2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO METHOXYCHLOR IN THE UNITED STATES

Methoxychlor is produced commercially in the United States, typically as a technical-grade product containing 88–90% of the pure chemical and 10–12% of impurities consisting of isomers of methoxychlor and other reaction products. Methoxychlor has been used as an insecticide against a wide range of pests, including houseflies, mosquitos, cockroaches, chiggers, and various arthropods commonly found on field crops, vegetables, fruits, stored grain, livestock, and domestic pets. There are no known natural sources of methoxychlor. It is moderately soluble in water and is soluble in a variety of organic solvents. Annual usage of methoxychlor in the United States was estimated to range from 500,000 to 900,000 pounds in 1986. The available data show that use patterns have remained fairly constant since 1974.

Methoxychlor is released to the environment mainly as a result of its application to crops and livestock as a pesticide. Smaller amounts may be released during its production, formulation, storage, shipment, and disposal. Most methoxychlor is probably removed from the air by wet and dry deposition processes in less than a month. Methoxychlor binds tightly to soils, but most does not persist due to degradation by microorganisms in the soil. Degradation products of methoxychlor are generally detected in lower levels of soil, suggesting that they are more mobile than methoxychlor. Methoxychlor is generally not detected in surface water or groundwater in the United States, probably due to its degradation and its affinity for sediments and organic matter. However, methoxychlor may be detected in waters near release sources. Although methoxychlor (a derivative of DDT) is not as persistent as DDT, it does have the potential for bioconcentration and has been shown to bioaccumulate to varying degrees in fish, insects, and mammals.

For the general population, the most likely source of methoxychlor exposure is from low-level contamination of food. The FDA's Total Diet Study program monitors chemical contaminants in the U.S. food supply and has calculated average daily intakes of methoxychlor in adults (age 25–65) ranging from 0.1 to 0.3 ng/kg/day for the period 1986–1991. Exposure to methoxychlor from food may be elevated in persons who consume large amounts of fish and seafood from methoxychlor-contaminated waters. Because methoxychlor is usually not detected in ground or surface water sources, exposure to methoxychlor from drinking water is not expected to be significant for the general population. Based on the results of the Non-Occupational Pesticide Exposure Study (conducted between 1986 and 1988),

inhalation exposure to methoxychlor ranged from 0.002 to 0.012 µg/day in one U.S. city. In a monitoring study of nonoccupational exposure to pesticides used in and around the home, methoxychlor was detected (air concentrations were not provided) in both indoor and outdoor samples.

Exposures may be greater in individuals who use methoxychlor-containing products for home gardening or animal-care purposes. Populations that live or work on or near a farm where methoxychlor has been used recently on crops or livestock or that live near a hazardous waste site that contains methoxychlor could be exposed to above-average levels of methoxychlor in soil and possibly in water.

The available data suggest that exposure of children to methoxychlor differs from that of adults. Small children may also play close to the ground and are therefore more likely than adults to come in contact with dirt and dust found in home carpets, dirt found outside the home, and lawns. Children also may intentionally or unintentionally ingest soil that contains low levels of methoxychlor.

Methoxychlor has been found in at least 58 of the 1,613 current or former NPL sites. However, the total number of NPL sites evaluated for methoxychlor is not known.

2.2 SUMMARY OF HEALTH EFFECTS

Available data on the toxicity of methoxychlor in humans are limited to a study that found no clinical or histopathological changes in four men and four women who ingested 2 mg/kg/day of methoxychlor for 6 weeks. These data are too limited to allow assessment of the health risks of methoxychlor to humans.

Oral exposure of animals to methoxychlor has shown that high doses of methoxychlor are capable of causing neurological injury (tremors, convulsions), but most studies indicate that the reproductive system is the most sensitive target for methoxychlor. The resultant types of reproductive effects are indicative of interference with the normal actions of estrogen or androgen. Mechanistic studies have confirmed that metabolites of methoxychlor can compete with estrogen for binding to estrogen receptors and can mimic some and antagonize other effects of estrogen. Additional studies have shown that methoxychlor or its metabolites can interact with the androgen receptor and antagonize androgenic effects. In females, these interactions can result in disruption of estrus cyclicity, reduced fertility, and increased pre- and post-implantation losses. Effects in males can include delayed sexual maturation, atrophy of reproductive organs and accessory glands, and altered sexual or socio-sexual behavior. Many of these effects may be mediated through altered hormone levels. Because methoxychlor and its metabolites are cleared fairly

rapidly from the body (approximately 92% in 24 hours in mice), there does not appear to be much potential for cumulative toxicity.

Observable changes in the liver (altered liver weight, altered enzyme and protein levels, pale and mottled appearance) and kidneys (cystic tubular nephropathy, elevated blood urea nitrogen [BUN]) of animals, as well as weight loss, are caused only by relatively large doses of methoxychlor; these effects are probably not mediated by an estrogenic mechanism.

Most carcinogenicity studies have not shown an increase in the cancer incidence following exposure to methoxychlor. Based on a review of all the available data, IARC has classified methoxychlor as a Group 3 carcinogen (not classifiable as to its carcinogenicity to humans). Similarly, EPA has classified methoxychlor as a Group D carcinogen (not classifiable as to human carcinogenicity).

Reproductive Effects. Although human data on the reproductive effects of methoxychlor are limited, the animal and *in vitro* data strongly suggest that sufficient exposure to methoxychlor may adversely affect the development, histopathology, and function of the human reproductive system.

Data from oral studies in animals indicate that the reproductive system is the primary and most sensitive target of methoxychlor-induced toxicity in both adult and developing animals. Some metabolites and contaminants of methoxychlor are estrogenic or anti-androgenic and are capable of producing adverse effects on the male and female reproductive system. These effects are thought to be mediated by interaction of methoxychlor or its metabolites with the estrogen receptor α, estrogen receptor β, or an as yet unknown estrogen receptor, or with the androgen receptor. These interactions can cause disruption of reproductive development or can alter reproductive function in adults. Altered serum and pituitary hormone levels have frequently been seen in animal studies, which may contribute to the changes in reproductive development and function. Developmental reproductive changes include precocious puberty and abnormal estrus cyclicity in females, delayed puberty in males, altered weights of reproductive organs and accessory glands, and impaired reproductive function in adulthood, including decreased pups/litter and increased resorptions. Similar effects have also been seen following exposure of adult animals. Additionally, gross and microscopic cellular changes have been observed in the reproductive organs of exposed adult females and males. While methoxychlor does have estrogenic properties, it is important to note that it is at least several thousand fold less potent than endogenous estrogen.

There are no human data that report adverse effects on the reproductive system following exposure to methoxychlor, but *in vitro* studies reveal that human liver microsomes are capable of metabolizing methoxychlor to estrogenic compounds. Therefore, it is likely that methoxychlor could produce reproductive estrogen-like effects in humans.

Developmental Effects. In animals, signs of fetotoxicity (decreased fetal body weight, increased incidence of wavy ribs, resorptions, and death) were noted following exposure to methoxychlor *in utero*. These effects may be due to the maternal toxicity of methoxychlor and may not be true signs of teratogenicity.

Methoxychlor exposure during development can adversely affect the reproductive system of both developing and adult animals. These effects were discussed with the reproductive effects above. These effects are the result of the disruption by estrogenic methoxychlor metabolites of the normal delicate balance of time-sensitive hormone levels during fetal and post-natal development. Taken together, the animal data suggest that human exposure to methoxychlor during critical stages of development may adversely affect reproductive development, causing effects that may not be detected until after puberty.

Neurological Effects. Animal studies suggest that exposure to large amounts of methoxychlor can produce neurological effects, such as apprehension, nervousness, increased salivation, decreased locomotor activity, tremors, convulsions, and death. Methoxychlor has been demonstrated to be a neurotoxicant even in the absence of metabolism. This suggests that it is the parent compound that is neurotoxic, and that neurotoxicity is of concern only when the metabolic capacity for *O*-demethylation is exceeded. This is supported by the observation that the neurological effects of methoxychlor are similar to those associated with exposure of humans and animals to DDT, a structurally similar chemical that is very slowly metabolized. The mechanism by which DDT, and therefore possibly methoxychlor, produces neurological effects has been proposed to involve the membrane-association of a lipophilic species, which alters ion transport across neural membranes.

2.3 MINIMAL RISK LEVELS

Inhalation MRLs

No inhalation MRLs for methoxychlor have been derived because adequate data were not available concerning the effects of methoxychlor via this route of exposure.

Oral MRLs

No acute oral MRL was derived for methoxychlor. A variety of candidate acute-duration MRL studies were considered. The acute oral MRL derived in the previous 1994 toxicological profile for methoxychlor was based on precocious vaginal opening (early puberty) observed in the study by Gray et al. at 25 mg/kg/day. However, since this study did not test doses as low as Chapin et al. (used as the basis of the intermediate-duration MRL), which demonstrated the same effect at 5 mg/kg/day administered from gestation day 14 to postnatal day 42, it is not known whether the premature puberty would have occurred at a lower acute dose than the 25 mg/kg/day observed in the Gray et al. study. There were several hypothesis-generating studies at extremely low doses that were not definitive enough to use for MRL derivation. The male reproductive parameters observed in these studies included increased prostate weight, increased territorial urine marking, increased killing of young mice by adults, and changes in aggression. These studies were not used for MRL derivation because the biological significance and relevance to human health of extremely low-dose effects has not been definitively established. Additionally, prostate weight is normally highly variable, even within a litter, and therefore may not be a good indicator of low-dose effects. These studies were all performed by the same laboratory and need to be replicated by other laboratories. See Appendix A for further discussion.

- An MRL of 0.005 mg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to methoxychlor.

This MRL is based on a LOAEL of 5 mg/kg/day from gestation day 14 to postpartum day 42 for accelerated onset of puberty (i.e., precocious vaginal opening) in immature female rats exposed to methoxychlor *in utero*, during lactation, and after weaning. Precocious vaginal opening was evident (statistically significant) in all methoxychlor-treated groups (vaginal opening occurred on postnatal days 37.4, 35.2, 30.8, and 33.4, respectively, for groups 0, 5, 50, and 150 mg/kg/day). The LOAEL was divided by an uncertainty factor of 1,000 (10 for variation in sensitivity among humans, 10 for extrapolation of animal data to humans, and 10 for extrapolation from a LOAEL to a NOAEL). The MRL is supported by other observations of reproductive effects associated with intermediate-duration exposure including elevated levels of prolactin in the pituitary of male rats exposed to 50 mg/kg/day, decreased seminal vesicle weight, caudal epididymal weight, and caudal epididymal sperm count, and increased gonadotropin releasing hormone in the mediobasal hypothalamus in male rats exposed to 50 mg/kg/day. At higher exposure levels, intermediate-duration studies show decreased fertility in male rats at doses of 60–400 mg/kg/day and in female rats at doses of 50–150 mg/kg/day. A study in humans that identified a NOAEL of 2 mg/kg/day for effects to the testes and menstrual cycle was not chosen as the basis for an MRL because reproductive function was not evaluated and the number of subjects was small (4/sex/exposure group), and such an MRL may not be protective of reproductive and developmental effects in the fetus or child.

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No chronic oral MRL was derived for methoxychlor. Studies in rats and mice reported no adverse histopathological effects on a number of organ systems, including the reproductive system, following chronic exposure to methoxychlor at dose levels of 77–599 mg/kg/day. However, these chronic studies did not evaluate sensitive indices of reproductive toxicity. A 3-generation study in rats reported a LOAEL of 79 mg/kg/day methoxychlor for decreased fertility, and a NOAEL of 18 mg/kg/day for this effect. An MRL was not based on this study because sensitive reproductive end points such as precocious vaginal opening were not monitored, and the resultant MRL might not be protective for these types of effects.