METOLACHLOR

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

DRAFT

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

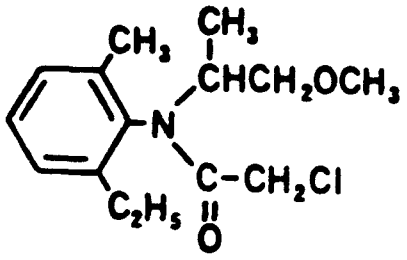
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. Health Advisories do not quantitatively incorporate any potential carcinogenic risk from such exposure. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 51218-45-2

Structural Formula



2-Chloro-N-(2-ethyl-6-methylphenyl)-N-(2-methoxy-1-methylethyl) acetamide

Synonyms

- o-Acetanilide; 2-chloro-6'-ethyl-N-(2-methoxy-1-methylphenyl); Dual®; Bicep®; Metetilachlor; Pimagram; Primextra; CGA-24705.

Uses (Meister, 1986)

- Selective herbicide for pre-emergence and preplant incorporated weed control in corn, soybeans, peanuts, grain sorghum, pod crops, cotton, safflower, woody ornamentals, sunflowers and flax.

Properties (Meister, 1986; Ciba-Geigy, 1977; Windholz et al., 1983; Worthing, 1983)

Chemical Formula	$C_{15}H_{22}NO_2Cl$
Molecular Weight	283.46
Physical State	White to tan liquid
Boiling Point	100°C (at 0.001 mm Hg)
Melting Point	--
Density	--
Vapor Pressure (20°C)	1.3×10^{-5} mm Hg
Specific Gravity	--
Water Solubility (20°C)	530 mg/L
Octanol/Water Partition Coefficient	--
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- Metolachlor has been found in 1,644 of 1,997 surface water samples analyzed and in 45 of 239 ground water samples (STORET, 1987). Samples were collected at 312 surface water locations and 297 ground water locations, and Metolachlor was found in 14 states. The 85th percentile of all nonzero samples was 11.5 ug/L in surface water and 0.25 ug/L in ground water sources. The maximum concentration found was 138 ug/L in surface water and 0.25 ug/L in ground water.

° Metolachlor residues resulting from agricultural use have also been detected in ground water in Iowa and Pennsylvania with concentrations ranging from 0.1 to 0.4 ppb.

Environmental Fate

(Forthcoming from OPP)

III. PHARMACOKINETICS

Absorption

° In studies conducted by Hambock (1974a,b), rats were administered a single oral dose (28.6 or 52.4 mg/kg) of metolachlor (purity not specified, but ^{14}C-labeled and unlabeled metolachlor were synthesized for these experiments). The chemical was readily absorbed, since 70 to 90% of the metolachlor was excreted as metabolites within 48 hours.

Distribution

° Data from rats given radioactive metolachlor (approximately 3.2 to 3.5 mg/kg) orally demonstrated that the chemical is rapidly metabolized. Residues in meat tissues and blood were very low and only blood contained residue levels in excess of 0.1 ppm (Hambock, 1974c).

Metabolism

° Studies conducted to identify urinary and fecal metabolites in the rat indicated that metolachlor is metabolized via dechlorination, O-methylation, N-dealkylation and side-chain oxidation (Hambock, 1974 a,b). Urinary metabolites included 2-ethyl-6-methylhydroxyacetanilide (MET-002) and N-(2-ethyl-6-methylphenyl)-N-(hydroxyacetyl)-DL-alanine) (MET-004). Fecal metabolites included 2-chloro-N-(2-ethyl-6-methyl-phenyl)-N-(2-hydroxy-1-methylethyl) (MET-003) and MET-004.

Excretion

° When treated with ^{14}C-metolachlor (approximately 31 mg/kg orally), male rats excreted 21.5% and 51.4% of the administered dose in the urine and feces, respectively, in 48 hours (Hambock, 1974a,b). The excreta contained 1, 15 and 22% of the administered dose as MET-002, MET-003 and MET-004, respectively. No unchanged chemical was isolated, and no glucuronide or sulfate conjugates were identified.

IV. HEALTH EFFECTS

Humans

° Signs of human intoxication from metolachlor and/or its formulations (presumably following acute deliberate or accidental exposures) include abdominal cramps, anemia, ataxia, dark urine, methemoglobinemia,

cyanosis, hypothermia, collapse, convulsions, diarrhea, gastrointestinal irritation, jaundice, weakness, nausea, shock, sweating, vomiting, CNS depression, dizziness, dyspnea, liver damage, nephritis, cardiovascular failure, skin irritation, dermatitis, sensitization dermatitis, eye and mucous membrane irritation, corneal opacity and adverse reproductive effects (HAZARDLINE, 1985).

Animals

Short-term Exposure

- The acute oral LD_{50} of technical metolachlor [>90% active ingredient (a.i.)] in the rat was reported to be 2,780 mg/kg (95% confidence range of 2,180 to 3,545 mg/kg; Bathe, 1973).

- Technical metolachlor in corn oil (>90% a.i.) was shown to be emetic in beagle dogs, precluding the establishment of an LD_{50} (AMR, Inc., 1974a). However, an "emetic dose" of 19 $\pm$ 9.7 mg/kg was established.

- Beagle dogs were fed technical metolachlor in the diet for 7 days in a range-finding study (Goldenthal et al., 1979). Each test group consisted of one male and one female. Doses were 1,000, 3,000 or 5,000 ppm with the controls receiving a basic diet plus the test material solvent (ethanol). The mean doses were 0, 13.7, 22.7 or 40.2 mg/kg. Decreased food consumption and body weight indicated that the two higher doses were unpalatable. No changes were observed at the lowest dose, although the animals exhibited soft stools and/or diarrhea over the study period. No other signs of overt toxicity, morbidity or mortality were observed in any animal. Accordingly, the lowest dose (13.7 mg/kg) is the NOAEL in this study.

Dermal/Ocular Effects

- The LD_{50} of technical metolachlor (> 90% a.i.) in the rabbit when tested by the unabraded dermal route is greater than 10,000 mg/kg (AMR, Inc., 1974b).

- Sachsse (1973b) evaluated the dermal irritation potential of technical metolachlor (>90% a.i.) on the New Zealand rabbits. The chemical was applied to abraded and unabraded skin for observation periods up to 72 hours. The results demonstrated that technical metolachlor is non-irritating to rabbit skin.

- Sachsse (1977) studied skin sensitization in the guinea pig by the intradermal-injection method. Technical metolachlor (>90% a.i.) dissolved in the vehicle (propylene glycol) and the vehicle alone were intradermally injected into the skin of two groups of Pilbright guinea pigs. A positive reaction was observed in the animals injected with metolachlor in vehicle, but not in animals treated with the vehicle alone. It was concluded that technical metolachlor is a skin sensitizer.

° A study of eye irritation by technical metolachlor (>90% a.i.) in the New Zealand White rabbit was conducted by Sachsse (1973a). The chemical was applied at a dose level of 0.1 mL/eye. Evaluation of both washed and unwashed eyes 24 hours and 7 days later revealed no evidence of irritation.

Long-term Exposure

° Beagle dogs (four/sex/dose) were administered technical metolachlor (>90% a.i.) in their feed for up to 15 weeks (Coquet et al., 1974). Initial doses were 0, 50, 150 or 500 ppm (equivalent to 0, 4 to 5, or 14 to 19 mg/kg/day). However, after 8 weeks, the group receiving 50 ppm was switched to a diet that delivered 1,000 ppm (27 to 36 mg/kg/day) for the remaining 6 weeks. The dose was increased because no signs of toxicity were observed in the 500-ppm group after 8 weeks. No animals died during the study and no significant changes were observed in gross or histological pathology, blood or urine analyses. Except for a decrease in food consumption and associated slight weight loss at the 1,000-ppm dose, no compound-related effects were observed. The NOAEL for this study is 500 ppm (14 to 19 mg/kg/day).

° A 6-month feeding study in dogs was conducted at levels of 0, 100, 300 or 1,000 ppm (Jessup et al., 1979). The average compound consumption was 0, 2.9, 9.7 or 29.6 mg/kg/day for the males and 0, 3, 8.8 or 29.4 mg/kg/day for the females, as determined by the investigators. The control and high-dose groups consisted of eight animals/sex; the low- and mid-dose groups consisted of six animals/sex. The extra control and high-dose animals were used in a recovery period study following sacrifice of the remaining animals at 6 months. The following significant changes were observed at the end of the study. Mean body weight gain was reduced in animals of both sexes fed 1,000 ppm; in addition, food consumption was reduced in the females at this level. Male dogs at the 300- and 1,000-ppm levels had significantly reduced activated partial thromboplastin time (APTT) after 5 and 6 months of observation. In females, significant changes in this parameter were observed for dogs at month 4 fed 100 ppm, at month 6 at the 300 ppm level, and at months 5 and 6 in the 1,000 ppm group. Additional studies demonstrated that the changes were not attributable to the pesticide. There were sporadic, but not treatment-related, changes in platelet and red blood cell counts and hemoglobin over the course of the study. Serum alkaline phosphate (SAP) levels decreased more slowly in the test groups than in the controls. These changes were significant in the groups fed 300 and 1,000 ppm. Therefore, the NOAEL in this study was 100 ppm (3 mg/kg/day).

° Tisdel et al. (1980) presented the results of a study in which metolachlor (95% a.i.) was administered to Charles River CD-1 mice (68/sex/dose) for 2 years at dietary concentrations of 0, 300, 1,000 or 3,000 ppm. Time-Weighted Average (TWA) concentrations, based upon diet analyses, were equal to 0, 287, 981 and 3,087 ppm. The dietary doses, from reported food intake and body weight data, were calculated to be equal to 0, 50, 170 or 526 mg/kg/day for the males and 0, 64, 224 or 704 mg/kg/day for the females. No treatment-related effects

were observed in terms of physical appearance, food consumption, hematology, serum chemistry, urinalysis or gross or histopathology. However, mortality was increased significantly in females fed 3,000 ppm (704 mg/kg/day). Statistically significant reductions in body weight gain were observed in both sexes at the highest dose. Also, statistically significant changes in absolute and organ-to-body weight ratios were noted occasionally (e.g. kidney- and liver-body weight ratios and decreased seminal vesicle to body weight ratio in high dose males). Based on this information, a NOAEL of 1,000 ppm (170 mg/kg/day for males and 224 mg/kg/day for females) is identified.

° Tisdel et al. (1983) presented the results of a study in which metolachlor (purity not specified) was administered to CD-Crl:CD (SD) BR rats for 2 years at dietary concentrations of 0, 30, 300 or 3,000 ppm. Assuming that 1 ppm in the diet of rats is equal to 0.05 mg/kg/day (Lehman, 1959), these dietary concentrations would be equal to 0, 1.5, 15 or 150 mg/kg/day. The control and 3,000-ppm groups consisted of 70 rats/sex. The 30- and 300-ppm groups consisted of 60 rats/sex. No treatment-related effects were noted in terms of mortality, organ weight and organ-to-body weight ratios. A variety of differences in clinical pathology measurements was found between control and treatment groups at various time intervals, but no consistent dose-related effects were apparent with the exception of a decrease in glutamic-oxaloacetic transaminase activity in high dose males at 12 months. Mean body weights of high-dose females were consistently less than controls from week 2 until termination of the study. This difference was statistically significant ($p < 0.01$) for 26 of the 59 intervals at which such measurements were made. Food consumption in high-dose females also was generally less than controls. Gross pathology findings were described by the investigators as being unremarkable. Microscopically, atrophy of the testes with degeneration of the tubular epithelium was noted to a greater extent in the 300- and 3,000-ppm groups than in the controls. Additionally, an increased incidence of eosinophilic foci was observed in the livers of both sexes exposed at 3,000 ppm. Based on this data, a NOAEL of 30 ppm (1.5 mg/kg/day) is identified.

Reproductive Effects

° A three-generation rat reproduction study was reported by Smith and Adler (1978). Targeted dietary exposures were 0, 30, 300 or 1,000 ppm. The actual exposures were analyzed to be 0, 30, 250 or 850 ppm. Assuming that 1 ppm equals 0.05 mg/kg/day (Lehman, 1959), the doses were calculated to be 0, 1.5, 22.5 or 42.5 mg/kg bw/day. No adverse effects were noted at any dose. A minimal NOAEL of 42.5 mg/kg is identified for reproductive effects.

° Smith et al. (1981) conducted a two-generation reproduction study in which Charles River CD rats (15 males and 30 females/dose) were administered technical-grade metolachlor (purity not specified) at dietary doses of 0, 30, 300 or 3,000 ppm. The TWA concentrations of metolachlor, based upon dietary analysis, were 0, 32, 294 or 959 ppm. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day

(Lehman, 1959), these dietary concentrations are approximately equal to 0, 1.6, 14.7 or 48 mg/kg/day. Mating, gestation, lactation, and female and male fertility indices were not affected in either generation. Additionally, pup survival was not affected. However, pup weights in the 959-ppm dose group, but not the 32- and 294-ppm dose groups, were significantly reduced in the F_{1a} and F_{2a} litters. Food consumption was reduced significantly for F_1 females receiving 32 ppm (1.6 mg/kg/day) and greater at various study intervals. Other effects that appeared to be treatment-related included increased liver-to-body weight ratios for both F_1 parental males and females at 1,000 ppm and increased thyroid-to-body weight and thyroid-to-brain weight in F_1 males at 1,000 ppm. Based on reduced pup weights, a reproductive NOAEL of 294 ppm (14.7 mg/kg/day) is identified.

- Tisdel et al. (1980) gave metolachlor (95% a.i.) to CD-1 mice (68/sex/dose) in the food for 2 years at concentrations of 0, 300, 1,000 or 3,000 ppm (the TWAs based on diet analyses were 0, 287, 981 or 3,087 ppm and corresponded to 0, 50, 170 or 520 mg/kg/day in males and to 0, 64, 224 or 704 mg/kg/day in the females). At the high dose, males were found to have a reduced seminal vesical-to-body weight ratio.

- Tisdel et al. (1983) exposed CD-Crl:CD (SD) BR rats (70/sex/dose) to metolachlor (purity not specified) in the diet for 2 years at 0, 30, 300 or 3,000 ppm (the doses correspond to 0, 1.5, 15 or 150 mg/kg/day). They observed greater testicular atrophy and degeneration of the tubular epithelium in the 300- and 3,000-ppm groups than in the control group.

Developmental Effects

- Fritz (1976) conducted a rat teratology study in which pregnant females (25/dose level) were administered doses of technical metolachlor (purity not specified) orally at 0, 60, 180 or 360 mg/kg/day during days 6 to 15 of gestation. No fetotoxic or developmental effects were noted.

- Lightkep et al. (1980) evaluated the teratogenic potential of metolachlor in New Zealand White rabbits (16/dose). The compound was administered as a suspension in aqueous 0.75% hydroxymethylcellulose at levels of 0, 36, 120 or 360 mg/kg/day. Single oral doses were given on days 6 to 18 of gestation. Abortions occurred in two rabbits: one in the 120-mg/kg/day group on day 25 (one early resorption) and one in the 360-mg/kg/day group on day 17 (one fetus) and day 20 (eight additional implantations). They did not consider these abortions to be treatment-related. Maternal toxicity (decreased food consumption and pupillary constriction) was observed in animals receiving the two highest doses. The highest dose group also exhibited blood in the cage pan and body weight loss over the treatment period. No significant developmental or fetotoxic effects were observed in the 319 fetuses, pups or late resorptions evaluated from all dose groups. Thus, a minimal NOAEL of 360 mg/kg/day for fetotoxicity and a NOAEL of 36 mg/kg/day for maternal toxicity were identified.

Mutagenicity

- Technical metolachlor (purity not specified) was tested in the Ames Salmonella test system, using S. typhimurium strains TA1535, TA1537, TA98 and TA100 (Arni and Muller, 1976). No increase in mutagenic response was observed, with or without microsomal activation, at concentrations of 10, 100, 1,000 or 10,000 ug/plate. Toxicity was observed at 1,000 and 10,000 ug/plate without activation and at 10,000 ug/plate with activation.

- Ciba-Geigy (1976) reported the results of a dominant lethal study in the mouse using technical metolachlor (purity not specified). The compound was administered orally in single doses of 0, 100 or 300 mg/kg to males that then were mated to untreated females over a period of 6 weeks. No evidence of adverse effects were observed, as expressed by increased implantation loss or resorptions.

Carcinogenicity

- Marias et al. (1977) presented the results of a study in which technical-grade metolachlor (purity not specified) was administered to Charles River CD-1 mice (50/sex/dose) at dietary concentrations of 0, 30, 300 or 3,000 ppm. Assuming that 1 ppm in the diet of the mouse is equal to 0.15 mg/kg/day (Lehman, 1959), these dietary levels are approximately 0, 4.5, 150 or 450 mg/kg/day. Males received the test material for 18 months; females received the test material for 20 months. Results of this study indicated no evidence of oncogenicity in either sex.

- Tisdel et al. (1980) presented the results of a study in which metolachlor (95% a.i.) was administered to Charles River CD-1 mice (68/sex/dose) for 2 years at dietary concentrations of 0, 300, 1,000 or 3,000 ppm. From food intake and body weight data, the doses were calculated to be equal to 0, 50, 170 or 526 mg/kg/day for the males and 0, 64, 224 or 704 mg/kg/day for the females. A statistically significant increase in the incidence of alveolar tumors in high-dose males was noted at the 18-month sacrifice; however, this effect was not confirmed by the final sacrifice at 24 months or by total tumor incidences for all animals.

- In 1979, Ciba-Geigy reported the results of a study in which technical metolachlor was administered to Charles River albino rats in their diet for 2 years at doses equivalent to 0, 1.5, 15 or 50 mg/kg/day. A statistically significant increase in the incidence of primary liver tumors was observed in the high-dose females (15/60 compared with 5/60 at mid doses and 3/60 at the low dose and control). These tumors included hypertrophic-hyperplastic nodules, angiosarcoma, cystic cholangioma and hepatocellular carcinoma. The variety of tumor expression forms suggests that a variety of cell types and locations may be affected in the liver.

- Tisdel et al. (1983) presented the results of a study in which metolachlor (purity not specified) was administered to CD-Crl:CD

(SD) BR rats for 2 years at dietary concentrations of 0, 30, 300 or 3,000 ppm. These doses were assumed to be equal to 0, 1.5, 15 or 150 mg/kg/day. An increased incidence of proliferative hepatic lesions (combined neoplastic nodules/carcinomas) was found in the high-dose females at terminal sacrifice ($p < 0.018$ by the Fisher exact test). Six of the 60 had neoplastic nodules ($p < 0.05$) and 7 of the 60 had liver tumors (one additional tumor was diagnosed as a carcinoma; $p < 0.01$).

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (approximately 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(NOAEL \text{ or } LOAEL) \times (BW)}{(UF) \times (\_\_\_ \text{ L/day})} = \_\_\_ \text{ mg/L } (\_\_\_ \text{ ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect-Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100 or 1,000), in accordance with NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No suitable information was found in the available literature for determination of a One-day HA for metolachlor. Accordingly, it is recommended that the Ten-day HA value for the 10 kg child (1.4 mg/L, calculated below) be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

The 7-day dietary study in dogs by Goldenthal et al. (1979) has been selected to serve as the basis for the Ten-day HA. Doses were 1,000, 3,000 or 5,000 ppm with the controls receiving a basic diet plus the solvent (ethanol) (one/sex/group). Actual mean doses were 0, 13.7, 22.7 or 40.2 mg/kg. The results indicated that the two higher doses were unpalatable, resulting in decreased food consumption and body weight. No changes were observed at the lowest dose, although the animals exhibited soft stools and/or diarrhea over the study period. No other signs of overt toxicity, morbidity or mortality were observed in any animal. The lowest dose, 13.7 mg/kg/day, is identified as the NOAEL.

The Ten-day HA for a 10-kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(13.7 \text{ mg/kg/day})\ (10 \text{ kg})}{(100)\ (1 \text{ L/day})} = 1.4 \text{ mg/L } (1{,}400 \text{ ug/L})$$

where:

13.7 mg/kg/day = NOAEL, based on absence of decreased food consumption and body weight loss.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

Longer-term Health Advisory

The study by Jessup et al. (1979) has been selected to serve as the basis for the Longer-term HA. A 6-month feeding study in dogs was conducted at average compound consumption levels of 0, 2.9, 9.7 and 29.6 mg/kg/day (males) and 0, 3.0, 8.8 and 29.4 mg/kg/day (females). Significant changes observed at the end of the study included reduced mean body weight gain in animals of both sexes fed 1,000 ppm and reduced food consumption in the females at this level. Serum alkaline phosphate levels decreased more slowly in the test groups than in the controls. These changes were statistically significant in the groups fed 300 and 1,000 ppm. Therefore, the NOAEL in this study is identified as 100 ppm (3 mg/kg/day).

The Longer-term HA for a 10-kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(3 \text{ mg/kg/day})(10 \text{ kg})}{(100)\ (1 \text{ L/day})} = 0.3 \text{ mg/L } (300 \text{ ug/L})$$

where:

3 mg/kg/day = NOAEL.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

The Longer-term HA for a 70-kg adult is calculated as follows:

$$\text{Longer-term HA} = \frac{(3 \text{ mg/kg/day})(70 \text{ kg})}{(100)\ (2 \text{ L/day})} = 1.05 \text{ mg/L } (1{,}050 \text{ ug/L})$$

where:

3 mg/kg/day = NOAEL.

70 kg = assumed body weight of an adult.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

2 L/day = assumed daily water consumption of an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed for synthetic organic chemicals and a value of 10% is assumed for inorganic chemicals. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986a), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The study by Tisdel et al. (1983) has been selected to serve as the basis for the Lifetime HA. In this study, rats were given dietary doses of metolachlor equivalent to 0, 1.5, 15 or 150 mg/kg/day. No treatment-related effects were noted in terms of mortality, organ weight and organ-to-body weight ratios. The investigators noted a statistically significant decrease in glutamic-oxaloacetic transaminase activity in high-dose males at 12 months. Mean body weights of high-dose females were consistently less than controls from week 2 until termination of the study. This difference was significant ($p < 0.01$) for 26 of the 59 intervals at which such measurements were made. Food consumption in high-dose females also was generally less than controls. Gross pathology findings were described as unremarkable. Microscopically, testicular atrophy with degeneration of the tubular epithelium was observed to a greater extent in the 300- and 3,000-ppm groups than in controls. Additionally, an increased incidence of eosinophilic foci was observed in the livers of both sexes exposed at 3,000 ppm. Based on the data presented, a NOAEL of 30 ppm (1.5 mg/kg/day) was identified.

The Lifetime HA is calculated as follows:

Step 1: Determination of the Reference Dose (RfD):

$$RfD = \frac{1.5 \text{ mg/kg/day}}{100} = 0.015 \text{ mg/kg/day}$$

where:

1.5 mg/kg/day = NOAEL, based upon the absence of systemic effects in rats exposed to metolachlor in the diet for two years.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$DWEL = \frac{(0.015 \text{ mg/kg/day})(70 \text{ kg})}{(2 \text{ L/day})} = 0.525 \text{ mg/L } (525 \text{ ug/L})$$

where:

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

$$\text{Lifetime HA} = \frac{(0.525 \text{ mg/L}) (20\%)}{(10)} = 0.01 \text{ mg/L } (10 \text{ ug/L})$$

where:

0.525 mg/L = DWEL.

20% = assumed relative source contribution from water.

10 = additional uncertainty factor per ODW policy to account for possible carcinogenicity.

Evaluation of Carcinogenic Potential

- Four studies evaluating the carcinogenic potential of metolachlor have been identified. In two of these studies (Marias et al., 1977, and Tisdel et al., 1980), no evidence of carcinogenicity in mice was observed. The other studies, both conducted using rats, showed an increased tumor incidence related to treatment. Ciba-Geigy (1979) reported a statistically significant increase in primary liver tumors in female Charles River rats exposed to 150 mg/kg/day in the diet for 2 years. Tisdel et al. (1983) also reported a statistically significant increase in the incidence of proliferative hepatic lesions (neoplastic nodules and carcinomas) in female rats at the same dietary dose over the same time period. Additionally, there was a

nonstatistically significant increase in the frequency of adenocarcinoma of the nasal turbinates and fibrosarcoma of the nasal tissue in the high-dose males (150 mg/kg/day).

- The International Agency for Research on Cancer has not evaluated the carcinogenicity of metolachlor.

- Applying the criteria described in EPA's guidelines for the assessment of carcinogenic risk (U.S. EPA, 1986a), metolachlor is classified in Group C: possible human carcinogen. This category is for substances with limited evidence of carcinogenicity in animals and absence of human data.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- EPA/OPP has identified an ADI for metolachlor of 0.015 mg/kg/day based on the NOAEL of 30 ppm (1.5 mg/kg/day) from the chronic rat feeding study (Tisdel et al., 1983) and an uncertainty factor of 100 (U.S. EPA, 1986b). Using this ADI and an assumed body weight of 60 kg, the maximum permissible intake has been calculated to be 0.9 mg/day. The total maximum residue concentration is 0.07209 mg/day or about 8% of the ADI.

- Residue tolerances ranging from 0.02 to 30 ppm have been established for a variety of agricultural products (CFR, 1985).

VII. ANALYTICAL METHODS

- Analysis of metolachlor is by a gas chromatographic (GC) method applicable to the determination of certain nitrogen-phosphorus containing pesticides in water samples (U.S. EPA, 1986c). In this method, approximately 1 liter of sample is extracted with methylene chloride. The extract is concentrated and the compounds are separated using capillary column GC. Measurement is made using a nitrogen phosphorus detector. The method detection limit has not been determined for metolachlor but it is estimated that the detection limits for analytes included in this method are in the range of 0.1 to 2 ug/L.

VIII. TREATMENT TECHNOLOGIES

- Whittaker (1980) experimentally determined adsorption isotherms for metolachlor on granular-activated carbon (GAC) Nuchar WV-G. Nuchar WV-G, reportedly, exhibited the following adsorption capacities at 20°C: 0.173, 0.148 and 0.105 mg metolachlor/mg carbon at concentrations of 79.84 mg/L, 10 mg/L and 1.74 mg/L, respectively.

- Holiday and Hardin (1981) reported the results of GAC treatment of wastewater contaminated with pesticides including metolachlor. The column, 3.5 ft in diameter, was packed with 10 ft of granular activated carbon, or 3,150 lb carbon/column. The column was operated at 1.04 gpm/ft^2 hydraulic load and 72 minutes contact time. Under these

conditions, 99.5% of the metolachlor was removed from wastewater at an initial average concentration of 16.4 mg/L.

- GAC adsorption appears to be the most promising treatment technique for the removal of metolachlor from water. However, more actual data are required to determine the effectiveness of GAC in removing metolachlor from contaminated drinking water supplies.

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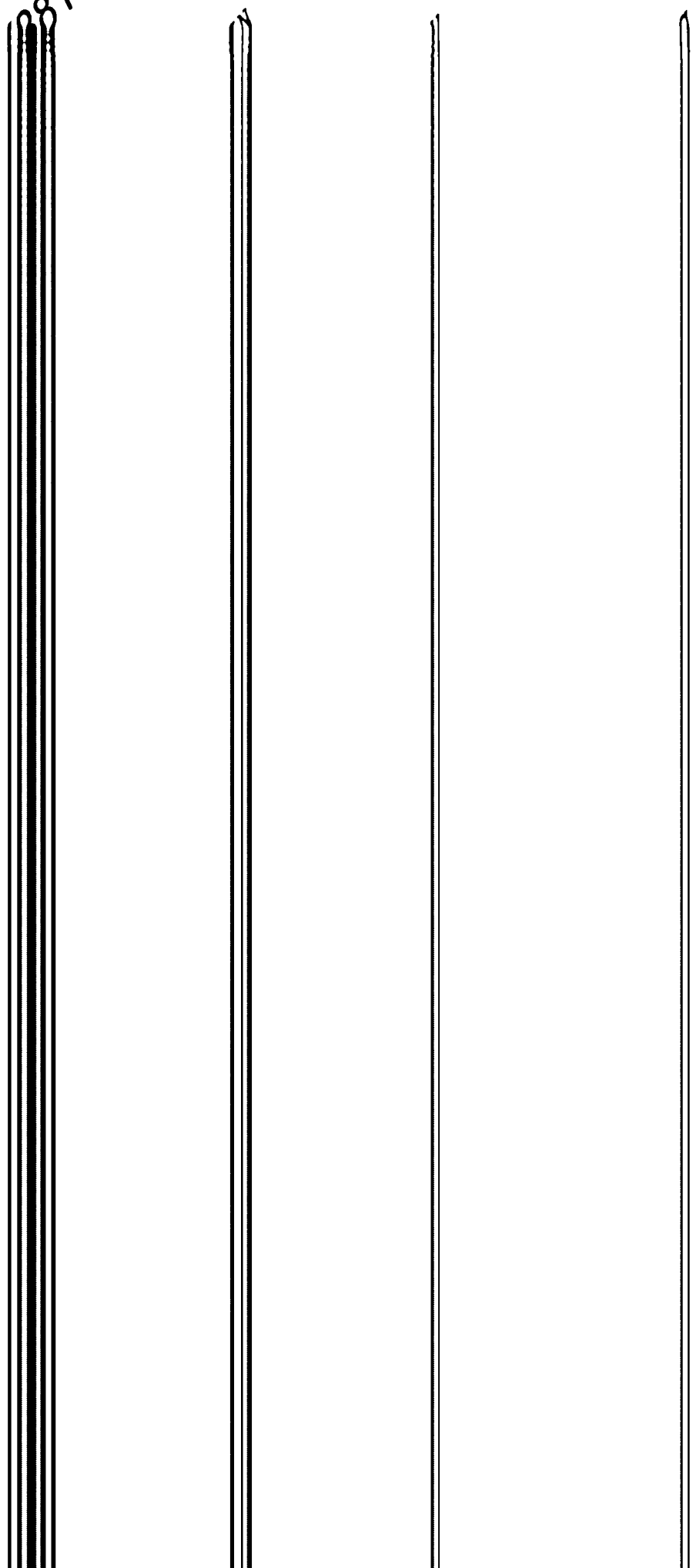

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