Methoxychlor; CASRN 72-43-5

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR Methoxychlor

File First On-Line 09/07/1988

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	09/01/1990
Inhalation RfC (I.B.)	qualitative discussion	12/01/1993
Carcinogenicity Assessment (II.)	yes	09/07/1988

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name —Methoxychlor
CASRN — 72-43-5
Last Revised — 09/01/1990

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of

information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
Excessive loss of litters **Rabbit Teratology Study** **Kincaid Enterprises, 1986**	NOEL: 5.01 mg/kg/day LEL: 35.5 mg/kg/day	1000	1	5E-3 mg/kg/day

* Conversion Factors: Actual dose tested

I.A.2. Principal and Supporting Studies (Oral RfD)

Kincaid Enterprises, Inc. 1986. MRID No. 0015992. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Young adult female New Zealand White rabbits were randomized by a computerized process which assigned 17 animals each into 3 dose groups, 5.01, 35.5, and 251.0 mg/kg/day, and a control (a total of 68 animals). The females were artificially inseminated and the day of insemination considered as gestation day 0. All animals were dosed from days 7 through 19 of gestation. Animals were observed twice daily for mortality and moribundity, further they were observed once daily for clinical signs of toxicity. Individual body weights were taken on gestation days 0, 7, 10, 14, 20, 24, and 29. All surviving dams were sacrificed on gestation day 29.

Maternal toxicity was observed as excessive loss of litters (abortions) in the mid- and high-dose groups along with statistically significant decreases in body weight gain during the dosing period for both mid- and high-dose groups and in the mid dose following the dosing period and overall for the gestation period (the high dose was not analyzed due to total loss of litters). There also was an increase in clinical signs in both the mid- and high-dose groups; the deaths at the high

dose were attributed to compound administration. The high incidence of lung agenesis noted in fetuses of all dose groups was unusual. No specific toxicity was noted in the low dose (5.01 mg/kg/day).

The tentative LEL for maternal toxicity is 35.5 mg/kg/day based on excessive loss of litters. The tentative NOEL for maternal toxicity is 5.01 mg/kg/day.

I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF — An uncertainty factor of 100 was used to account for the inter-and intraspecies differences. An additional UF of 10 was used to account for the poor quality of the critical study and for the incompleteness of the database on chronic toxicity.

MF — None

I.A.4. Additional Studies/Comments (Oral RfD)

Methoxychlor is considered to have an estrogenic activity. Several recent papers in the open literature have addressed this action of methoxychlor. Kupfer and Bulger (1987) found that both methoxychlor and metabolites have estrogen-like activity with several metabolites having proestrogen activity. They used an in vitro system involving rat liver microsomes and NADPH for a metablizing system with estrogen receptors from immature rat uteri as a detection system.

Gray et al. (1989) investigated the effects of methoxychlor on the pubertal development and reproductive function in the male and female rat (Long-Evans hooded) by dosing rats from gestation, weaning, lactation, through puberty with either 25, 50, 100, or 200 mg/kg/day of methoxychlor. In females they found an acceleration of vaginal opening, abnormal estrus cycle, inhibition of luteal function and a blockage of implantation. In males they found an inhibition of somatic growth and accessory gland weight, elevated pituitary and serum prolactin levels, and a suppression of testicular Leydig cell function. Some of these effects occurred at levels as low as 25 mg/kg/day. These observations are consistent with the earlier reports that Methoxychlor mimics estrogen both in vivo and in vitro.

Goldman et al. (1986) investigated the subchronic effects of methoxychlor on the rat (Long-Evans hooded) reproductive system by dosing for 8 weeks with 25 or 50 mg/kg of methoxychlor by oral gavage. No effect was observed on the pituitary weight, serum LH, FSH, or prolactin levels and the pituitary LH of FSH concentrations. Pituitary prolactin levels were increased at both levels. There was an increase in GnRH levels in the mediobasal hypothalamus at the high-dose level. The authors determined that the reproductive effects of methoxychlor are mediated in

part by an increase in prolaction release which in turn influences the hypothalamic levels of GnRH. This may be considered an early effect of methoxychlor on the rat reproductive system.

Cummings and Gray (1987) of the US EPA Health Effects Research Laboratory found that methoxychlor affects the decidual cell response of the rat uterus, suggesting a direct effect of the compound on the uterus with no effects on uterine weight, serum progesterone levels, or corpora lutea maintenance. Long-term exposure to methoxychlor reduced fertility and induced fetotoxicity. The effects of reduced fertility and fetotoxicity were noted in a 3-generation reproduction study (see study #4). Although the available data for these 3 studies were limited, it is apparent that methoxychlor at 1000 ppm produced reproductive effects in the form of reduced fertility index, reduced litter size, and reduced viability index.

Khera et al. (1978) on the teratogenicity of methoxychlor found that treatment of pregnant rats with either technical grade or formulation of methoxychlor produced maternal toxicity in the form of reduced body weight gain at all doses tested (50 to 400 mg/kg/day). Developmental toxicity was noted as fetotoxicity at doses of 200 and 400 mg/kg/day and as a dose-related increase of wavy ribs at 100, 200, and 400 mg/kg/day.

A 2-year chronic rat study by du Pont de Nemours & Co. (1951) reported a systemic NOEL of 100 ppm (5 mg/kg/day); a 2-year chronic study by Hodge, et al. (1952) reported a systemic NOEL of 200 ppm (10 mg/kg/day). Altough these studies are not definitive, they, along with the submitted studies from the registrant, support the NOEL of 5.01 mg/kg/day used for the calculation of the RfD for methoxychlor.

Data Considered for Establishing the RfD

1) Teratology - rabbit: Principal study - see previous description; core grade supplementary (Kincaid Enterprises, Inc., 1986)

2) Teratology - rat: Dietary levels tested: 0, 200, 500, and 1250 ppm (10, 25, and 62.5 mg/kg/day); Female ChR-CD albino rats (animals were received pregnant) were administered methoxychlor in the diet on gestation days 6 through 15. There was maternal toxicity in the mid- and high-dose groups in the form of reduced body weight gain, reduced food consumption, increased postimplantation loss, and a decreased number of liver fetuses per dam. There was 1 and 2 dams in the mid- and high-dose groups, respectively, with total resorptions of litters. The increase in postimplantation loss resulted in a decrease in the litter size in the mid-and high-dose groups. There was an indication of 4 runts in one litter in the mid dose group, however, there was no change in the mean fetal weight among dose groups. The mid- and high-dose group had statistically significantly increased numbers of litters with wavy ribs. Study deficiencies included the following: no individual animal data were provided; animals were received pregnant; and

although dosing was by feed, the concentration analysis of the diet, diet preparation schedule, and stability of the test compound in the diet mixtures was not provided. Therefore the tentative LEL is 500 ppm (25 mg/kg/day) based on the above effects. The tentative NOEL is 200 ppm (10 mg/kg/day).; core grade supplementary (E.I. du Pont de Nemours and Co,, Inc., 1976a)

3) Teratology - rat: Dietary levels tested: 0, 34.6, 138.4, 242.2, and 346.0 mg/kg/day; Female Sprague-Dawley rats were dosed by gavage from gestation day 6 through 15. Control animals received corn oil in equivalent volumes to the test material which was administered at the high dose. There was evidence of reduced body weight gain at all doses tested. Further, at 138.4 mg/kg/day and above there was an increased number of resorptions, dead fetuses, and increased postimplantation loss. There was evidence of altered growth in the form of delayed ossification of skull bones and sternebrae and the reduced fetal body weight at the high dose. All doses tested had an increased incidence of hydronephrosis, and reduced or no ossification of skull bones, sternebrae and vertebrae along with wavy ribs. Study deficiencies include lack of stability and concentration analysis, dosing data, summary litter incidence, and maternal examination data. Based on the above effects observed at the lowest dose tested, the tentative LEL for maternal and developmental toxicity is 34.6 mg/kg/day. An NOEL for maternal and developmental toxicity could not be established.; core grade supplementary (Chemical Formulators, Inc. 1976b)

4) 3-Generation Reproduction - rat: Dietary levels tested: 0, 200, and 1000 ppm (0, 10, and 50 mg/kg/day); Male and female ChR-CD rats were administered methoxychlor in the diet for three generations. Three separate studies were conducted and reported in this study. The first reproduction study used dose levels of 0 and 200 ppm and the second reproduction study used dose levels of 0, 0 (2 control groups) and 1000 ppm. The third study was a pair feeding study with rats given 1000 ppm. The available data was limited for these 3 studies, however, it is apparent that methoxychlor at 1000 ppm produced reproductive effects in the form of reduced fertility index, reduced litter size, and reduced viability index. There was evidence of possible systemic toxicity at the 200 ppm dose, however, there was also evidence of reduced food consumption. Therefore the tentative NOEL and LEL are 200 ppm (10 mg/kg/day) and 1000 (50 mg/kg/day), respectively.; core grade supplementary (E.I. du Pont de Nemours and Co., Inc., 1966)

Other Data Reviewed:

1) Carcinogenicity Study - rat: Dietary levels tested: Male: 0, 360, 500, 720, and 1000 ppm (0, 18, 25, 36, and 50 mg/kg/day); Female: 0, 750, and 1500 ppm (0, 37.5, and 75 mg/kg/day); Male and female Osborne-Mendel rats were administered methoxychlor in the diet for 2 years. The initial dose levels for males were 360 and 720 ppm but were increased to 500 and 1000 ppm after week 30. Based on the data provided in this study, there is no substantial evidence that the MTD had been reached. The reduced male and female body weights noted in treated groups may be

due to reduced food consumption (no food consumption data provided), also other studies with methoxychlor indicate that mixing the compound in the food tends to reduce food consumption and therefore weight.; core grade supplementary (U.S. Department of Health, Education, and Welfare, 1977a)

2) Carcinogenicity Study - mouse: Dietary levels tested: Male: 0, 1400, 1750, 2800, and 3500 ppm (0, 210, 262.5, 420, and 525 mg/kg/day); Female: 0, 750, 1000, 1500, and 2000 ppm (0, 112.5, 150, 225, and 300 mg/kg/day); Male and female B6C3F1 were administered methoxychlor in the diet for 78 weeks. The initial dose levels for males were 1400 and 2800 ppm while females initially received 750 and 1500 ppm. After week two, doses were increased to 1750 and 3500 ppm for males and to 1000 and 2000 ppm for females. Based on the data provided in this study, there is no substantial evidence that the MTD had been reached. The reduced body weights noted in treated males (high dose only) and in treated females (all dose levels) may be due to reduced food consumption (no food consumption data provided). Other studies with methoxychlor indicate that mixing the compound in the food tends to reduced food consumption and therefore weight.; core grade supplementary (U.S. Department of Health, Education, and Welfare, 1977b)

Data Gap(s): Chronic Rat Feeding/Carcinogenicity Study; Chronic Dog Feeding Study; Rat Reproduction Study; Rat Developmental toxicity Study; Rabbit Developmental toxicity Study; Chronic Mouse Feeding/Carcinogenicity Study

I.A.5. Confidence in the Oral RfD

Study — Low
Database — Low
RfD — Low

The critical study is given a low confidence rating since no conclusions could be made relative to the maternal or developmental toxicity of Methoxychlor due to the total loss of litters in the high-dose group and the small number of litters available for evaluation in the mid-dose group. The database is given a low confidence rating because of the lack definitive chronic toxicity studies. Low confidence in the RfD follows.

I.A.6. EPA Documentation and Review of the Oral RfD

Source Document — This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation — Pesticide Registration Standard, August 1988; Pesticide Registration Files

Agency Work Group Review — 04/18/1990, 05/17/1990, 06/21/1990

Verification Date — 06/21/1990

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfD for Methoxychlor conducted in August 2003 identified one or more significant new studies. IRIS users may request the references for those studies from the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Methoxychlor
CASRN — 72-43-5

The health effects data for methoxychlor were reviewed by the U.S. EPA RfD/RfC Work Group and determined to be inadequate for the derivation of an inhalation RfC. The verification status for this chemical is currently NOT VERIFIABLE. For additional information on the health effects of this chemical, interested parties are referred to the U.S. EPA documentation listed below.

NOT VERIFIABLE status indicates that the U.S. EPA RfD/RfC Work Group deemed the database at the time of review to be insufficient to derive an inhalation RfC according to the Interim Methods for Development of Inhalation Reference Concentrations (U.S. EPA, 1990). This status does not preclude the use of information in cited references for assessment by others.

Derivation of an inhalation RfC for methoxychlor is not recommended at this time. No adequate long-term studies examining the effects of inhalation exposure to methoxychlor exist. No inhalation pharmacokinetic data exist for this compound. No data exist to definitively rule out portal-of-entry effects. The requirements for a minimal database have not been met (U.S. EPA, 1990).

Methoxychlor [2,2-bis(4-methoxyphenyl)-1,1,1-trichloroethane], also known as methoxy-DDT, is a pale yellow, crystalline organochlorine insecticide. It is used principally as a larvacide. Vapor pressure data on methoxychlor are not available. Methoxychlor is the p-methoxy

derivative of the insecticide dichlorodiphenyltrichloroethane (DDT). Technical grade methoxychlor contains approximately 88% methoxychlor, with the remaining 12% comprising at least 50 impurities.

The only study of methoxychlor using inhalation exposure is that of Haag et al. (1950) who exposed two dogs, two rabbits, and 10 rats to an atmosphere containing micronized dust in which 10% recrystallized methoxychlor was mixed with Pyrax (composition not described) plus 3% Santo-Cel (a dehydrated silica gel) for 2 hours/day, 5 days/week. Concentrations and duration of exposures for three replicate experiments were reported as 300 mg/cu.m for 4 weeks, 360 mg/cu.m for 4 weeks, and 430 mg/cu.m for 5 weeks. This diluent was itself toxic and caused death and weight changes in the control dogs and rats at about the same incidence as the group exposed to methoxychlor. Further, it is not clear from the report whether the amount of diluent was normalized for all the exposed groups. The toxicity of DDT was also investigated in this study. DDT and methoxychlor were of comparable toxicity in dogs and rabbits, but methoxychlor was less toxic than DDT in rats.

No reliable information is available on the effects of methoxychlor in humans, via inhalation or oral exposure. Ziem (1982) reported the case of a 49-year-old man who suffered from fatigue and bruising several weeks after he used a tomato dust pesticide containing methoxychlor. Two months after exposure he was diagnosed with aplastic anemia, and he died within 6 months. The man was well and had not been taking any drugs prior to exposure to methoxychlor. This is the only case of aplastic anemia reported in association with exposure to methoxychlor. Lehman (1949, as cited in U.S. EPA, 1987a) estimated that the lethal oral dose of methoxychlor in humans is 450 g (6.4 g/kg for a 70 kg human). Stein (1970) reported the results of an experiment in which 16 human volunteers (prisoners) were orally administered either 0.5, 1.0, or 2.0 mg/kg methoxychlor for 5 to 8 weeks. Histopathological examination of biopsies of several tissues (liver, fat, bone marrow, and testicle) evidenced no abnormality. No weight disturbances or changes in clinical pathology (parameters measured not specified) were noted in the treated volunteers. Stein (1970) also reported the results of a study in which Sprague-Dawley rats (number not indicated) and Rhesus monkeys (3/group, sex not indicated) were administered 400-2500 mg/kg methoxychlor in 1% gum tragacanth by gavage for approximately 3 months (rats) or 6 months (monkeys). The rats demonstrated a dose-related depression in body weight gain after 4-6 weeks of treatment, but no weight disturbances were observed in the monkeys. No treatment-related effects on any of the clinical chemistry parameters measured were noted in either the rats or the monkeys. Similarly, no gross or microscopic evidence of treatment-related pathology was noted in either the rats or the monkeys. A decrease in hepatic triglycerides in both rats and monkeys was noted.

Several investigators have demonstrated that methoxychlor and its metabolites possess estrogenic properties (Bulger et al., 1978; Kupfer and Bulger, 1987). These estrogenic effects are

manifested by changes in both male and female reproductive function and morphology in rodents. Administration of methoxychlor at rather high doses by gavage, in feed, or parenterally has been reported to stimulate the development of the reproductive tract in neonatal female rodents and their offspring, as evidenced by early vaginal opening, vaginal cornification, and an increase in the weight of reproductive organs (i.e., ovary and uterus) (Bulger et al., 1978; Eroschenko and Cooke, 1990; Gray et al., 1989; Harris et al., 1974). Methoxychlor administered to mature female rodents has been reported to inhibit reproductive function, as evidenced by inhibited folliculogenesis and atresia of follicles (Bal, 1984); decreased fertility; reduced implantations; and abnormal estrous cyclicity and/or persistent vaginal estrus (Gray et al., 1988, 1989; Martinez and Swartz, 1991). Atypical cell growth has also been noted in the uterus and oviducts (Eroschenko and Cooke, 1990; Gray et al., 1988). In a series of experiments conducted by Cummings and coworkers, it was demonstrated that the estrogenic, antifertility effects of methoxychlor are mediated in part by a direct effect on the uterus to suppress decidualization (Cummings and Gray, 1987), by suppression of serum progesterone levels (Cummings and Gray, 1989), and by accelerated transport of fertilized ova through the oviducts resulting in a loss of viable embryos that could account for the increase in preimplantation loss observed with methoxychlor (Cummings and Perreault, 1990). The estrogenic effects of methoxychlor have also been observed with regard to behavior. Behaviors thought to be mediated by estrogen (running wheel activity and sexual behavior) were enhanced in intact and ovariectomized female rats treated with methoxychlor, and the enhanced behaviors were suppressed by progesterone, which is known to block the effects of estrogen (Gray et al., 1988).

Effects on male reproductive function have also been reported following the administration of methoxychlor to rodents. Bal (1984) reported inhibited spermatogenesis, degeneration of spermatogonia and spermatocytes, and cytoplasmic vacuolation in the epithelium of the ductus epididymis in male rats following the administration of 100-200 mg/kg/day methoxychlor. A decrease in seminal vesicle and caudal epididymal weight and caudal sperm count as well as delayed puberty were observed in neonatal rats administered 25-200 mg/kg/day methoxychlor for one generation, indicating that the endocrine function of the testes and pituitary gland were affected (Gray et al., 1989). Cooke and Eroschenko (1990) also noted that the development of the neonatal male rat reproductive tract was inhibited by methoxychlor administration, as evidenced by a decrease in serum testosterone levels and decreased DNA content of the seminal vesicles, bulbourethral glands, and the ventral prostate. Rats fed 2000 ppm methoxychlor for 90 days exhibited decreased prostate size and cell content (Shain et al., 1977). Goldman et al. (1986) hypothesized that part of methoxychlor's effects on male reproductive function may be mediated by a prolactinemic effect since administration of 25 or 50 mg/kg/day methoxychlor to 21-day-old male rats caused an increase in serum prolactin levels and an increase in hypothalamic-gonadotropin-releasing hormone levels.

Methoxychlor has been demonstrated to be fetotoxic. Khera et al. (1978) studied the effects of oral administration of 50, 100, 200, or 400 mg/kg/day methoxychlor to pregnant Wistar rats on gestational days 6-15. Two formulations of methoxychlor were used: (1) technical grade and (2) a formulation that was 50% methoxychlor (the composition of the remaining 50% was unknown). Maternal body weight gain was depressed in all treatment groups and remained depressed after removal of the uterine contents, implying an adverse effect on the dam. Treatment with either formulation of methoxychlor at the two highest doses resulted in a reduced number of rats with live fetuses at term and a reduced number of live fetuses per pregnancy. Reduced fetal weight gain was observed at the two highest dose levels with both formulations. An increased incidence of fetal skeletal anomalies (mostly wavy ribs) was observed at the two highest dose levels with both formulations.

Several chronic oral carcinogenicity bioassays have been conducted with methoxychlor (see review by Reuber, 1980), the results of which have been equivocal such that methoxychlor has yet to be classified as a carcinogen by the U.S. EPA. Aside from a depression in body weight gain observed in both rats fed at 1500 ppm and mice fed at 1994 ppm in a 2-year study conducted by NCI, no dose-related nonneoplastic effects were reported in these studies. Deichmann et al. (1967), however, fed 1000 ppm methoxychlor for 27 months to Osborne-Mendel rats and reported other nonneoplastic hepatic effects, including decreased absolute weight accompanied by hydropic swelling and some necrosis and congestion. Reuber (1980) reevaluated the slides from the carcinogenicity study of miniature swine and described the occurrence of moderate hyperplasia of the mammary gland with milk-like secretion, hyperplasia of the uterus, and chronic interstitial renal fibrosis. These lesions are similar to those observed in the subchronic study in swine reported by Stein (1970) and Tegeris et al. (1966) and may be interpreted to be due to the estrogenic properties of methoxychlor.

A series of studies conducted in dogs and swine indicates that the two species respond differently with respect to the toxicity of methoxychlor (Stein, 1970; Tegeris et al., 1966). Technical grade methoxychlor (1, 2, or 4 g/kg) was administered in the feed 7 days/week to groups of six animals each (with 12 animals serving as controls) for up to 6 months. Clinical examinations were conducted daily, weights were recorded weekly, and blood samples were taken for hematological and clinical chemical analyses at 6-week intervals throughout the experiment. Bone marrow morphology and complete necropsies, with histopathological evaluation of approximately 18 tissues, were conducted at study termination. All dogs that were fed methoxychlor lost weight throughout the experiment, but, after an initial 8-week weight loss, the swine receiving the two lower doses of methoxychlor began to gain weight, whereas the high-dose swine continued to lose weight. Most of the medium-dose (5/6) and all of the high-dose dogs (6/6) began exhibiting clinical signs of toxicity after 6 weeks of treatment. Symptoms included nervousness and apprehension, progressing to salivation, fasciculations, tremors, hyperesthesia, mydriasis, tonic seizures, and tetanic convulsions. Most of these dogs died 3 weeks thereafter. The swine

exhibited no clinical signs of toxicity. No treatment-related changes in any of the hematological parameters studied were noted in either the dogs or the swine. The dogs exhibited dose-dependent elevations in SGOT, SGPT, and alkaline phosphatase (AP). At 24- weeks exposure, the enzyme values of the high-exposure group relative to control values were increased eightfold for SGOT, 30-fold for SGPT, and 30- fold for AP, whereas the swine exhibited only a two-fold increase in BUN. The only changes attributed to methoxychlor noted at gross and microscopic examination in dogs (including the liver) were a dose-dependent absence of adipose tissue from the normal depots and congestion of the small intestinal mucosa (without accompanying histopathology). In the swine, advanced chronic renal nephritis, hyperplastic and hypertrophic mammary glands, and hypertrophic uteri were noted in the treated animals. These latter effects on sex organs are most likely due to the estrogenic properties of methoxychlor.

Very little quantitative information is available on the toxicokinetics of methoxychlor, and the available information is for oral or parenteral routes of exposure only. Absorption of methoxychlor from the gastrointestinal tract can be inferred from the observation of toxic effects following oral administration. Kapoor et al. (1970) administered radiolabeled methoxychlor to mice and found that 98.3% of the administered radioactivity was eliminated within 24 hours, mostly in the feces. A number of studies show that methoxychlor does not accumulate in the body to any appreciable degree (e.g., Villeneuve et al., 1972), but accumulation of methoxychlor in fat has been observed following administration of very high dietary levels of methoxychlor (U.S. EPA, 1987b). Methoxychlor is metabolized in the liver to readily excretable polar compounds (U.S. EPA, 1987b). Methoxychlor and 26 metabolites were identified in the feces, urine, and bile of intact, colostomized, and bile-fistulated chickens orally administered methoxychlor (Davison et al., 1984). Lactating goats also eliminate methoxychlor and its metabolites primarily in the feces (Davison et al., 1982). The results of studies by Villeneuve et al. (1972) indicate that methoxychlor does not induce hepatic microsomal enzymes.

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Agency Work Group Review — 11/07/1991

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfC for Methoxychlor conducted in August 2003 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

EPA Contacts:

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name —Methoxychlor
CASRN — 72-43-5
Last Revised — 09/07/1988

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

II.A. Evidence for Human Carcinogenicity

II.A.1. Weight-of-Evidence Characterization

Classification — D; not classified as to human carcinogenicity

Basis — Human data are unavailable, and animal evidence is inconclusive.

II.A.2. Human Carcinogenicity Data

None

II.A.3. Animal Carcinogenicity Data

A number of chronic dietary studies have been done to test the carcinogenicity of methoxychlor in rats and mice (Nelson and Fitzhugh, 1951; Hodge et al., 1952, 1966; Radomski et al., 1965; Davis, 1969; Deichmann et al., 1967; NCI, 1978). In addition, two limited studies using mice (Hodge et al., 1966) have been performed by subcutaneous administration and skin application. Reuber (1980) reviewed these chronic studies, reevaluating raw data and the histological sections when possible.

In the Nelson and Fitzhugh (1951) study, Osborne-Mendel rats (12 rats/sex/group) ingested 0, 10, 25, 100, 200, 500 or 2000 ppm methoxychlor in the diet for 2 years. Animals were examined for gross lesions. Histological preparations were made only from the gross lesions found at autopsy. In the highest dose group four hepatic cell adenomas were observed, but this was not a statistically significant increase. No other changes or malignant lesions were noted in other organs. In his review of this study, Reuber (1980) concluded that the incidence of hepatic neoplasms in the treated animals was significantly greater than that in controls when hyperplastic nodules were included.

Groups of 25 male and 25 female rats (strain not specified) ingested 0, 25, 200, or 1600 ppm methoxychlor in the diet for 2 years (Hodge et al., 1952). At the end of 2 years, surviving animals were killed and many organs were examined grossly and histopathologically. In treated female rats, a greater number of total tumors was observed compared with controls. The authors considered this increase to be of no biological relevance because there was no significant increase in tumors of any one organ. Interpretation of these results is limited by the fact that many of the animals were not accounted for at the end of the study and that the liver was not routinely examined histologically.

Radomski et al. (1965) administered methoxychlor for 2 years in the diet at levels of 0 and 80 ppm to Osborne-Mendel rats (30 rats/sex/group). No increase in tumor incidence was found in the treated rats as compared with controls. Methoxychlor was also administered under the same regimen in a mixture with aramite, DDT, and thiourea at concentrations of 50 ppm each to 50 rats/sex/group. In this study an apparent increase in total tumors was observed in animals treated with the mixture as compared to controls.

Deichmann et al. (1967) administered methoxychlor in the diet to Osborne- Mendel rats (30/sex/dose) at levels of 0 and 1000 ppm for 27 months. The concentration was chosen to be 50% of the highest dose reported in the Nelson and Fitzhugh study (1951). An increase in the number of total tumors was observed in treated males as compared with controls, but the increase was not statistically significant.

NCI (1978) tested groups of 50 male and 50 female Osborne-Mendel rats and 50 male and 50 female B6C3F1 mice. Control groups of each species consisted of 20 males and 20 females. Rats were exposed to technical grade methoxychlor (95% pure) in the diet for 78 weeks, followed by a 33-week observation period without exposure to the test compound. Concentrations given the low-dose male rats were 360 ppm for the first 29 weeks followed by 500 ppm for the next 49 weeks. The high-dose group was given 720 ppm for 29 weeks, 1000 ppm for the following 29 weeks, then 1000 ppm administered in a cyclic pattern for 20 weeks of one dosage-free week followed by 4 weeks of treatment. The low-dose female rats were given 750 ppm for the entire 78 weeks. The high-dose group received 1500 ppm for 55 weeks followed by 23 weeks of the cyclic pattern of administration at the same concentration. The time-weighted average (TWA) concentration for the high- and low-dose groups, respectively, was 845 and 448 mg/kg for the male rats and 1385 and 750 mg/kg for female rats, respectively.

Male mice were given a concentration of 1400 ppm for 1 week, then 1750 ppm for 77 weeks or 2800 ppm for 1 week, then 3500 ppm for 77 weeks. Female mice were given concentrations of 750 ppm for 1 week, then 1000 ppm for 77 weeks or 1500 ppm for 1 week, then 2000 ppm for 77 weeks. The mice were observed for an additional 15 weeks with no methoxychlor treatment. The TWA concentration for high- and low-dose groups, respectively, was 3491 and 1746 mg/kg for the male mice and 1994 and 997 mg/kg for female mice. Necropsy was performed on all animals that died spontaneously or were killed when moribund or at the termination of the study. Histological examinations were performed on major organs and on any gross lesions of all animals, except where cannibalism or autolysis precluded such studies.

The only tumors observed at a higher incidence than in controls were hemangiosarcomas in male rats (1/20 control, 9/50 low-, 2/50 high-dose groups). Although historically this tumor type is not frequently observed in this strain or rats, the authors concluded that the increase was not a good indicator of the carcinogenicity of methoxychlor because the response was neither dose-related

nor statistically different from control values. Other tumors observed in the treated rats also occurred in the controls at the same frequency. NCI concluded that under this experimental regimen, methoxychlor was not tumorigenic to Osborne-Mendel rats. In mice, a variety of tumors was observed, but the incidence was similar in both control and experimental groups. Recent reviews by Greiesemer and Cueto (1980) and Harper et al. (1982) indicated that the bioassays did not meet the current criteria for maximum tolerated doses and so were not powerful enough to detect carcinogenicity. The evidence of carcinogenicity was, therefore, judged to be inconclusive, rather than negative.

In the Davis (1969) study, male and female BALB/c and C3H mice (100/sex/strain) were fed diets containing 0 or 750 ppm methoxychlor for 2 years. Liver tumors were found in male and female BALB/c mice and in male C3H mice. Carcinomas of the testes were observed in male BALB/c mice. It was the author's preliminary judgment that the data did not show that methoxychlor was carcinogenic but suggested that a more complete statistical analysis was needed. In reviewing the original data, Reuber (1980) concluded that the increased incidences of liver carcinoma in C3H males and in BALB/c males and females were statistically significant, as well as increases in testicular carcinoma in BALB/c males and neoplasms at all sites in male and female BALB/c mice.

Nelson and Radomski (1953) fed methoxychlor at a dose of 300 mg/kg/day to four dogs. Two of the dogs died early in the study, but two female dogs survived the dosing period of 3.5 years. Liver foci were observed in one dog, and the other was described as exhibiting slight fibrosis in the liver. Reuber (1980) reexamined the histological sections and reported that one dog had developed liver carcinoma. The small number of animals used in this study precludes any definitive interpretation of these findings.

There is considerable disagreement between Reuber and the original authors in the interpretation of the histology and data from several of the chronic studies. NCI (1978), IARC (1979), and U.S. EPA (1983) have concluded that the experimental evidence does not support the contention that methoxychlor is a carcinogen. U.S. EPA (1987) has suggested that the differences in the conclusions may be due in part to the difficulty in distinguishing between regenerative hyperplasia, hyperplastic nodules, benign neoplasia, and malignant neoplasia, as well as the use of inappropriate control data in some of Reuber's statistical analyses.

II.A.4. Supporting Data for Carcinogenicity

In mutagenicity assays, negative results were obtained (with or without metabolic activation) in bacteria, yeast, in assays of methoxychlor-induced DNA damage, or in assays of unscheduled DNA synthesis in mammalian cell cultures (Probst et al., 1981). A weakly positive increase was

observed in a transformation study using BALB/3T3 cell line (Dunkel et al., 1981). Methoxychlor is a structural analog of DDT.

II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

Not available.

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

Not available.

II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

II.D.1. EPA Documentation

Source Document — U.S. EPA, 1987, 1983

The 1987 Drinking Water Criteria document received OHEA review. The Multimedia Risk Assessment received Agency Review.

II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Work Group Review — 10/07/1987

Verification Date — 10/07/1987

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the cancer assessment for Methoxychlor conducted in August 2003 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

II.D.3. EPA Contacts (Carcinogenicity Assessment)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

III. [reserved]
IV. [reserved]
V. [reserved]

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Substance Name — Methoxychlor
CASRN — 72-43-5

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VII. Revision History

Substance Name —Methoxychlor
CASRN — 72-43-5

Date	Section	Description
09/07/1988	II.	Carcinogen summary on-line
09/01/1990	I.A.	Oral RfD summary on-line

Date	Section	Description
04/01/1992	I.B.	Inhalation RfC discussion on-line
12/01/1993	I.B.	Replaced with expanded assessment
10/28/2003	I.A.6., I.B., II.D.2.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name —Methoxychlor
CASRN — 72-43-5
Last Revised — 09/07/1988

- 72-43-5
- 2,2-di-p-anisyl-1,1,1-trichloroethane
- DMDT
- marlate
- methorcide
- Methoxychlor
- methoxy-DDT
- moxie
- 1,1,1-trichloro-2,2-bis(p-methoxyphenyl)ethane