS®.
    Rabbits were exposed via intramuscular injection to 2500 mg/kg on 2D prior to mating. Toxic effects included: Effects On Fertility - Female fertility index; Effects On Fertility - Pre-implantation mortality; Specific Developmental Abnormalities- Other developmental abnormalities. Reference: Biology of Reproduction 14:451, 1976.
16. Author not provided, as cited in RTECS®.
    Rabbits were exposed via intramuscular injection to 8 mg/kg on gd 2-9. Toxic effects included: Effects On Fertility - Pre-implantation mortality. Reference: Australian Journal of Biological Sciences 28:291, 1975.
17. Author not provided, as cited in RTECS®.
    Rabbits were exposed via an intrauterine route to 105 µg /kg on 21D prior to mating. Toxic effects included: Effects On Fertility - Female fertility index. Reference: Contraception 17:465, 1978.

18. Author not provided, as cited in RTECS®.
    Rabbits were exposed via an intrauterine route to 260 µg /kg on 21D prior to mating and gd 1-31. Toxic effects included: Effects On Fertility - Post-implantation mortality. Reference: Contraception 17:465, 1978.
19. Author not provided, as cited in RTECS®.
    Rabbits were exposed via an intrauterine route to 684 µg /kg on 14D prior to mating and gd 1-10. Toxic effects included: Effects On Fertility - Pre-implantation mortality. Reference: American Journal of Obstetrics and Gynecology 109:536, 1971.
20. Author not provided, as cited in RTECS®.
    Rabbits were exposed orally to 1 mg/kg on 1D prior to mating and gd 1. Toxic effects included: Effects On Fertility - Other measures of fertility. Reference: Endocrinology 79:939, 1966.
21. Author not provided, as cited in RTECS®.
    Rabbits were exposed orally to 100 mg/kg on 1D prior to mating. Toxic effects included: Effects On Fertility - Mating Performance; Effects On Fertility - Other measures of fertility. Reference: Acta Endocrinologica, Supplementum 73:17, 1963.
22. Author not provided, as cited in RTECS®.
    Rabbits were exposed via dermal route to 1 mg/kg on 1D prior to mating. Toxic effects included: Effects On Fertility - Other measures of fertility. Reference: Steroids 5:699, 1965.
23. Author not provided, as cited in RTECS®.
    Rabbits were exposed via dermal route to 500 µg /kg on 1D prior to mating. Toxic effects included: Effects On Fertility - Pre-implantation mortality. Reference: Steroids 7:341, 1966.
24. Author not provided, as cited in RTECS®.
    Rabbits were exposed via subcutaneous injection to 100 µg /kg on 1D prior to mating. Toxic effects included: Maternal Effects- Ovaries, fallopian tubes. Reference: Journal of Physiology 181:568, 1965.
25. Author not provided, as cited in RTECS®.
    Rabbits were exposed via subcutaneous injection to 150 µg /kg on 1D prior to mating. Toxic effects included: Effects On Fertility - Mating Performance. Reference: Acta Endocrinologica, Supplementum 73:3, 1963.
26. Author not provided, as cited in RTECS®.
    Rabbits were exposed via subcutaneous injection to 300 µg /kg on 2D prior to mating and gd 1. Toxic effects included: Effects On Fertility - Pre-implantation mortality. Reference: American Journal of Obstetrics and Gynecology 117:167, 1973.
27. Author not provided, as cited in RTECS®.
    Rabbits were exposed via subcutaneous injection to 50 µg /kg on 1D prior to mating. Toxic effects included: Effects On Fertility - Other measures of fertility. Reference: Acta Endocrinologica, Supplementum 73:3, 1963.
28. Author not provided, as cited in RTECS®.
    Rats were exposed via subcutaneous injection to 500 µg /kg on 2D prior to mating. Toxic effects included: Effects On Fertility. Reference: Endocrinologica, Supplementum 105:7, 1966.
29. Author not provided, as cited in RTECS®.
    Rats were exposed intracerebrally to 250 µg /kg on 1D prior to mating. Toxic effects included: Effects On Fertility - Other measures of fertility. Reference: Journal of Reproduction and Fertility 27:445, 1971.
30. Author not provided, as cited in RTECS®.
    Rats were exposed via intramuscular injection to 900 µg /kg on gd 6-14. Toxic effects included: Effects On Fertility - Post-implantation mortality. Reference: Folia Biologica 16:343, 1968.
31. Author not provided, as cited in RTECS®.
    Rats were exposed orally to 25 mg/kg on 1D prior to mating. Toxic effects included: Effects On Fertility - Mating Performance. Reference: Fertility and Sterility 5:282, 1954.
32. Author not provided, as cited in RTECS®.
    Rats were exposed orally to 50 mg/kg on 1D prior to mating. Toxic effects included: Effects On Fertility - Mating Performance. Reference: Acta Endocrinologica, Supplementum 28:18, 1956.
33. Author not provided, as cited in RTECS®.
    Rats were exposed via subcutaneous injection to 7 mg/kg on gd 10-16. Toxic effects included: Effects On Fertility - Abortion. Reference: Journal of Physiology 164:138, 1962.

34. Author not provided, as cited in RTECS®.
Cattle were exposed via intramuscular injection to 1700 µg /kg on 39-41W of pregnancy. Toxic effects included: Maternal Effects- Parturition. Reference: Theriogenology 20:267, 1983.
35. Author not provided, as cited in RTECS®.
Dogs were exposed via implant to 600 mg/kg on week 60 prior to mating. Toxic effects included: Maternal Effects- Breasts, lactation (prior to or during pregnancy). Reference: Fertility and Sterility 36:373, 1981.
36. Author not provided, as cited in RTECS®.
Dogs were exposed via subcutaneous injection to 16 mg/kg on 5D prior to mating. Toxic effects included: Maternal Effects- Uterus, cervix, vagina. Reference: Contraception 12:529, 1975.
37. Author not provided, as cited in RTECS®.
Goats/Sheep were exposed via subcutaneous injection to 1273 µg /kg on 14D prior to mating. Toxic effects included: Maternal Effects. Reference: Endocrinology 43:208, 1948.
38. Author not provided, as cited in RTECS®.
Hamsters were exposed via subcutaneous injection to 2 mg/kg on 1D prior to mating. Toxic effects included: Maternal Effects- Uterus, cervix, vagina. Reference: Journal of Reproduction and Fertility 42:341, 1975.
39. Author not provided, as cited in RTECS®.
Horses were exposed via a parenteral route to 16667 µg /kg on 45-47W of pregnancy. Toxic effects included: Maternal Effects- Parturition. Reference: Journal of Reproduction and Fertility, Supplement 23:637, 1975.
40. Author not provided, as cited in RTECS®.
Mice were exposed via implant to 3 g/kg on 5D prior to mating. Toxic effects included: Maternal Effects- Uterus, cervix, vagina. Reference: Contraception 16:357, 1977.
41. Author not provided, as cited in RTECS®.
Mice were exposed via subcutaneous injection to 1500 µg /kg on 3D prior to mating. Toxic effects included: Maternal Effects- Uterus, cervix, vagina. Reference: Journal of Reproduction and Fertility 5:331, 1963.
42. Author not provided, as cited in RTECS®.
Monkeys were exposed intravaginally to 17155 µg /kg on 52W prior to mating. Toxic effects included: Maternal Effects- Ovaries, fallopian tubes. Reference: Contraception 20:339, 1979.
43. Author not provided, as cited in RTECS®.
Monkeys were exposed intravaginally to 85410 µg /kg on 52W prior to mating. Toxic effects included: Maternal Effects- Uterus, cervix, vagina; Effects On Fertility - Other measures of fertility. Reference: Contraception 20:339, 1979.
44. Author not provided, as cited in RTECS®.
Monkeys were exposed via subcutaneous injection to 2600 µg /kg on 13D prior to mating. Toxic effects included: Maternal Effects- Menstrual cycle changes or disorders. Reference: Proceedings of the Society for Experimental Biology and Medicine 94:298, 1957.
45. Author not provided, as cited in RTECS®.
Pigs were exposed via a parenteral route to 5833 µg /kg on 14D prior to mating. Toxic effects included: Maternal Effects- Menstrual cycle changes or disorders. Reference: Journal of Animal Science 10:665, 1951.
46. Author not provided, as cited in RTECS®.
Pigs were exposed via subcutaneous injection to 40 mg/kg on 16D prior to mating. Toxic effects included: Maternal Effects- Ovaries, fallopian tubes. Reference: Journal of Reproduction and Fertility 19:541, 1969.
47. Author not provided, as cited in RTECS®.
Rabbits were exposed via intramuscular injection to 8 mg/kg on 25-32D of pregnancy. Toxic effects included: Maternal Effects- Postpartum. Reference: Journal of Animal Science 42:131, 1976.
48. Author not provided, as cited in RTECS®.
Rabbits were exposed via subcutaneous injection to 50 µg /kg on 5D prior to mating. Toxic effects included: Maternal Effects- Uterus, cervix, vagina. Reference: Anatomical Record 142:469, 1962.
49. Author not provided, as cited in RTECS®.
Rats were exposed via implant to 250 µg /kg on 2D after birth. Toxic effects included: Maternal Effects- Postpartum. Reference: Biology of Reproduction 7:109, 1972.

50. Author not provided, as cited in RTECS®.
    Rats were exposed via implant to 30 mg/kg on 24D prior to mating. Toxic effects included: Maternal Effects- Ovaries, fallopian tubes. Reference: Biology of Reproduction 2:315, 1970.
51. Author not provided, as cited in RTECS®.
    Rats were exposed via a parenteral route to 8750 µg /kg on 7D prior to mating. Toxic effects included: Maternal Effects- Uterus, cervix, vagina. Reference: Journal of Experimental Medicine 102:347, 1955.
52. Author not provided, as cited in RTECS®.
    Rats were exposed via subcutaneous injection to 20 mg/kg on gd 23. Toxic effects included: Maternal Effects- Parturition; Maternal Effects- Postpartum; Effects On Newborn- Growth statistics. Reference: Proceedings of the Society for Experimental Biology and Medicine 145:1047, 1974.
53. Author not provided, as cited in RTECS®.
    Rats were exposed via an unreported route to 100 mg/kg on gd 20-24. Toxic effects included: Maternal Effects- Parturition. Reference: Biology of Reproduction 16:479, 1977.
54. Author not provided, as cited in RTECS®.
    Rats were exposed orally to 700 mg/kg on day 14 prior to mating. Toxic effects included: Maternal Effects- Uterus, cervix, vagina. Reference: Fertility and Sterility 24:284, 1973.
55. Author not provided, as cited in RTECS®.
    Rats were exposed via subcutaneous injection to 188 mg/kg on 30D prior to mating. Toxic effects included: Maternal Effects- Menstrual cycle changes or disorders. Reference: Proceedings of the Society for Experimental Biology and Medicine 108:3, 1961.

Male reproductive toxicity in humans

1. Author not provided, as cited in RTECS®.
   Men were exposed via intramuscular injection to 15 mg/kg on 21D prior to mating. Toxic effects included: PATERNAL EFFECTS - Impotence. Reference: Annals of the New York Academy of Sciences 71:649, 1958.
2. Author not provided, as cited in RTECS®.
   Men were exposed via intramuscular injection to 50 mg/kg on 70D prior to mating. Toxic effects included: PATERNAL EFFECTS - Spermatogenesis; PATERNAL EFFECTS - Breast Development. Reference: Annals of the New York Academy of Sciences 71:649, 1958.

Male reproductive toxicity in animals

1. Author not provided, as cited in RTECS®.
   Cattle were exposed via subcutaneous injection to 3 mg/kg on 30D prior to mating. Toxic effects included: PATERNAL EFFECTS - Spermatogenesis; PATERNAL EFFECTS - Other effects on. Reference: Endocrinology 77:203, 1965.
2. Author not provided, as cited in RTECS®.
   Guinea pigs were exposed via intramuscular injection to 1480 mg/kg on 70D prior to mating. Toxic effects included: PATERNAL EFFECTS - Testes, epididymis, sperm duct; Effects On Fertility - Mating Performance. Reference: Nature 209:1322, 1966.
3. Author not provided, as cited in RTECS®.
   Mice were exposed via subcutaneous injection to 2400 mg/kg on 20D prior to mating. Toxic effects included: PATERNAL EFFECTS - Testes, epididymis, sperm duct. Reference: Endocrinology 28:129, 1941.
4. Author not provided, as cited in RTECS®.
   Monkeys were exposed via inhalation to 30 µg /kg/30 min on 60D prior to mating. Toxic effects included: PATERNAL EFFECTS - Spermatogenesis; PATERNAL EFFECTS - Testes, epididymis, sperm duct. Reference: Biology of Reproduction 22:935, 1980.
5. Author not provided, as cited in RTECS®.
   Rabbits were exposed via subcutaneous injection to 70 mg/kg on 14D prior to mating. Toxic effects included: PATERNAL EFFECTS - Spermatogenesis; PATERNAL EFFECTS - Other effects on. Reference: Nature 204:261, 1964.

6. Author not provided, as cited in RTECS®.
   Rats were exposed via intramuscular injection to 200 mg/kg on 48D prior to mating. Toxic effects included: PATERNAL EFFECTS - Testes, epididymis, sperm duct; PATERNAL EFFECTS - Prostate, seminal vesicle. Cowper's gland, accessory glands; PATERNAL EFFECTS - Other effects on. Reference: Indian Journal of Experimental Biology 5:45, 1967.
7. Author not provided, as cited in RTECS®.
   Rats were exposed orally to 180 mg/kg on 9D prior to mating. Toxic effects included: PATERNAL EFFECTS - Prostate, seminal vesicle. Cowper's gland, accessory glands. Reference: Proceedings of the Society for Experimental Biology and Medicine 100:540, 1959.
8. Author not provided, as cited in RTECS®.
   Rats were exposed dermally to 240 mg/kg on 30D prior to mating. Toxic effects included: PATERNAL EFFECTS - Prostate, seminal vesicle. Cowper's gland, accessory glands; PATERNAL EFFECTS - Prostate, seminal vesicle. Cowper's gland, accessory glands. Reference: Steroids 10:687, 1967.

Secondary Sources

HSDB. Hazardous Substances Data Bank. National Library of Medicine. (TOMES JULY 31, 1995)

IARC. International Agency for Research on Cancer (IARC, 1979). *Monographs On The Evaluation Of Carcinogenic Risk To Humans, Volume 21*. World Health Organization.

Reprotox™. Dr. Anthony M. Scialli. (TOMES APRIL 30, 1995)

RTECS®. Registry of Toxic Effects of Chemical Substances. National Institute of Occupational Safety And Health. (TOMES APRIL 30, 1995)

Shepard's Catalog of Teratogenic Agents. Dr. Thomas H. Shepard. (TOMES APRIL 30, 1995)

CARBAMAZEPINE:
DEVELOPMENTAL/REPRODUCTIVE TOXICITY DATA SUMMARY

Carbamazepine (Tegretol, 5H-Dibenz(b,f)azepine-5-carboxamide; CAS no. 298-46-4) is a iminostilbine used as an anticonvulsant, primarily in the treatment of grand mal seizures, and as a specific analgesic for trigeminal neuralgia. It has the chemical formula $C_{15}H_{12}N_2O$. Carbamazepine is an FDA pregnancy category C drug, and is not a Proposition 65 carcinogen. (Note: the compound 6H-Dibenz(b,f)oxiren(d)azepine-6-carboxamide, 1a, 10b-dihydro-; CAS no. 36507-30-9, chemical formula $C_{15}H_{12}N_2O$ is also identified as carbamazepine in some sources.)

Overview of Developmental/Reproductive Toxicity Concern

There is a **HIGH** level of developmental/reproductive toxicity concern over carbamazepine, due to reports of its developmental toxicity from clinical and epidemiological human studies, and supporting animal studies. The incidence of malformations in children of women taking carbamazepine during pregnancy is reported to be 2-3 times that in general population. Very few studies have investigated effects of carbamazepine on male or female reproduction.

Developmental toxicity

A large body of data from human clinical and epidemiological studies and reports indicates an association between carbamazepine treatment during pregnancy and adverse developmental effects, including the possible existence of a fetal carbamazepine syndrome. Similar results from studies in rats and mice support this association.

Female reproductive toxicity

No data on human female reproductive toxicity associated with carbamazepine were identified. A small number of studies in animals have reported associations between carbamazepine exposure and parameters such as pre- and post-implantation mortality, litter size and live birth index.

Male reproductive toxicity

A single study in human males involving semen analysis revealed no abnormalities other than elevated semen fructose levels, which were considered unlikely to indicate an effect on fertility. A study in rats exposed by injection for 3 months post weaning revealed lowered epididymal sperm count but no effect on fertility.

Overview of Exposure Concern

There is a **LOW** level of concern over exposure to carbamazepine, since it is a drug that is available only under prescription. The therapeutic dose range for carbamazepine is 200-1200 mg/day, resulting in plasma levels of 4-8 μg/ml.

Data on developmental and reproductive toxicity

NOTE: Unless otherwise indicated, all information, including the citation, is obtained from secondary sources. Full citations of all studies are not provided here.

Developmental toxicity in humans

1. Author not provided. (Eur. J. Pediat. 150:136. 1990), as cited in RTECS®.
   Women were exposed to a total of 3492 mg/kg throughout pregnancy and to day 17 postnatal. Undefined biochemical and metabolic effects on the newborns were reported.
2. Author not provided. (Neuropediatrics 16:167. 1985), as cited in RTECS®.
   Women were exposed to a total of 3492 mg/kg from weeks 26-42 of pregnancy. Undefined abnormalities of skin and appendages in offspring were reported.
3. Author not provided. (Obstet. Gynecol. 82:705. 1993), as cited in RTECS®.
   Women were exposed to a total of 96 mg/kg for 3 weeks during pregnancy (period undefined). Undefined abnormalities of the CNS in offspring were reported.
4. Battino *et al.* (1992), as cited in TERIS.
   Several cohort studies, each involving <100 epileptic women treated with carbamazepine during the first trimester, showed a frequency of malformations 2-3 times higher than normal populations. (This was similar to the incidence in populations of epileptics treated with other anticonvulsants). (See also Lindhout *et al.* (1982); Lindhout *et al.* (1992); Kaneko *et al.* (1988); Nakane *et al.* (1980); Starreveld-Zimmerman *et al.* (1973)).
5. Bertollini *et al*. (1985), as cited in TERIS.
   No association with maternal carbamazepine treatment during pregnancy in 7607 infants with congenital anomalies in a case-control study.
6. Bertollini *et al*. (1987), as cited in Shepard's Catalog of Teratogenic Agents, Schardein.
   Reduced head circumference, body weight and length in offspring of mothers who were treated with carbamazepine during pregnancy.
7. Bod (1989), as cited in TERIS.
   Features of a fetal carbamazepine syndrome of growth and developmental delay associated with minor facial and other anomalies were seen in most of 35 children born to women treated with carbamazepine monotherapy. Malformations included hypoplastic fingernails and craniofacial abnormalities (upslanting eyes, long philtrum, short nose); no increase in major birth defects was observed. The basis for these results has been questioned by some. (See also Jones *et al.* (1989a); Gladstone *et al.* (1992); Lindhout *et al.* (1992b); Rosa (1991)).
8. Czeizel *et al.* (1992), as cited in Reprotox™, TERIS.
   No association with maternal carbamazepine use was found in a Hungarian case-control study of 10,698 infants with congenital malformations.
9. Gaily *et al.* (1990a), as cited in TERIS.
   Normal intellectual function and IQ was reported for children aged 5.5 years who had had significantly reduced head circumference at birth, and who's mothers had been treated with Carbamazepine during pregnancy. Head circumference was not significantly decreased at age 5.5 years. (See also Hiilesma *et al*., (1981); Gaily *et al*., (1988); (1990b)).
10. Gaily *et al.* (1990b), as cited in TERIS.
    Normal intellectual function and IQ was reported for children aged 5.5 years who had had significantly reduced head circumference at birth, and who's mothers had been treated with Carbamazepine during pregnancy. Head circumference was not significantly decreased at age 5.5 years. (See also Hiilesma *et al*., (1981); Gaily *et al*., (1988); (1990a)).
11. Gaily *et al.* (1988), as cited in TERIS.
    Normal intellectual function and IQ was reported for children aged 5.5 years who had had significantly reduced head circumference at birth, and who's mothers had been treated with Carbamazepine during pregnancy. Head circumference was not significantly decreased at age 5.5 years. (See also Hiilesma *et al*., (1981); Gaily *et al*., (1990a); (1990b)).
12. Gladstone *et al.* (1992), as cited in Reprotox™, Shepard's Catalog Of Teratogenic Agents, TERIS.
    In a prospective study, one of 23 women treated with carbamazepine give birth to an infant with myleomeningocele. (See also Bod (1989); Jones *et al.* (1989a); Lindhout *et al.* (1992b); Rosa (1991)).
    Hiilesmaa *et al.* (1981), as cited in Shepard's Catalog of Teratogenic Agents, Schardein, TERIS.
    Reduced head circumference, but no increase in congenital anomalies or mental retardation, in offspring of mothers who were treated with carbamazepine during pregnancy.
13. Jones *et al.* (1989a), as cited in RTECS®, Reprotox™, Shepard's Catalog of Teratogenic Agents, Schardein, TERIS.

Features of a fetal carbamazepine syndrome of growth and developmental delay associated with minor facial and other anomalies were seen in most of 35 children born to women treated with carbamazepine monotherapy. Malformations included hypoplastic fingernails and craniofacial abnormalities (upslanting eyes, long philtrum, short nose); no increase in major birth defects was observed. The basis for these results has been questioned by some. (See also Bod (1989); Gladstone *et al.* (1992); Lindhout *et al.* (1992b); Rosa (1991)).

14. Jones *et al.* (1989b), as cited in TERIS.
    Rebuttal to the criticisms offered to Jones *et al.* (1989a).
15. Jones *et al.* (1988), as cited in Reprotox™, Schardein.
    Increased risk to the unborn baby and association with a number of abnormalities similar to those seen in the fetal hydantoin syndrome suggested. (Abstract only).
16. Kallen *et al.* (1989), as cited in TERIS.
    A putative association between gestational carbamazepine exposure and neural tube defects was not statistically confirmed. (See also Bertollini *et al.* (1985); Czeizel *et al.* (1992); Omtzigt *et al.* (1992)).
17. Kallen (1994), as cited in Reprotox™, Shepard's Catalog of Teratogenic Agents.
    A nested case-control study found an association between carbamazepine treatment during pregnancy and spina bifida, with an odds ration of 6.0 (C.I. 0.9 - 56.9). Although not statistically significant, this finding was considered very suggestive by the authors of the study.
18. Kaneko *et al.* (1988), as cited in TERIS.
    Several cohort studies, each involving <100 epileptic women treated with carbamazepine during the first trimester, showed a frequency of malformations 2-3 times higher than normal populations. (This was similar to the incidence in populations of epileptics treated with other anticonvulsants). (See also Battino *et al.* (1992); Lindhout *et al.* (1982); Lindhout *et al.* (1992); Nakane *et al.* (1980); Starreveld-Zimmerman *et al.* (1973)).
    Higher frequencies of anomalies have also been observed among infants born to mothers treated with carbamazepine in combination with other anticonvulsants, especially valproic acid. (See also Lindhout *et al.* (1984); Kaneko *et al.* (1988); Shakir and Abdulwahab (1991); Kaneko *et al.* (1992)).
19. Kaneko *et al.* (1986), as cited in Shepard's Catalog of Teratogenic Agents.
    Statistically significant increase in malformations in offspring of women treated with carbamazepine and another drug (except valproic acid).
    Kaneko *et al.* (1992), as cited TERIS.
    Higher frequencies of anomalies have been observed among infants born to mothers treated with carbamazepine in combination with other anticonvulsants, especially valproic acid. (See also Lindhout *et al.* (1984); Kaneko *et al.* (1988); Shakir and Abdulwahab (1991)).
20. Legido *et al.* (1991), as cited in Reprotox™, Schardein.
    Case report of effects that included some or all of the following: spina bifida, rib anomalies, optic nerve hypoplasia, retardation. No comparison was done with successful pregnancies in the same time span. (See also West *et al.* (1990); Vestermark and Vestermark (1991); Oakeshott and Hunt (1991)).
21. Lindhout *et al.* (1984), as cited in Reprotox™, TERIS.
    Higher frequencies of anomalies have been observed among infants born to mothers treated with carbamazepine in combination with other anticonvulsants, especially valproic acid. This increased risk may putatively be due to an accumulation of carbamazepine epoxide. (See also Kaneko *et al.* (1988); Shakir and Abdulwahab (1991); Kaneko *et al.* (1992)).
22. Lindhout *et al.* (1982), as cited in TERIS.
    Several cohort studies, each involving <100 epileptic women treated with carbamazepine during the first trimester, showed a frequency of malformations 2-3 times higher than normal populations. (This was similar to the incidence in populations of epileptics treated with other anticonvulsants). (See also Battino *et al.* (1992); Lindhout *et al.* (1992); Kaneko *et al.* (1988); Nakane *et al.* (1980); Starreveld-Zimmerman *et al.* (1973)).
23. Lindhout *et al.* (1992a), as cited in TERIS.
    Several cohort studies, each involving <100 epileptic women treated with carbamazepine during the first trimester, showed a frequency of malformations 2-3 times higher than normal populations. (This was similar to the incidence in populations of epileptics treated with other anticonvulsants). (See also Battino *et al.* (1992); Lindhout *et al.* (1982); Kaneko *et al.* (1988); Nakane *et al.* (1980); Starreveld-Zimmerman *et al.* (1973)).
24. Lindhout *et al.* (1992b), as cited in TERIS.
    Increased frequency of neural tube defects suggested in offspring of women treated with carbamazepine during

pregnancy. (See also Bod (1989); Gladstone *et al.* (1992); Jones *et al.* (1989a); Lindhout *et al.* (1992b); Rosa (1991)).

25. Millar and Nevin (1973), as cited in Shepard's Catalog of Teratogenic Agents.
    Case report of an infant with myelomeningocele that was gestationally exposed to phenobarbital and carbamazepine.
26. Nakane *et al.* (1980), as cited in Schardein, TERIS.
    Several cohort studies, each involving <100 epileptic women treated with carbamazepine during the first trimester, showed a frequency of malformations 2-3 times higher than normal populations. (This was similar to the incidence in populations of epileptics treated with other anticonvulsants). (See also Battino *et al.* (1992); Lindhout *et al.* (1982); Lindhout *et al.* (1992); Kaneko *et al.* (1988); Starreveld-Zimmerman *et al.* (1973)).
27. Niebyl *et al.* (1979), as cited in Reprotox™, Schardein.
    No obvious teratogenic potential of the drug was noted in humans (no information provided on the type of study).
28. Oakeshott and Hunt (1991), as cited in Reprotox™
    Case report of effects that included some or all of the following: spina bifida, rib anomalies, optic nerve hypoplasia, retardation. No comparison was done with successful pregnancies in the same time span. (See also Legido *et al.* (1991); West *et al.* (1990); Vestermark and Vestermark (1991)).
29. Omtzigt *et al.* (1992), as cited in TERIS.
    A putative association between gestational carbamazepine exposure and neural tube defects was not statistically confirmed. (See also Bertollini *et al.* (1985); Czeizel *et al.* (1992); Kallen *et al.* (1989)).
30. Rosa (1991), as cited in Reprotox™, Shepard's Catalog of Teratogenic Agents, Schardein, TERIS.
    Increased frequency of neural tube defects suggested in offspring of women treated with carbamazepine during pregnancy; 2 of 107 infants born to women who took carbamazepine during pregnancy had spina bifida (estimated risk from this and other data was 1%). (See also Bod (1989); Gladstone *et al.* (1992); Jones *et al.* (1989a); Lindhout *et al.* (1992b)).
31. Shakir and Abdulwahab (1991), as cited in TERIS.
    Higher frequencies of anomalies have been observed among infants born to mothers treated with carbamazepine in combination with other anticonvulsants, especially valproic acid. (See also Kaneko *et al.* (1992); Lindhout *et al.* (1984); Kaneko *et al.* (1988)).
32. Starreveld-Zimmerman *et al.* (1973), as cited in TERIS.
    Several cohort studies, each involving <100 epileptic women treated with carbamazepine during the first trimester, showed a frequency of malformations 2-3 times higher than normal populations. (This was similar to the incidence in populations of epileptics treated with other anticonvulsants). (See also Battino *et al.* (1992); Lindhout *et al.* (1982); Lindhout *et al.* (1992); Kaneko *et al.* (1988); Nakane *et al.* (1980)).
33. Van Allen *et al.* (1988), as cited in Shepard's Catalog of Teratogenic Agents, Schardein, TERIS.
    Use of carbamazepine during pregnancy poses a risk of a developmental syndrome including round faces, upslanting palpebral fissures, hypertelorism, hypoplastic nasal bridge, short upturned nose, flamus nevus, large anterior fontanel and variable nail hypoplasia.
34. van der Pol *et al.* (1991), as cited in TERIS.
    The frequency of neurological dysfunction and school problems were no greater than expected in offspring of epileptic women treated with carbamazepine during pregnancy.
35. Vestermark and Vestermark (1991), as cited in Reprotox™, Schardein.
    Case reports of effects that included some or all of the following: spina bifida, rib anomalies, optic nerve hypoplasia, retardation. No comparison was done with successful pregnancies in the same time span. (See also Legido *et al.* (1991); West *et al.* (1990); Oakeshott and Hunt (1991)).
36. West *et al.* (1990), as cited in Reprotox™.
    Case report of effects that included some or all of the following: spina bifida, rib anomalies, optic nerve hypoplasia, retardation. No comparison was done with successful pregnancies in the same time span. (See also Legido *et al.* (1991); Vestermark and Vestermark (1991); Oakeshott and Hunt (1991)).

Developmental toxicity in animals

1. Author not provided. (E. Afr. Med. J. 60:407. 1983), as cited in RTECS®.
   Rats were administered a total of 765 mg/kg orally over the period of gd 9-17 (presumably 85mg/kg/d). Fetal death and fetotoxicity (undefined) were reported. (Also cited under animal female reproductive toxicity).
2. Author not provided. (Terat. Carcinog. Mutag. 6:393. 1986), as cited in RTECS®.
   Male and female mice were administered a total of 92 g/kg orally over the period beginning 2 weeks prior to mating and continuing to gd 18 in females. Effects on pre- and post-implantation mortality were reported, as well as fetotoxicity (undefined). (Also cited under animal female reproductive toxicity).
3. Author not provided. (Teratology 23:33A. 1981), as cited in RTECS®.
   Mice were administered a total of 765 mg/kg orally over the period of gd 7-12. Craniofacial abnormalities including eye, ear, nose and tongue were reported. (Abstract only).
4. Author not provided. (Teratology 29(3):33A. 1984), as cited in RTECS®.
   Female rats were administered a total of 3600 mg/kg orally over the period beginning 2 weeks prior to mating and continuing to gd 22. Effects on the live birth index, weaning/lactation index and growth statistics in the newborns were reported. (Abstract only). (Also cited under animal female reproductive toxicity).
5. Finnell and Dansky (1991), as cited in TERIS.
   Offspring of mice treated with 5-100 times the therapeutic dosage had CNS and other anomalies. Teratology studies in mice exposed to 2-10 human therapeutic doses produces inconsistent results. (No information on period, duration or route of exposure).
6. Finnell *et al.* (1986), as cited in TERIS.
   Offspring of mice treated with 5-100 times the therapeutic dosage had CNS and other anomalies (no information on period, duration or route of exposure).
7. Fritz *et al.* (1976), as cited in TERIS.
   Teratology studies in mice exposed to 2-10 human therapeutic doses produces inconsistent results (no information on period, duration or route of exposure).
8. McElhatton and Sullivan (1977), as cited in Schardein.
   Reported to be teratogenic in mice (no information on dose, route, period or duration of exposure).
9. Paulson and Paulson (1981), as cited in Shepard's Catalog of Teratogenic Agents.
   Rats exposed to 250 mg/kg/d (period and route not given) had an incidence of 2/135 malformed fetuses.
10. Paulson *et al.* (1979), as cited in RTECS®, TERIS.
    Offspring of mice treated orally with a total of 9984 mg/kg over gd 8-13 had fetotoxicity described in TERIS as CNS and other anomalies.
11. Sullivan and McElhatton (1977), as cited in RTECS®, TERIS.
    Offspring of mice treated orally with a total of 440 mg/kg over gd 6-16 had abnormalities of the musculoskeletal system.
12. Vorhees *et al.* (1990), as cited in RTECS®, Shepard's Catalog of Teratogenic Agents, Schardein, TERIS.
    Rats were gavaged with 200, 400 or 600 mg/kg/d on gd 7-18 (17-25 times human therapeutic doses, produced blood level 2-3 times higher than therapeutic levels in humans). Maternal toxicity occurred at the two higher doses, and fetal weight was reduced at those doses. A dose-dependent increase in congenital anomalies (generalized edema and musculoskeletal abnormalities) was reported, but these may have occurred only at the higher doses. Fetotoxicity (undefined) was reported at the lowest dose level. An increase in post-implantation mortality was reported at the highest dose level. (Also cited under animal female reproductive toxicity).
13. Wray *et al.* (1982), as cited in TERIS.
    Teratology studies in mice exposed to 2-10 human therapeutic doses produces inconsistent results (no information on period, duration or route of exposure).

Female reproductive toxicity in humans

No studies identified.

Female reproductive toxicity in animals

1. Author not provided. (E. Afr. Med. J. 60:407. 1983), as cited in RTECS®.
   Rats were administered a total of 765 mg/kg orally over the period of gd 9-17 (presumably 85 mg/kg/d). Effects on litter size (undefined) were reported. (Also cited under animal developmental toxicity).
2. Author not provided. (Terat. Carcinog. Mutag. 6:393. 1986), as cited in RTECS®.
   Male and female mice were administered a total of 92 g/kg orally over the period beginning 2 weeks prior to mating and continuing to gd 18 in females. Effects on pre- and post-implantation mortality were reported. (Also cited under animal developmental toxicity).
3. Author not provided. (Teratology 29(3):33A. 1984), as cited in RTECS®.
   Female rats were administered a total of 3600 mg/kg orally over the period beginning 2 weeks prior to mating and continuing to gd 22. Effects on the live birth index, weaning/lactation index and growth statistics in the newborns were reported. (Abstract only). (Also cited under animal developmental toxicity).
4. Vorhees, CV *et al*. (1990), as cited in RTECS®, Shepard's Catalog of Teratogenic Agents, Schardein, TERIS.
   Rats were gavaged with 200, 400 or 600 mg/kg/d on gd 7-18 (17-25 times human therapeutic doses, produced blood level 2-3 times higher than therapeutic levels in humans). Maternal toxicity occurred at the two higher doses, and an increase in post-implantation mortality was reported at the highest dose level. (Also cited under animal developmental toxicity).

Male reproductive toxicity in humans

1. Shechter-Amir *et al.* (1993), as cited in Reprotox™.
   Semen analysis in a small number of men who had received carbamazepine for at least three months revealed no abnormalities other than elevated semen fructose levels, which were considered unlikely to indicate an effect on fertility.

Male reproductive toxicity in animals

1. Cohn *et al*. (1982), as cited in HSDB.
   Rats exposed by injection (specific route and dose not specified) for 3 months post weaning had lowered epididymal sperm count but no effect on fertility.

Other relevant data

1. Chemical Society (1979), as cited in HSDB.
   Carbamazepine crosses the placenta rapidly and yields fetal:maternal plasma level ratios of 0.5 - 0.8 (species not defined). Carbamazepine 10,11 epoxide is also present in fetal plasma and tissues.
2. Froesher *et al*. (1984); Kaneko *et al*. (1979); Kuhnz *et al*. (1983); Niebyl *et al*. (1979); Pynnonen *et al*. (1977)), as cited in Reprotox™.
   Carbamazepine enters breast milk at levels 25-70% of that in maternal blood, and accumulation in nursing infants has been reported.
3. Levy and Yerby (1985), as cited in Reprotox™.
   Increased clearance of carbamazepine during pregnancy in humans.
4. Lindhout *et al*. (1984), as cited in Reprotox™, TERIS.
   Carbamazepine in combination with other anticonvulsants has been suggested to increase the risk of teratogenesis due to accumulation of carbamazepine epoxide.
5. Omtzigt *et al*. (1993), as cited in Reprotox™.
   Suggested that it has not been established whether the presence of carbamazepine epoxide in carbamazepine monotherapy is associated with adverse fetal effects.

Secondary Sources

HSDB. Hazardous Substances Data Bank. National Library of Medicine. (TOMES JULY 31, 1995)

Reprotox™. Dr. Anthony M. Scialli. (TOMES JULY 31, 1995)

RTECS®. Registry of Toxic Effects of Chemical Substances. National Institute of Occupational Safety and Health. (TOMES JULY 31, 1995)

Schardein J. L. (1993) *Chemically Induced Birth Defects*. Second Edition, Marcel Dekker.

Shepard's Catalog of Teratogenic Agents. Dr. Thomas H. Shepard. (TOMES JULY 31, 1995)

TERIS. Teratogen Information System. University of Washington. (TOMES JULY 31, 1995)

CHROMIUM (includes tri and hexavalent forms): DEVELOPMENTAL/REPRODUCTIVE TOXICITY DATA SUMMARY

Note: the final priority assignment for chromium contained in this data summary pertains only to hexavalent chromium. The final priority assignment for trivalent chromium will be released at a future date.

Uses for chromium include: pigments (inks, paints, dyes, ceramics, colored glass), metal finishing (corrosion inhibitor), electroplating, leather tanning, alloys, fertilizers, and wood preservative. Chromium is an essential nutrient, and chromium picolinate is currently popular as a nutritional supplement. Cr^{+6} is a Proposition 65 carcinogen. ("Chromium trioxide" and "chromium" were individual candidates in the master list; a decision to combine them was made at the time of prioritization).

Overview of Developmental/Reproductive Toxicity Concern

There is a **MEDIUM** level of concern for developmental/reproductive toxicity over chromium (hexavalent form) due to reports of teratogenic effects in animals and male reproductive effects in humans and animals. Most of the studies were conducted in the 1970's and used the injection route. However, in one 1989 study using administration via drinking water to mice, growth retardation, developmental delay and embryolethality were reported at doses below those producing maternal toxicity. Also, one 1990 study with dietary administration found decreased sperm count and testicular pathology in mice. Direct examination of these and possibly more recent information would be valuable.

Developmental toxicity

Malformations have been reported in mouse and hamster studies using parenteral administration. In a single study using administration via drinking water, growth retardation, developmental delay and embryolethality were reported in mice at doses below those producing maternal toxicity; however, a single generation study with diet administration in rats failed to report developmental toxicity. Effects are likely to depend on the route, dose and form (Cr^{+3}, Cr^{+6}) of chromium, but more thorough review will be necessary to determine this. In a study reported as an abstract, no association was found between chromium concentrations in drinking water and CNS malformations in humans.

Female reproductive toxicity

A Russian-language study with a small sample size was described as finding an increased incidence of toxicosis and postnatal hemorrhage in female workers exposed to dichromate. Studies in mice and rats using administration in feed and drinking water reported reduced fertility and embryotoxicity; however, inhalation studies have not demonstrated such effects and the role of general toxicity needs to be clarified.

Male reproductive toxicity

Dominant lethal effects and testicular and sperm pathology have been reported in mice, rabbits and rats using i.p. administration. One study with dietary administration found decreased sperm count and testicular pathology in mice; however, rodent multigeneration studies using inhalation and oral exposure have reported no effects on fertility.

Overview of Exposure Concern

There is a **HIGH** level of concern over the extent of exposure. The U.S. imported 270,001 metric tons of Cr_2O_3 in 1988. There are 130 facilities in California that manufacture or process chromium. Moss Landing, CA is a major producer and Occidental Petroleum is a major manufacturer of CrO_3 in Los Angeles. The 1994 TRI reports releases of 1,491,183 lbs of chromium, which included 6,204 lbs to environmental media, and 1,250,395 lbs of chromium compounds, which included 14,496 lbs to environmental media. Uses include: pigments (inks, paints, dyes, ceramics, colored glass), metal finishing (corrosion inhibitor), electroplating, leather tanning, alloys, fertilizers, and wood preservative. CrO_3 is used to manufacture magnetic tapes. It was also formerly used as a topical antiseptic, but is now used only in veterinary medicine. The daily intake from diet for chromium is 5-115 microg/day. The daily intake from air and water is 0.4 microg/day. Cr^{+3} is the predominant form in biosystems, Cr^{+6} predominates in anthropogenic sources. The bioconcentration factor is low (1-100).

Recently, chromium picolinate has been advertised as dietary supplement for weight control to improve utilization of energy. The advertisements state that adequate evidence exists to demonstrate the safety of chromium picolinate, but developmental and reproductive toxicity studies are not mentioned.

Data on Developmental and Reproductive Toxicity

NOTE: Unless otherwise indicated, all information, including the citation, is obtained from secondary sources. Full citations of all studies are not provided here.

Developmental toxicity in humans

1. Morton and Elwood (1974), as cited in IPCS.
   No relationship was found between Cr in drinking water and CNS malformations in this study which was reported as an abstract.

Developmental toxicity in animals

1. Gale (1978), Gale and Bunch (1979), Gale (1982), as cited in ATSDR, RTECS®, USEPA HAD.
   In several studies by the same group using i.v. administration of CrO_3 to hamsters, cleft palate, hydrocephalus, skeletal and kidney defects were produced with an ED50=0.5LD75. At the 8 mg/kg dose, which was effective in producing malformations, maternal toxicity in the form of weight loss and kidney tubular necrosis was noted.
2. Iijima *et al.* (1975), as cited in ATSDR, Schardein, USEPA HAD.
   In mice, i.p. administration of $CrCl_3$ 10 or 20 mg Cr/kg on gd 7, 8, 9, 10, or 11 led to exencephaly and rib defects. In a second study, where the highest dose, 20 mg/kg, was equal to the LD30, cleft palate was produced (Iijima *et al.* (1979), as cited in ATSDR).
3. Ivankovic and Preussman (1975), as cited in ATSDR
   Rats were given Cr_2O_3 in feed for a single generation at a dose of 1806 mg Cr/kg/day. No developmental toxicity effects were reported.
4. Mason *et al.* (1989), as cited in ATSDR
   Rats were given i.p. $Na_2Cr_20_7$ at a dose of 2 mg Cr/kg on gd 8. No developmental toxicity effects were reported.
5. Matsumoto *et al.* (1976), as cited in ATSDR, USEPA HAD.
   In mice, i.p. exposure to $CrCl_3$, 2 mg/kg on gd 7, 8, or 9 led to increased fetal and embryonic death (gd 8 and 9) and external malformations (gd 8) including exencephaly, open eyelids, and skeletal. In a second experiment, 10, 15, 20 or 24 mg Cr/kg were given i.p. on gd 8. Fetal weights were decreased in all groups, and there was an increase in external malformations (exencephaly, open eyelids, acephalia) at doses greater than or equal to 15 mg/kg.
6. Trivedi *et al.* (1989), as cited in ATSDR.
   In mice oral exposure to $K_2Cr_20_7$ in drinking water at a dose of 57 mgCr/kg/day led to increased resorptions and

post implantation loss, decreased fetal weight, and decreased ossification. Maternal toxicity was recorded at >120 mg/kg/day.

Female reproductive toxicity in humans

1. Shmitova (1978), as cited in ATSDR, USEPA HAD.
   Women exposed to dichromate in a manufacturing facility in Russia reportedly had an increased incidence of toxicosis and postnatal hemorrhage. This study had a small sample size.

Female reproductive toxicity in animals

1. Glaser *et al.* (1985), as cited in ATSDR
   A rat three generation study with inhalation exposure to $Na_2Cr_2O_7$ reported no reproductive toxicity.
2. Glaser *et al.* (1985), as cited in ATSDR.
   A rat inhalation study with Cr_2O_3 reported no ovarian pathology.
3. Gross and Heller (1946), as cited in HSDB, USEPA HAD.
   Sterility and impaired reproductive function were reported in rats given Cr^{+6} (zinc chromate and potassium chromate) in feed at concentrations greater than 0.125%.
4. Ivankovic & Preussman (1975), as cited in ATSDR.
   A rat single generation study using oral Cr_2O_3 at a dose of 1806 mg Cr/kg/day reported no reproductive toxicity.
5. Trivedi *et al.* (1989), as cited in ATSDR.
   Increased pre and post implantatation loss, and decreased litter size were reported in mice exposed to $K_2Cr_2O_7$, in drinking water at 57 mg Cr/kg. No implantations were found at 234 mg Cr/kg.

Male reproductive toxicity in humans

No studies were identified.

Male reproductive toxicity in animals

1. Behari *et al.* (1978), as cited in ATSDR, USEPA HAD.
   Rabbits treated i.p. with $K_2Cr_2O_7$ 2 mg/kg for 3 or 6 weeks had edema of the testes, biochemical changes and absence of spermatocytes.
2. Glaser *et al.* (1985), as cited in ATSDR, USEPA HAD.
   No testicular pathology or reproductive effects were found in rats exposed by inhalation to chronic Cr_20_2 over three generations.
3. Ivankovic and Preussman (1975) as cited in ATSDR.
   No effects were reported in rats exposed orally to Cr_2O_3 at a dose of 1806 mg/kg/day over three generations.
4. Lee *et al.* (1989), as cited in ATSDR.
   No testicular pathology was found in rats exposed by inhalation to chronic Cr_20_2,
5. Murthy *et al.* (1991), as cited in ATSDR.
   Rats given $K_2Cr_2O_7$, by the i.p. route (2 mgCr/kg/day, 15 days) showed no effect on sperm but demonstrated spermatid morphology changes and leakage of Sertoli cell tight junctions.
6. Pashin *et al.* (1982), as cited in IPCS.
   In a dominant lethal study, mice received 0.5-20 mg/kg $K_2Cr_2O_7$ as a single i.p. injection or 1 or 2 mg/kg $K_2Cr_2O_7$ daily i.p. for 21 days. The daily injections, or the single injection at doses above 2 mg/kg, produced dominant lethal effects manifested as decreased embryo survival.
7. Zahid *et al.* (1990), as cited in ATSDR.
   Mice fed $Cr_2(SO_4)_3$, 14 mg Cr/kg/day and $K_2Cr_2O_7$, 9.1 mg Cr/kg/day in diet had decreased sperm count and testicular pathology.

Other relevant data

1. ATSDR (1993).
   Placental transfer has been demonstrated for chromium in humans.
2. Daniellson *et al.* (1982), as cited in ATSDR.
   In mice, 19% of an i.v. dose of $Na_2Cr_2O_7$ administered on gd 8-18, was found in the fetal skeleton and yolk sac.
3. HSDB (1995).
   The human fetus showed an accumulation factor of 10 for total chromium. Chromium is an essential trace element. Deficiency affects glucose tolerance; the RDA is 50-200 µg/day. In rats, <1% of Cr^{+6} is absorbed. There is greater absorption of Cr^{+3} than Cr^{+6}. Cr^{+3} salts are not corrosive, but are poorly soluble, and have low membrane permeability.
4. Iijima *et al.* (1975), as cited in ATSDR.
   In mice, $CrCl_3$, administered i.p. on gd 8, produced pyknotic cells in the neuroepithelium. This was considered a possible mechanism for neural tube defect.

Secondary Sources

ATSDR. (1993) Agency for Toxic Substances and Disease Registry. Toxicological Profile for Chromium.

HSDB. Hazardous Substances Data Bank. National Library of Medicine. (TOMES JULY 31, 1995)

IPCS. International Programme on Chemical Safety (1988) Environmental Health Criteria 61. Chromium. World Health Organization, Geneva, Switzerland.

RTECS®. Registry of Toxic Effects of Chemical Substances. National Institute of Occupational Safety and Health. (TOMES JULY 31, 1995)

Schardein J. L. (1993) *Chemically Induced Birth Defects*. Second Edition, Marcel Dekker.

USEPA HAD. US Environmental Protection Agency. Health Assessment Document for Chromium. (EPA-600/8-83-014F, 1984).

FORMAMIDE:
DEVELOPMENTAL/REPRODUCTIVE TOXICITY DATA SUMMARY

Formamide (CAS No. 75-12-7) is an organic compound with formula $HCONH_2$. It appears to be used mainly in the pharmaceutical industry as a chemical intermediate or a solvent. It has some use in molecular biology laboratories. It is also used in some glues, and has been used in water soluble inks (including felt-tipped pens).

Overview of Developmental/Reproductive Toxicity Concern

There is a **MEDIUM** level of developmental/reproductive toxicity concern. This is due to reports of developmental toxicity in animals, including resorptions, malformations, and reduced fetal weight. However, the very high dosages used, and other weaknesses in the data, temper the level of concern.

Developmental toxicity

There are several reports in animals, including mice, rats, and rabbits, of developmental toxicity. Increased resorptions and malformations, and reduced fetal weight have been observed. However, most of these effects occurred at high dosages (in the grams/kg/d range). Also, most of the studies are old, in foreign languages and are not readily available in English translation, and/or are available only in abstract.

Female reproductive toxicity

One report in rats observed reduced fertility and litter size in the continuous breeding protocol. However, the dosage was high (750 ppm in water) and the report was available only in abstract.

Male reproductive toxicity

There is one report in rats of testicular lesions from injection (ip) at grams/kg dosages. These effects were seen only in animals which died, but not in animals which survived for 1 month after treatment (if testicular lesions occurred, they were reversed in this time).

Overview of Exposure Concern

There is a **LOW** level of concern over the extent of exposure. Formamide appears to be used mainly in the pharmaceutical industry as a chemical intermediate or a solvent. It is used in molecular biology laboratories in denaturing gel electrophoresis. It is also used in some glues, and has been used in water soluble inks (including felt-tipped pens). It is miscible in water and has low volatility. Formamide is biodegraded and degraded by hydroxyl radicals in the atmosphere. It is not expected to bioconcentrate or biomagnify.

Data on Developmental and Reproductive Toxicity

NOTE: Unless otherwise indicated, all information, including the citation, is obtained from secondary sources. Full citations of all studies are ot provided here.

Developmental toxicity in humans

No studies were identified.

Developmental toxicity in animals

1. Fail *et al.* (1993), as cited in Reprotox™.
   Mice (male and female) were treated orally (water) at 750 ppm in a continuous breeding protocol. Reduced fertility and litter size were observed. Effects were female mediated. (Note: abstract only.) (Also cited in the female repro section.)
2. Gleich (1974), as cited in Barlow and Sullivan.
   a. Mice (female) were treated by injection (ip) at 0.076 or 0.19 ml/kg/d on gd 6-15. Fetal losses (13% or 27%) and malformations (4% or 25% of survivors) were observed.
   b. Mice (female) were treated dermally at 0.008 or 0.076 ml/d [if 35 g mice, about 0.26 or 2.4 g/kg/d, respectively] on gd 10 and 11. Increased resorptions (8% or 61%) and malformations (0% or 36%) were observed. LD50 is 0.4 ml(/d?). (Note: abstract only.)
   Kreybig (1968), as cited in Schardein.
   Rats were treated by injection (no details). Various malformations were observed. (NOTE: probably redundant to von Kreybig (1968)).
3. Merkle and Zeller (1980), as cited in HSDB, RTECS®, Reprotox™, Schardein.
   Rabbits were treated orally (gavage) at 70 mg/kg/d for gd 6-18. No maternal toxicity was observed. Increased post-implantation mortality, malformations, and other fetotoxicity were observed.
4. Oettel and Frohberg (1964), as cited in Barlow and Sullivan, Schardein.
   Mice (female) were treated dermally with 0.1 ml or 2x0.1 ml [if 35 gram mice, about 3.2 or 6.4 g/kg, respectively] on gd 11. Increased resorptions (50% or 80%) and malformations (>50% or unreported %) were observed. These doses correspond to 1/4 and 1/2 of the LD50.
5. Stula and Kraus (1977), as cited in HSDB, RTECS®, Shepard's Catalog Of Teratogenic Agents, Barlow and Sullivan.
   Rats (female) were treated dermally at 0.6 g/kg on 1 or 2 days between gd 9-13. Increased embryonic death (control: 2%, treated gd 9, 10, or 13: 5%; gd 11, or 12: 13%; stat sig not addressed) was observed. Fetal weight was reduced (2.4g in controls, 2.1g in "some treated groups"; stat sig not addressed). Malformations were similar in treated groups to historical controls, although increased subcutaneous hemorrhages (4/60) may have been observed. LD50 reported to be about 17 g/kg on gd 11.
6. Thiersch (1962), as cited in Barlow and Sullivan.
   a. Rats (female) were treated orally at 2 g/kg on gd 7. Resorption (50%) and stunting (26% of survivors) was observed. No malformations were observed.
   b. Rats (female) were treated orally at 3x2 g/kg after gd 7 (days not specified). Complete resorption of litters was observed.
   c. Rats were treated orally: the LD50 was found to be 6 g/kg (not specified if this is male or female, pregnant or non-pregnant). Note: abstract only. See also Thiersch (1971).
7. Thiersch (1971), as cited in RTECS®, Reprotox™, Shepard's Catalog of Teratogenic Agents.
   a. Rats (female) were treated by injection (ip) at 1 ml/d [if 300 g rat, about 3.8 g/kg/d] on gd 11-16. Increased resorptions (36%), stunting (46% of survivors) and increased malformations (palate and extremities) were observed.
   b. Rats (female) were treated orally at 2 g/kg, on gd 7. Increased post-implantation mortality and "fetotoxicity" were observed. (NOTE: reads like Thiersch (1962).)
   c. Rats (female) were treated orally at 1.6 g/kg/d for gd 7-12. Increased developmental abnormalities - musculoskeletal system were observed. (Note: malformations and variations are combined under the category "abnormalities".)
8. Von Kreybig (1968), as cited in Barlow and Sullivan.
   Rats were treated by injection (sc) at above 3 g/kg on gd 13. The LD50 was over 4 g/kg. Teratogenic effects at over 3 g/kg were observed. (Note: probably redundant to Kreybig (1968)).

Female reproductive toxicity in humans

No studies were identified.

Female reproductive toxicity in animals

1. Fail *et al.* (1993), as cited in Reprotox™.
   Mice (male and female) were treated orally (water) at 750 ppm in the continuous breeding protocol. Reduced fertility and litter size were observed. Effects were female mediated. (Note: abstract only.) (Also cited in the developmental section.)

Male reproductive toxicity in humans

No studies were identified.

Male reproductive toxicity in animals

1. Chanh *et al.* (1971), as cited in HSDB, Barlow and Sullivan.
   Rats (male) were treated by a single injection (ip) at 5.0-5.4 g/kg. Some rats died. In the dead rats, testicular atrophy with complete disruption of seminiferous epithelium and hyperplasia of interstitial tissue was observed. These lesions were not observed in animals which survived the treatment for 1 month.

Other relevant data

Formamide is absorbed directly through guinea pig skin (as cited in HSDB). It is probably hydrolyzed in liver to formic acid and ammonia.

Secondary Sources

Barlow S.M. and Sullivan F.M. (1982) *Reproductive Hazards Of Industrial Chemicals,* Academic Press.

HSDB. Hazardous Substances Data Bank. National Library of Medicine. (TOMES JULY 31, 1995)

Reprotox™. Dr. Anthony M. Scialli. (TOMES JULY 31, 1995)

RTECS®. Registry of Toxic Effects of Chemical Substances. National Institute of Occupational Safety and Health. (TOMES JULY 31, 1995)

Schardein J. L. (1993) *Chemically Induced Birth Defects*. Second Edition, Marcel Dekker.

Shepard's Catalog of Teratogenic Agents. Dr. Thomas H. Shepard. (TOMES JULY 31, 1995)

METHYL BUTYL KETONE: DEVELOPMENTAL/REPRODUCTIVE TOXICITY DATA SUMMARY

Methyl butyl ketone (MBK), (CAS No. 591-78-6), synonym 2-hexanone, has the molecular formula $C_6H_{12}O$. It was previously used as a solvent in lacquers, varnishes, inks, and as a chemical intermediate (1970s and 1980s). It is not currently produced, processed, or used in the U.S.

Overview of Developmental/Reproductive Toxicity Concern

There is a **MEDIUM** level of toxicological concern. This is due to reports of male reproductive toxicity in rats, specifically reduced testicular weight and atrophy of the germinal epithelium. Concern is tempered by the high dosages used, and the lack of fertility studies.

Developmental Toxicity

There is one study in rats, by inhalation, which found reduced litter size, birth weight, postnatal growth, and behavioral effects at high, maternally toxic, levels of exposure.

Female Reproductive Toxicity

Same as developmental toxicity.

Male Reproductive Toxicity

There are 3 studies in rats, by inhalation, drinking water, and gavage, all at high levels, which showed testicular effects (reduced weight, atrophy of germinal epithelium). No studies of reproduction were found.

Overview of Exposure Concern

There is a **LOW** level of concern over the extent of exposure. MBK was previously used as a solvent in lacquers, varnishes, inks etc., and as a chemical intermediate (1970s and 1980s). It is not currently produced, processed, or used in the U.S. The reason for the current lack of use in U.S. may be related to a well-reported occupational poisoning (neurotoxicity) from the early 1970s, and numerous subsequent supporting animal studies. It is photooxidized in air with a half-life of approximately 36 hours. It is probably biodegraded in soil and water. It is not expected to bioconcentrate or biomagnify.

Data on Developmental and Reproductive Toxicity

NOTE: Unless otherwise indicated, all information, including the citation, is obtained from secondary sources. Full citations of all studies are not provided here.

Developmental toxicity in humans

No studies were identified.

Developmental toxicity in animals

1. Peters *et al*. (1981), as cited in ATSDR, HSDB, RTECS.
   Rats were treated with MBK by inhalation at 1,000 or 2,000 ppm for 6 hr/d on gd 1-21. Reduced maternal weight gain (by 10% at 1,000 ppm and 14% at 2,000 ppm) was observed. Reduced litter size, birth weight and postnatal growth at 2,000 ppm were observed. Behavioral alterations (increased activity, reduced learning) at 1,000 and 2,000 ppm were observed. RTECS reports gastrointestinal and urogenital abnormalities at 1,000 ppm. (Note: RTECS combines variations and malformations under the category abnormalities.)

Female reproductive toxicity in humans

No studies were identified.

Female reproductive toxicity in animals

1. Peters *et al*. (1981), as cited in ATSDR, HSDB, RTECS.
   Rats were treated with MBK by inhalation at 1,000 or 2,000 ppm for 6 hr/d for gd 1-21. Reduced maternal weight gain (by 10% at 1,000 ppm and 14% at 2,000 ppm) was observed. Reduced litter size, birth weight and postnatal growth at 2,000 ppm were observed (which could potentially have resulted from toxicity to the maternal reproductive system).

Male reproductive toxicity in humans

No studies were identified.

Male reproductive toxicity in animals

1. Boekelheide (1987), as cited in ATSDR.
   Rats (male) were treated with MBK orally (water) at 1% (est. 1,400 mg/kg/d) for 4 weeks. Reduced testicular weight and histopathologyical lesions of the testes were observed.
2. Katz *et al*. (1980), as cited in ATSDR, RTECS®.
   Rats (male) were treated with MBK by inhalation at 692 ppm for 18 hr/d, 72 hr/wk, 11 weeks. Reduced testicular weight and atrophy of the germinal epithelium were observed.
3. Krasavage (1980), as cited in ATSDR.
   Rats (male) were treated with MBK orally (gavage) at 660 mg/kg/d for 90 days. Atrophy of the germinal epithelium was observed (statistical significance not addressed).

Other relevant data

MBK appears to readily cross the placenta. Neurotoxicity was observed within 2 weeks in Katz *et al*. (1980), as cited in ATSDR, RTECS®, above. Neurotoxicity is a commonly observed endpoint in adult animals.

Secondary Sources

ATSDR. (1992) Agency for Toxic Substances and Disease Registry. Toxicological Profile 2-Hexanone.

HSDB. Hazardous Substances Data Bank. National Library of Medicine. (TOMES JULY 31, 1995)

RTECS®. Registry of Toxic Effects of Chemical Substances. National Institute of Occupational Safety and Health. (TOMES JULY 31, 1995)

1,2-DICHLOROPROPANE: DEVELOPMENTAL/REPRODUCTIVE TOXICITY DATA SUMMARY

1,2-Dichloropropane (synonym: propylene dichloride) (CAS No. 78-87-5) is an organochlorine compound with the formula $C_3H_6Cl_2$. It is used as a chemical intermediate, and in pesticides, industrial and commercial solvents, and as a lead scavenger in anti-knock compounds. 1,2-Dichloropropane is on the Proposition 65 list as a carcinogen.

Overview of Developmental/Reproductive Toxicity Concern

There is a **LOW** level of developmental/reproductive toxicity concern. This is due to the existence of several studies in animals which show lack of major effects, lack of consistent effects, and/or lack of effects at dosages not substantially toxic to the adult.

Developmental toxicity

There are 3 relevant industry studies in animals. There are 2 developmental studies, in rat and rabbit by gavage, which found delayed fetal ossification, but no other effects, at dosages where reduced maternal weight gain was observed in rats and rabbits and maternal anemia was observed in rabbits. A 2-generation study in rats by water found reduced neonatal survival and weight gain in the F1 generation, but no other effects, at a dosage where adult weight gain was reduced, and anemia was observed in adult females. No reduced neonatal survival was observed in the F2 generation.

Female reproductive toxicity

There is 1 case report in humans of a 20 year old female who sniffed a stain remover containing 60-100% 1,2-dichloropropane “every night”. She was admitted to the hospital with uterine bleeding, hematuria, acute kidney and liver failure, and other signs. Following blood transfusions and dialysis, she recovered.

In animals, a 2-generation study in rats by water found reduced neonatal survival and weight gain in the F1 generation, but no other effects (including fertility or litter size), at a dosage where adult weight gain was reduced, and anemia was observed in adult females. No reduced neonatal survival was observed in the F2 generation. A 13 week study by inhalation found no effect on female reproductive organs in mice, rats, or rabbits.

Male reproductive toxicity

In animals there is one study in rats by gavage in which testicular degeneration and reduced sperm production was observed. Reduced body weight gain and anemia were observed at lower dosages than testicular and sperm effects. Also, long-term exposure to the dosages at which testes and sperm effects were observed produced death in the animals. Short-term and sub-chronic studies in rat, mouse, and rabbit by inhalation found no effects on testes. A 2-year NTP study by gavage in rats and mice also found no effects on testes. A dominant lethal study in rats by water found no effects on fertility or litter size. A 2-generation study in rats exposed via water provided no evidence of male reproductive effects.

Overview of Exposure Concern

There is a **MEDIUM** level of concern over the extent of exposure. 1,2- dichloropropane is used as a chemical intermediate, pesticide, industrial and commercial solvent, and as a lead scavenger in anti-knock compounds. Annual U.S. production was 60 million lbs. in 1984. Annual releases to the environment in the U.S. were 1.1 million lbs. in 1986. Most information on use and exposure is from the 1980’s; information from 1990’s is sparse. It is a component of a mixture of 3-carbon compounds used as a pesticide; 319 lbs. were reported to have been used in California in 1993. Use patterns are reported to be changing, but recent information is lacking. It was found in

groundwater in 75 wells in 9 counties in California in the early 1980s (12 wells over 10 ppb, peak level 1200 ppb), probably from use in pesticides. Degradation in water has a half life of 25-200 weeks.

Data on Developmental and Reproductive Toxicity

NOTE: Unless otherwise indicated, all information, including the citation, is obtained from secondary sources. Full citations of all studies are not provided here.

Developmental toxicity in humans

No studies were identified.

Developmental toxicity in animals

1. Hanley *et al*. (1989a), as cited in IRIS®.
   Rabbits were treated orally (gavage) at 0, 15, 50, or 150 mg/kg/d for gd 7-19. Maternal anemia, and reduced maternal body weight gain at 150 mg/kg/d were observed. Delayed ossification of skull bones of fetuses at 150 mg/kg/d was observed.
2. Hanley *et al*. (1990), as cited in Schardein.
   Rats and rabbits were treated (no details given). No teratogenicity was observed. (Probably abstract, redundant to Hanley et al. (1989a) and Kirk et al. (1989).)
3. Kirk *et al*. (1989), as cited in ATSDR, IRIS®.
   Rats were treated orally (gavage) at 0, 10, 30 or 125 mg/kg/d for gd 6-21 (or possibly 6-15). Reduced maternal weight gain at 125 mg/kg/d on gd 8-16 was observed. Delayed fetal ossification was observed at 125 mg/kg/d. No adverse developmental effects were observed at 30 mg/kg/d or less. No effect on number of pregnancies, implantation sites, litter size, resorptions, malformations, or gravid uterine weight was observed.
4. Kirk *et al*. (1990), as cited in IRIS®.
   Rats (males and females) were treated orally (water) at 0, 0.024, 0.10, or 0.24% (w/v) (approx. 24, 100, or 200 mg/kg/d) for 2 generations. In the F0 generation, a statistically significant reduction in body weight gain before mating, during gestation and lactation at 0.24% was observed. Anemia in F0 females at 0.24% was observed. No effects on F0 reproductive organs, fertility, mating index, conception index, viable litters, gestation length, litter size, live pups, or sex ratio were observed. In F1 neonates reduced neonatal survival and body weight at 0.24% were observed. In F1 parental animals reduced weight gain at 0.24% was observed. In F1 parental animals no histopathological changes in reproductive organs were observed. In F2 neonates no reduced neonatal survival was observed. (Also cited in the female and male reproductive toxicity in animals sections.)

Female reproductive toxicity in humans

1. Pozzi *et al*. (1985), as cited in ATSDR, HSDB, IRIS®.
   Trielina is a stain remover sold in Italy which contains 60-100% 1,2-dichloropropane. A 20 year old female was admitted to the hospital with vomiting, abdominal pain, widespread ecchymoses (bluish spots on skin), hematuria, and uterine bleeding. Symptoms regressed. Nine months later, the patient was readmitted with oliguria, epistaxis, hematuria, uterine bleeding, and periorbital and conjunctival hemorrhages. Clinical tests found severe renal failure, acute liver damage, hemolytic anemia, and disseminated intravascular coagulation. She admitted to sniffing Treilina every night. No information on concentration was given. Following transfusion with fresh blood, and dialysis, she was discharged with recovery of renal and liver function.

Female reproductive toxicity in animals

1. Kirk *et al*. (1990), as cited in IRIS®.
   Rats (males and females) were treated orally (water) at 0, 0.024, 0.10, or 0.24% (w/v) (approx. 24, 100, or 200 mg/kg/d) for 2 generations. In the F0 generation, a statistically significant reduction in body weight gain before mating, during gestation and lactation at 0.24% was observed. Anemia in F0 females at 0.24% was observed. No effects on F0 reproductive organs, fertility, mating index, conception index, viable litters, gestation length, litter size, live pups, or sex ratio were observed. In F1 neonates reduced neonatal survival and body weight at 0.24% were observed. In F1 parental animals reduced weight gain at 0.24% was observed. In F1 parental animals no histopathological changes in reproductive organs were observed. In F2 neonates no reduced neonatal survival was observed. (Also cited in the developmental and male reproductive toxicity in animals sections.)
2. Nitschke *et al*. (1988), as cited in ATSDR, IRIS®.
   a. Rats (males and females) were treated by inhalation at 0, 15, 50, or 150 ppm for 6 hr/d, 5 d/wk, for 13 weeks. No effects on reproductive organs (female: ovaries, oviduct, uterus, cervix, mammary glands; male: testes, epididymus, or prostate) were found. A statistically significant reduction in body weights were reported at 150 ppm.
   b. Mice (males and females) were treated by inhalation at 0, 15, 50, or 150 ppm for 6 hr/d, 5 d/wk, for 13 weeks. No effects on reproductive organs (female: ovaries, oviduct, uterus, cervix, mammary glands; male: testes, epididymus, or prostate) were found. No treatment related pathological effects were observed.
   c. Rabbits (males and females) were treated by inhalation at 0, 150, 500, or 1,000 ppm for 6 hr/d, 5 d/wk, for 13 weeks. No effects on reproductive organs (female: ovaries, oviduct, uterus, cervix, mammary glands; male: testes, epididymus, or prostate) were found. Anemia was observed at 150 ppm and up. (Also cited in the male reproductive toxicity in animals section.)
3. National Toxicology Program (NTP) (1986), as cited in ATSDR, IRIS®.
   a. Mice (male and female) were treated orally (gavage) at 0, 125 or 250 mg/kg/d for 5 d/wk for 103 weeks. In females, increased infections of ovary, uterus, or other organs were observed, but it is not clear if this was treatment related, since controls also had infections. No histopathology of male reproductive organs was observed. No reduced body weight was observed.
   b. Rats (female) were treated orally (gavage) at 0, 125, or 250 mg/kg/d for 5 d/wk for 103 wks. Rats (male) were treated at 0, 62, or 125 mg/kg/d. No histopathology of male reproductive organs was observed. No reduced body weight was observed. (Also cited in the male reproductive toxicity in animals section.)

Male reproductive toxicity in humans

No studies were identified.

Male reproductive toxicity in animals

1. Bruckner *et al*. (1989), as cited in ATSDR, IRIS®, Reprotext®.
   a. Rats were treated orally (gavage) at 100, 250, 500, or 1,000 mg/kg/d for 1, 5, or 10 consecutive days. Testicular degeneration, with reduced sperm production, increased numbers of degenerate sperm, and reduced numbers of sperm in the epididymus, was observed at 500 mg/kg/d. No testicular effects were observed at 250 mg/kg/d. Reduced body weight gain and slight anemia at 250 mg/kg/d, and pronounced anemia at 500 mg/kg/d were also observed.
   b. Rats were treated orally (gavage) at 100, 250, 500, or 750 mg/kg/d for 5d/wk for 13 weeks. Increased mortality and testicular degeneration, with reduced sperm production, increased numbers of degenerate sperm, and reduced numbers of sperm in the epididymus, was observed at 500 and 750 mg/kg/d. No testicular effects were observed at 250 mg/kg/d. Reduced body weight gain and slight anemia at 100 mg/kg/d, and pronounced anemia at 250 mg/kg/d were also observed.
2. Hanley *et al*. (1989b) as cited in ATSDR.
   Rats (male) were treated orally (water) at 162 mg/kg/d for at least 10 weeks prior to breeding. Two days after

exposure was ended, males were bred with untreated females. No effect on mating performance, fertility, number of implantations, resorptions, or liter sizes were observed.

3. Kirk *et al*. (1990), as cited in IRIS®.
   Rats (males and females) were treated orally (water) at 0, 0.024, 0.10, or 0.24% (w/v) (approx. 24, 100, or 200 mg/kg/d) for 2 generations. In the F0 generation, a statistically significant reduction in body weight gain before mating, during gestation and lactation at 0.24% was observed. Anemia in F0 females at 0.24% was observed. No effects on F0 reproductive organs, fertility, mating index, conception index, viable litters, gestation length, litter size, live pups, or sex ratio were observed. In F1 neonates reduced neonatal survival and body weight at 0.24% were observed. In F1 parental animals reduced weight gain at 0.24% was observed. In F1 parental animals no histopathological changes in reproductive organs were observed. In F2 neonates no reduced neonatal survival was observed. (Also cited in the developmental and female reproductive toxicity in animals sections).
4. National Toxicology Program (NTP) (1986), as cited in ATSDR, IRIS®.
   a. Mice (male and female) were treated orally (gavage) at 0, 125 or 250 mg/kg/d for 5 d/wk for 103 weeks. Females had increased infections of ovary, uterus, or other organs, but it is not clear if this was treatment related, since controls also had them. No histopathology of male reproductive organs was observed. No reduced body weight was observed.
   b. Rats (female) were treated orally (gavage) at 0, 125, or 250 mg/kg/d for 5 d/wk for 103 wks. Rats (male) were treated at 0, 62, or 125 mg/kg/d. No histopathological changes of male reproductive organs were observed. No reduced body weight was observed. (Also cited in the female reproductive toxicity in animals section.)
5. Nitschke and Johnson (1983), as cited in ATSDR, IRIS®.
   a. Rats (male and female) were treated by inhalation at 0, 100, 300, or 1,000 ppm for 6 hr/d, 4-5d/wk, for 2 weeks (9 exposures). No histopathological changes in testes were observed. There was a statistically significant reduction in body weight (male and female) at 100 ppm exposure and upwards.
   b. Rabbits were treated by inhalation at 0, 100, 300, or 1,000 ppm for 6 hr/d, 4-5d/wk, for 2 weeks (9 exposures). No histopathological changes in testes were observed.
   c. Mice were treated by inhalation at 0, 30, 100 or 300 ppm for 6 hr/d, 4-5d/wk, for 2 weeks (9 exposures). No histopathological changes in testes were observed. No effect on body weight was observed.
6. Nitschke *et al*. (1988), as cited in ATSDR, IRIS®.
   a. Rats (males and females) were treated by inhalation at 0, 15, 50, or 150 ppm for 6 hr/d, 5 d/wk, for 13 weeks. No effects on reproductive organs (female: ovaries, oviduct, uterus, cervix, mammary glands; male: testes, epididymus, or prostate) were found. A statistically significant reduction in body weights were reported at 150 ppm.
   b. Mice (males and females) were treated by inhalation at 0, 15, 50, or 150 ppm for 6 hr/d, 5 d/wk, for 13 weeks. No effects on reproductive organs (female: ovaries, oviduct, uterus, cervix, mammary glands; male: testes, epididymus, or prostate) were found. No treatment related pathological effects were observed.
   c. Rabbits (males and females) were treated by inhalation at 0, 150, 500, or 1,000 ppm for 6 hr/d, 5 d/wk, for 13 weeks. No effects on reproductive organs (female: ovaries, oviduct, uterus, cervix, mammary glands; male: testes, epididymus, or prostate) were found. Anemia was observed at 150 ppm and up. (Also cited in the female reproductive toxicity in animals section.)

Other relevant data

1. ATSDR
   Following oral ingestion or inhalation, 1,2-dichloropropane is relatively rapidly exhaled, metabolized, and/or excreted in the urine.

Secondary Sources

ATSDR. (1989) Agency for Toxic Substances and Disease Registry. Toxicological Profile for 1,2-dichloropropane.

HSDB. Hazardous Substances Data Bank. National Library of Medicine. (TOMES JULY 31, 1995)

IRIS®. Integrated Risk Information System. US Environmental Protection Agency. (TOMES JULY 31, 1995)

Reprotext®. Micromedex, Inc. (TOMES JULY 31, 1995)

Schardein J. L. (1993) *Chemically Induced Birth Defects.* Second Edition, Marcel Dekker.

BERYLLIUM:
DEVELOPMENTAL/REPRODUCTIVE TOXICITY DATA SUMMARY

Beryllium (CAS No. 7440-41-7) is used in the defense, semiconductor, and computer industries as an alloy, in ceramics, and in the mantels of gas lanterns. The review includes beryllium (Be) and Be salts. Beryllium and beryllium compounds are on the Proposition 65 list as carcinogens.

Overview Developmental/Reproductive Toxicity Concern

There are **INSUFFICIENT DATA** to determine a level of developmental/reproductive toxicity concern for beryllium. There are fewer than five relevant animal studies, and these studies are limited by the use of nonstandard study designs and methodologies.

Developmental toxicity

Two studies reported effects after intratracheal administration during pregnancy in rats. One study is complicated by methodological issues, and the other is a Russian language report which was minimally described in the secondary sources.

Female reproductive toxicity

A study in female workers reported no reproductive toxicity. A single rat study using intratracheal administration reported no effects on reproduction, and chronic toxicity studies reported no reproductive organ pathology.

Male reproductive toxicity

A study in male workers reported no reproductive toxicity. Chronic toxicity studies with dietary administration in rats found decreased testes/body weight but no reproductive tract pathology.

Overview of Exposure Concern

There is a **MEDIUM** level of concern over the extent of exposure. The US is a leading producer and user of beryllium (although there do not appear to be any manufacturers or processors in California). According to 1986-88 data, 490,000 lbs. were produced in the US per year and 375,000 lbs were released. It is used in the defense, semiconductor, and computer industries as an alloy and is used in ceramics. Occupational exposures occur primarily via inhalation. Air sources include manufacturing, fuel combustion, and municipal waste incinerators. There are increased concentrations in urban air due to coal burning. Potential consumer exposures could occur from the mantels of gas lanterns. It is present in food but poorly (<1%) absorbed. The average daily intake for beryllium is estimated at 12 micrograms, mostly from drinking water and food. It has a low BCF (19-100).

Data on Developmental and Reproductive Toxicity

NOTE: Unless otherwise indicated, all information, including the citation, is obtained from secondary sources. Full citations of all studies are not provided here.

Developmental toxicity in humans

1. ATSDR (1993).
   This recent review reported no human studies. No studies were identified in other secondary sources

Developmental toxicity in animals

1. Mathur *et al.* (1987), as cited in IPCS.
   Rats were given Be nitrate intravenously at 0.316 mg/kg (0.1LD50). When administered on gd 1 or gd 2,13,15 or 17, postnatal death resulted, and when administered on gd 11 intrauterine death resulted. No malformations were noted. This study is complicated by anesthesia and surgery involved in two laparoscopies conducted during pregnancy (gd 11 and 20).
2. Selinova *et al.* (1986), as cited in ATSDR, Shepard's Catalog of Teratogenic Agents.
   Rats were given an intratracheal administration of 50 mg/kg Be oxide suspension and chloride solution on gd 3, 5, 8 or 20. Effects reported in this Russian language paper were increased death, decreased fetal weight (no effect on fetal length) and edema of internal organs.
3. Tsuji *et al.* (1979), as cited in IPCS.
   This Japanese language report described postnatal neurobehavioral effects of Be sulfate administered by i.p. injection to mice.

Female reproductive toxicity in humans

1. ATSDR (1993)
   This recent review reported no human studies by the oral or inhalation routes.
2. Kline *et al.* (1951), as cited in IARC.
   In one case report of a pregnant woman with occupational exposure, newborn hypoglycemia was found.
3. Savitz *et al.* (1989), as cited in TERIS.
   No effects on stillbirth, low birthweight, or small for gestational age were reported with maternal occupational exposure.

Female reproductive toxicity in animals

1. ATSDR (1993).
   This recent review reported no animal studies with DART endpoints by the oral or inhalation routes.
2. Clary *et al.* (1975), as cited in ATSDR.
   In a single generation study in rats, a single intratracheal administration of Be oxide (0.6 mg/kg prior to mating) had no effect on pregnancy outcome. The purpose was to study the effect of pregnancy on the onset of chronic symptoms of Be toxicity.
3. Morgareidge *et al.* (1975), as cited in ATSDR.
   A chronic diet study in rats using <31 mg Be/kg/day as Be sulfate tetrahydrate showed no reproductive tract pathology.

Male reproductive toxicity in humans

1. Savitz *et al.* (1989), as cited in Shepard's Catalog of Teratogenic Agents.
   No effects were reported on stillbirth, low birthweight, or small for gestational age, with paternal occupational exposure.

Male reproductive toxicity in animals

1. ATSDR (1993)
   This recent review reported no animal studies by the oral or inhalation routes and no dominant lethal study.
2. Morgareidge *et al.* (1975), as cited in IPCS.
   No reproductive tract pathology was found in a chronic diet study in rats using Be sulfate tetrahydrate, <31 mg Be/kg/day. However decreased testes/body weights were reported in this study as cited in ATSDR.

Other relevant data

Absence of teratologic effects was reported in chicks using Be chloride by Ridgway *et al.* (1952) (as cited in Reprotox™), but malformations were described in chicks using Be sulfate (Puzanova *et al.* (1978), as cited in IPCS).

Be is poorly absorbed orally and dermally, and transplacental transport is "relatively poor" in mice (Bencko *et al.* (1979), as cited in IPCS) and rats (Clary *et al.* (1975), Schulert *et al.* (1969), as cited in Barlow and Sullivan). <1% of the oral dose is excreted in milk in cows (Mullen *et al.* (1972), as cited in IARC).

Secondary Sources

ATSDR. (1993) Toxicological Profile for Beryllium. Agency for Toxic Substances and Disease Registry.

Barlow S.M. and Sullivan F.M. (1982) *Reproductive Hazards Of Industrial Chemicals*, Academic Press.

IARC. International Agency for Research on Cancer (IARC, 1993). *Monographs On The Evaluation Of Carcinogenic Risk To Humans, Volume 58.* World Health Organization.

IPCS. (1990) International Programme on Chemical Safety. Environmental Health Criteria 160. Beryllium. World Health Organization, Geneva, Switzerland.

Reprotox™. Dr. Anthony M. Scialli. (TOMES JULY 31, 1995)

Shepard's Catalog of Teratogenic Agents. Dr. Thomas H. Shepard. (TOMES JULY 31, 1995)

TOLUENE-2,4-DIISOCYANATE: DEVELOPMENTAL/REPRODUCTIVE TOXICITY DATA SUMMARY

Toluene-2,4-diisocyanate (CAS No. 584-84-9) is a clear-to-yellow volatile liquid with the formula $C_9H_6N_2O_2$. It is used in the manufacture of polyurethane foams, paints, varnishes, sealers, spandex and nylon. Toluene-2,4-diisocyanate is usually (>95%) sold as a 80:20 mixture with toluene-2,6- diisocyanate. The commercial toluene diisocyanate mixture (CAS No. 26471-62-5) is on the Proposition 65 list as a carcinogen.

Overview of Developmental/Reproductive Toxicity Concern

There are **INSUFFICIENT DATA** to prioritize toluene-2,4-diisocyanate with regard to its developmental/reproductive toxicity.

Developmental toxicity

No studies were identified.

Female reproductive toxicity

No studies were identified.

Male reproductive toxicity

One study, citing an incident involving an industrial fire, reported impotence in 2 out of 35 firefighters. The two men affected also showed signs of neurological problems (including memory problems and depression). The impotence was most likely secondary to the neurological effects. No animal studies were identified for the 2,4 isomer.

Overview of Exposure Concern

There is a **MEDIUM** level of concern over exposure due to toluene-2,4-diisocyanate. Toluene diisocyanate is used as an industrial chemical for the production of polyurethane foams, paints, varnishes, sealers, spandex and in nylon. Polyurethane foams are commonly used in furniture, automobile seats and home insulation. Toluene-2,4- diisocyanate is usually (>95%) sold as a 80:20 mixture with toluene-2,6-diisocyanate. The CAS number for the mixture is 26471-62-5. None of the major manufacturing sites appear to be located in California. According to the 1994 California TRI, 2,000 lb. were released to the air and 5,000 lb. were disposed of offsite. TDI is released primarily through stack and fugitive emissions (0.005% of TDI used in flexible foam slabstock is released in vent stack exhaust). It rapidly hydrolyzes in water and has an atmospheric half-life of 3.3 hours.

Data on Developmental and Reproductive Toxicity

NOTE: Unless otherwise indicated, all information, including the citation, is obtained from secondary sources. Full citations of all studies are not provided here.

Developmental toxicity in humans

No studies identified.

Developmental toxicity in animals

No studies identified.

Female reproductive toxicity in humans

No studies identified.

Female reproductive toxicity in animals

No studies identified.

Male reproductive toxicity in humans

1. Le Quesne *et al.* (1976) as cited in Reprotext®, Barlow and Sullivan.
   Thirty-five firefighters were exposed to high levels of toluene-2,4-diisocyanate while fighting a fire in a polyurethane foam factory. They were exposed over an 8 hour period via inhalation and possibly dermal routes. The exposure resulted in neurological problems for 23 of the firefighters (two of which complained of impotence lasting 2 weeks). Of the two reporting impotence, one lost consciousness during the fire and the other reported confusion for 3 weeks following the fire. Both showed signs of ataxia and abnormal EEG three weeks after the fire as well as persistent neurological effects 4 years later.

Male reproductive toxicity in animals

No studies identified.

Other relevant data

1. Le Quesne *et al.* (1976) as cited in Barlow and Sullivan.
   Non-reproductive effects include respiratory sensitization (and the accompanying asthma), gastrointestinal problems and neurological problems, which in some cases persisted for months to years after the exposure.
2. Tyl (1988), as cited in IRIS®.
   Rats were exposed via inhalation to 0, 0.021, 0.120 and 0.480 ppm of an unspecified TDI mixture for 6 hr/day on gd 6-15 for 23 h/day. No embryotoxicity or teratogenicity was noted. Maternal toxicity was noted at 0.480 ppm.
3. Tyl and Neeper-Bradley (1989), as cited in IRIS®.
   Male and female rats were exposed via inhalation to 0, 0.020, 0.079 and 0.290 ppm of an unspecified TDI mixture for 6 hr/day, 5 days/week for 10 weeks in a 2 generation reproduction study. The study reported no effects on any of the reproduction parameters evaluated (no specifics given).

Secondary Sources

Barlow S.M. and Sullivan F.M. (1982) *Reproductive Hazards Of Industrial Chemicals,* Academic Press.

IRIS®. Integrated Risk Information System. US Environmental Protection Agency. (TOMES JULY 31, 1995)

Reprotext®. Micromedex, Inc. (TOMES JULY 31, 1995)