Fact Sheet Date: June 2004

NEW YORK STATE
HUMAN HEALTH FACT SHEET

Ambient Water Quality Value for
Protection of Human Health and Sources of Potable Water

SUBSTANCE: Metolachlor ESA (metolachlor ethanesulfonic acid)

CAS REGISTRY NUMBER: 171118-09-5

AMBIENT WATER QUALITY VALUE: 50 micrograms/liter (50 ug/L)

BASIS: General Organic Guidance Value (6 NYCRR 702.15(a)(2))

INTRODUCTION

Metolachlor (2-chloro-N-(2-ethyl-6-methylphenyl)-N-(2-methoxy-1-methylethyl)acetamide is a chloroacetanilide herbicide. There are four isomers of metolachlor: two S-enantiomers (named CGA-77102 by Ciba-Geigy Corporation, the US registrant of the pesticide products containing metolachlor) and two R-enantiomers (named CGA-77101 by the registrant) (Figure 1). A manufactured 50:50 mixture of the S- and R-enantiomers is called metolachlor (named CGA-24705 by the registrant). A manufactured 80:20 mixture of the S- and R-enantiomers is called alpha- or S-metolachlor (named CGA-77102 by the registrant). A separate fact sheet describes the derivation of an ambient water quality value for metolachlor, which applies to all four isomers of the metolachlor molecule (NYS, 2002a).

Recent studies have shown that environmental degradates of metolachlor are found in ambient water at levels higher than those of metolachlor itself (Kolpin et al., 2000). Metolachlor oxanilic acid (also known as metolachlor OA) is one commonly found degradate and a separate fact sheet describes the derivation of an ambient water quality value for metolachlor OA (NYS, 2002b). A second commonly found degradate is metolachlor ethanesulfonic acid (also known as

metolachlor ESA, CGA-376944, or 2-[(2-ethyl-6-methylphenyl)(2-methoxy-1-methylethyl)amino]-2-oxoethanesulfonic acid). This fact sheet describes the derivation of an ambient water quality value for metolachlor ESA.

Metolachlor ESA is formed when the chlorine attached to the terminal carbon atom in the chloroacetyl group of the parent molecule is replaced by a sulfonic acid group (Figure 1).. Metolachlor ESA has been used in some pharmacokinetic studies (Novartis, 1997, 1999a), but the sodium salt of metolachlor ESA (known as CGA-354743, Figure 1)) has been used in toxicology studies.

Metolachlor ESA is poorly absorbed from the gastrointestinal tract of rats. When an oral dose of radioactive metolachlor ESA was given to male and female rats, 95.6% and 93.0% of the administered dose was eliminated in the feces of males and females, respectively, within 24 hours (Novartis, 1997). After 72 hours, the corresponding percentage was 96.5% and 94.2%, respectively. Only 2.05% and 4.39% of the administered dose given males and females, respectively, was eliminated in the urine within 72 hours. Less than 0.01% of the administered dose remained in the tissues, carcass, and gastrointestinal tract of males and females after 72 hours. Total recovery of administered radioactivity was 98.4% and 98.7% in males and females, respectively. These data suggest that 5% or less of the administered dose of metolachlor ESA may be absorbed from the gastrointestinal tract over 72 hours.

A second study (Novartis, 1999a) with bile-duct cannulated rats was done to determine whether or not metolachlor ESA is absorbed from the gut and then secreted back (in bile) into the gut for excretion in feces. This enteropathic circulation could lead to an underestimation of the amount of metolachlor ESA absorbed in a study with normal rats (i.e., Novartis, 1997) because such a study could not distinguish between metolachlor ESA not absorbed and excreted in feces and metolachlor ESA absorbed, re-circulated into the gut, and excreted in feces. Of a single oral dose of radioactive metolachlor ESA given to bile-duct cannulated rats, 17% of the administered dose was absorbed and excreted in urine (5%) and bile (12%) within 48 hours, 76.8% was excreted in feces, 1.4% remained in the gastrointestinal tract, and 0.49% remained in the carcass

(total recovery 96.4%). Thus, the data indicate some metolachlor ESA is rapidly absorbed and re-circulated back into the gut via bile duct secretions. Metabolism of absorbed metolachlor ESA was limited. About 17% and 80% of the dose in urine and bile, respectively, was the parent compound. Overall, about 10% of the administered dose was absorbed and excreted as the parent compound and 7% was absorbed and excreted as metabolites.

In summary, the pharmacokinetic data on metolachlor ESA in rats indicate poor absorption, limited metabolism, and rapid excretion. In contrast, administered doses of metolachlor (the parent compound) were almost completely absorbed (84-99%) and extensively metabolized in rats (Ciba-Geigy, 1996b,c).

Metolachlor ESA is a minor rat metabolite of metolachlor (Novartis, 1998a). In male and female rats given a single metolachlor dose of 0.5 mg/kg or 100 mg/kg and killed 72 hours after dosing, 0.28% and 0.14% of the administered dose, respectively, was excreted as metolachlor ESA. Almost all (97.9% and 89.0% in the low and high dosed animals, respectively) of the metabolite was found in the feces.

Data on the health effects of oral exposure to metolachlor ESA are limited to acute studies in rats, 3-month subchronic studies in rats and dogs, and a developmental toxicity study in rats. These data were reviewed and evaluated. As described below, the general organic guidance value of 50 ug/L is selected as the ambient water quality value for metolachlor ESA.

SPECIFIC MCL AND PRINCIPAL ORGANIC CONTAMINANT CLASS (702.3)

Metolachlor ESA does not have a Specific MCL (maximum contaminant level) as defined in 700.1 and is not in a principal organic contaminant (POC) class as defined in 700.1. Consequently, an ambient water quality value cannot be derived under 702.3.

However, the New York State Department of Health (DOH) drinking-water regulations (10 NYCRR Part 5) does have a MCL of 50 ug/L for metolachlor ESA, based on its

categorization as an unspecified organic contaminant (UOC). This DOH general MCL applies as a drinking water standard to any organic compound that is not in a POC class and does not have a Specific MCL. However, this UOC MCL is not used as the basis for an ambient water quality value under 702.3.

ONCOGENIC EFFECTS (702.4)

Studies on the oncogenicity of metolachlor ESA were not found. Metolachlor ESA was inactive in short-term tests indicative of oncogenicity. These were point mutation tests in bacteria (Salmonella (five strains) and E. coli with and without metabolic activation by rat liver S9 homogenate), gene mutation tests with chinese hamster cells V79 (with and without S9 activation), a DNA repair test (in vivo) with rat hepatocytes, and a chromosome aberration test in mice (micronucleus test on bone marrow, in vivo) (Ciba-Geigy, 1996a, Novartis, 1998b,c, 1999b). The data are insufficient to determine whether metolachlor ESA is oncogenic. Thus, a value based on oncogenic effects cannot be derived.

NON-ONCOGENIC EFFECTS (702.5)

Acute single-dose toxicity studies of metolachlor ESA in rats show that the minimum lethal oral and dermal doses are >5,000 mg/kg and >2,000 mg/kg, respectively (Ciba-Geigy, 1995a; Novartis, 1998d,e). These were the highest doses tested in the studies. Dermal doses of metolachlor ESA may be a weak skin sensitizer in Guinea pigs (Novartis, 1999c).

Limited data from three studies on the oral toxicity of repeated doses of metolachlor ESA show that vomiting and changes in the chemical composition of blood (indicative of liver toxicity) are early indicators of its toxicity (Novartis, 1999d,e,f).

In a subchronic study (Novartis, 1999d), groups of male and female SD rats (10/sex/dosed groups, 20/sex/control group) were fed diets containing 0, 360, 1,200, 6,000 or 20,000 ppm metolachlor ESA for 3 months. Estimated daily doses were 0, 26.7, 90.6, 461, and

1,640 mg/kg/day for male rats and 0, 30.1, 103, 560, and 1,790 mg/kg/day for female rats. A weight-of-evidence analysis (similar to that described in US EPA, 2000) was used to determine if any results, including those statistically significant ($p < 0.05$), were toxicologically significant.

Water consumption rates of males and females were about 25% higher than those of the respective control groups (Table 1). There was no observed evidence of treatment-related clinical or eye toxicity, mortality, body weight changes, changes in food consumption, increases in biochemical indices of liver toxicity, including serum enzymes levels indicative of liver toxicity (aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and gamma-glutamyl transpeptidase (GGT), or changes in hematology, urine content, organ weights (brain, heart, liver, kidneys, adrenal glands, thymus, spleen, thyroid gland, ovaries, testes, and epididymis) or histological lesions (32 tissues/organs).

Although there were minor changes in the levels of blood chemistry (i.e., serum phosphate and glucose levels) that were potentially dependent exposure to metolachlor ESA (Novartis, 1999d), a weight-of-evidence analysis does not support a causal relationship between metolachlor ESA and the observed effects (Table 2), particularly given the lack of observed effects on organ function or structure. First, the results of the study with metolachlor ESA differed between male and female rats. In male rats, glucose levels were elevated only at the highest dose (20,000 ppm) whereas in female rats, glucose levels were elevated only at the lowest dose level (360 ppm). In male rats, serum phosphate levels were depressed at the lowest (360 ppm) and highest (20,000 ppm) dose levels, whereas in female rats serum phosphate levels were elevated at all levels (1,200, 6,000, and 20,000 ppm) except the lowest dose level (360 ppm). Second, results of studies chronic or subchronic studies with metolachlor ESA, metolachlor, or S-metolachlor on different, but related strain of rats (i.e., *Tif:RAIf* rats and CD rats) do not show that serum glucose or phosphate levels are consistent indicators of toxicity. Based on the analysis of the data on blood chemistry and the absence of any observable effects of metolachlor ESA in rats, the no-observed-effect level (NOEL) and the lowest-observed-effect level (LOEL) of the study are $\geq$1,640 mg/kg/day and >1,640 mg/kg/day of metolachlor ESA, respectively (i.e., there were no observed effects at the highest tested dose).

For comparative purposes, the subchronic study with metolachlor ESA also included groups of 10 male and female SD rats exposed to 5,000 ppm of the parent compound S-metolachlor for 3 months (Novartis, 1999d). Estimated daily doses of S-metolachlor were 454 and 597 mg/kg/day for male and female rats, respectively. Mean body weights of S-metolachlor treated males and females were consistently lower than those of controls throughout the study and the differences were significant ($p < 0.05$) once in males (at 1 week of study) and once in females (at 11 weeks of the study) (Table 1). Other important effects of S-metolachlor were higher serum levels of GGT (males and females), globulin (males), and cholesterol (females), and increased relative liver and kidney weights (males and females) and relative thyroid weights (females). Most important, dosed females also showed minimal to slight hypertrophy of the centrilobular hepatocytes (4/10, compared to 0/20 in controls).

Collectively, the data on the toxicity of dietary doses of metolachlor ESA and S-metolachlor in SD rats show differences in their toxic effects (Table 1). A variety of effects, including unequivocal effects on liver function and structure, including liver hypertrophy, were caused by a 3-month exposure to 500 - 600 mg/kg/day (5,000 ppm in diet) of S-metolachlor. In contrast, a 3-month exposure to 500 - 600 mg/kg/day (6,000 ppm in diet) or 1,600 - 1,800 mg/kg/day (20,000 ppm in diet) of metolachlor ESA did not induce any observable unequivocal effects on liver function. Thus, S-metolachlor (under the conditions of a subchronic study in rats) induced a broader range of effects at a lower dose that did metolachlor ESA.

A subchronic dietary study on the effects of S-metolachlor on SD rats provides additional information on the relative toxic potency of metolachlor ESA compared to metolachlor (Ciba-Geigy, 1995b). In this study, groups of male and female rats were fed diets containing 0, 30, 300, 3,000, or 10,000 ppm S-metolachlor for 3 months. Estimated daily doses were 0, 2.6, 26, 260, and 860 mg/kg/day for male rats and 2.9, 29, 290, and 980 mg/kg/day for female rats, using recommended values for body weight and food intake for male and female SD rats in subchronic studies (US EPA, 1987). Both the US EPA (1997) and Ciba-Geigy (1995b) reported that the major toxicological effects of S-metolachlor were limited to the two highest dose levels. The effects noted were increased serum GGT levels at the 10,000-ppm diet (males and females) and

several effects at the 3,000-ppm and 10,000-ppm diets (reduced body weight and food consumption (males and females), increased relative kidney weight (males and females), and increased absolute kidney weight (males), all $p < 0.05$). Both organizations also noted that that the number of males with hepatocytes with eosinophilic intracytoplasmic inclusion bodies was increased ($p < 0.05$) at the highest dose level. Both organizations concluded, based on the effects observed at ≥3,000 ppm (i.e., ≥260 mg/kg/day), that the NOEL and LOEL of the study are 26 mg/kg/day and 260 mg/kg/day, respectively, of S-metolachlor. However, the relative liver weight of the males at all dose levels were elevated ($p < 0.05$) compared to that of the control males. This suggests the study did not identify a NOEL for S-metolachlor.

In a third subchronic study (Novartis, 1999e), groups of male and female dogs (4/sex/group) were given capsules containing metolachlor ESA doses of 0, 50, 200, 500, or 1,000 mg/kg/day for 3 months. A weight-of-evidence analysis (e.g., US EPA, 2000) was used to determine if any results, including those statistically significant ($p < 0.05$), were toxicologically significant.

There was no observed evidence of treatment-related mortality, eye toxicity, body weight loss, reductions in food consumption, or changes in urine content, organ weights (brain, heart, kidneys, adrenal glands, thymus, spleen, thyroid gland, ovaries, testes) or histological lesions (41 tissues/organs). However, metolachlor ESA toxicity was observed at the two highest doses (Table 3). Female dogs given the highest dose vomited. Male and female dogs given the highest dose showed elevated serum eosinophil counts. Males and females also showed changes in blood chemistry indicative of liver toxicity: serum alkaline-phosphatase levels were elevated in males and females at ≥500 mg/kg/day; serum GGT levels were elevated in males at 1,000 mg/kg/day and in females at ≥500 mg/kg/day; and serum albumin levels were reduced in females at ≥500 mg/kg/day. Female dogs at 1,000 mg/kg/day also showed increased relative liver weights. Based on the findings in male and female dogs, the NOEL and LOEL of the study are 200 mg/kg/day and 500 mg/kg/day of metolachlor ESA, respectively.

For comparative purposes, the subchronic study with metolachlor ESA also included

groups of 4 male and female dogs given capsules containing S-metolachlor (200 mg/kg) daily for 3 months (Novartis, 1999e). S-metolachlor induced numerous effects (Table 3) including vomiting, reductions in body weight, higher prothrombin activity, higher serum levels of alkaline phosphatase, GGT, cholesterol, phospholipids (females only), triglycerides, and globulin (males only), and lower serum albumin levels. S-metolachlor also increased relative liver weight and induced microscopic lesions in the gall bladder (cystic hyperplasia) and liver (perilobular fatty changes and bile duct hyperplasia) in both male and female dogs.

Qualitatively, the data from dogs show that metolachlor ESA induced some, but not all, of the effects induced by S-metolachlor (Table 3). Common effects were vomiting, and changes in serum levels of alkaline phosphatase, GGT, and albumin, and increased relative liver weight (females only). Quantitatively, the data show that S-metolachlor (administered dose of 200 mg/kg/day) a greater potency to cause these effects in dogs than did metolachlor ESA (administered doses of 200, 500, or 1,000 mg/kg/day). Vomiting occurred in male and female dogs given S-metolachlor but occurred only in female dogs given 1,000 mg/kg/day. Serum liver enzyme levels were elevated in male and female dogs given S-metolachlor, but were elevated only in male and female dogs given 500 or 1,000 mg/kg/day metolachlor ESA. Relative liver weight was elevated in male and female dogs given S-metolachlor, but was elevated only in female dogs given 1,000 mg/kg/day of metolachlor ESA. Furthermore, the increases in serum liver-enzyme levels (e.g., GGT) and reductions in relative liver weight induced by exposure to 500 and/or 1,000 mg/kg/day of metolachlor ESA were smaller than those induced by exposure to 200 mg/kg/day of S-metolachlor (see Table 3). Other effects indicative of more severe liver damage (liver and gall bladder histopathology) were observed only in dogs exposed to S-metolachlor. Thus, S-metolachlor (under the conditions of a subchronic study in dogs) induced a broader range of effects at a lower dose than did metolachlor ESA.

In a developmental toxicity study with metolachlor ESA, pregnant Wistar rats were given gavage doses of 0, 250, 500, or 1,000 mg/kg on day 6 through day 15 of gestation (Novartis, 1999f). Dams were killed on day 21 of gestation and dams and fetuses were examined for reproductive and fetotoxic/teratogenic effects, respectively. A weight-of-evidence analysis (e.g.,

US EPA, 2000) was used to determine if any results, including those statistically significant ($p < 0.05$), were toxicologically significant.

There were no observed treatment-related clinical signs during the study. Mean maternal body weight, body-weight gain, food consumption, and uterine weight were similar among all groups. There were no observed treatment-related effects on any reproductive parameters (implantation sites/dam, pre- and post-implantation losses, resorptions/dam, litter size, or fetal body weights). There was no observed evidence of any treatment-related fetotoxic or teratogenic effects on external features, internal viscera, or the skeleton. The NOEL and LOEL of the study for maternal and fetal effects are ≥1,000 and >1,000 mg/kg/day of metolachlor ESA, respectively (i.e., there were no observed effects at the highest tested dose).

The rat and dog subchronic studies with metolachlor ESA are comparable in quality, and are preferred over the rat developmental study as the basis of the acceptable daily intake for metolachlor ESA given the lack of any effects in the latter study. The dog study is preferred over the rat study because it has a lower NOEL and LOEL (200 and 500 mg/kg/day) than the rat study (≥1,640 mg/kg/day and >1,640 mg/kg/day, or alternatively, 461 and 1,640 mg/kg/day under the health-protective assumption (not supported by the weight-of-evidence analysis) that the decreased blood glucose levels in male rats were caused by exposure to metolachlor ESA). In addition, there are no data to indicate which species is the better surrogate for humans. Thus, the dog study is used to derive a potential water quality value based on non-oncogenic effects.

If an uncertainty factor of 3,000 is applied to the NOEL (200 mg/kg/day) from the subchronic study in dogs, an acceptable daily intake of 0.067 mg/kg/day (67 ug/kg/day) can be derived for metolachlor ESA using procedures consistent with those outlined in paragraphs (a) and (b) of 702.5. Under 702.5(b)(3), an uncertainty factor of 1,000 is selected because the acceptable daily intake is based on a NOEL from a subchronic animal study and neither experimental results from prolonged exposures of humans nor valid results of long-term ingestion studies on experimental animals are available. However, 702.5(b) also states that the magnitude of the uncertainty factor used to obtain an acceptable daily intake shall reflect the

quantity and quality of the toxicological data, the degree of confidence in the data and the nature of the effects of concern. Consequently, an additional uncertainty factor of 3 was used because there are gaps, and thus uncertainties, in the toxicological information of metolachlor ESA, particularly with regard to non-oncogenic (including reproductive) and oncogenic effects of chronic exposure.

A water value of 470 ug/L can be derived assuming a 70-kg adult drinks 2 liters of water per day and allowing 20% of the acceptable daily intake (67 ug/kg/day) to come from drinking water (702.2(c) and 702.5(c)).

CHEMICAL CORRELATION (702.7)

Metolachlor ESA is an environmental degradate of metolachlor and a minor (<0.5%) rat metabolite of metolachlor. The ambient water quality value for metolachlor is 9 ug/L (based on oncogenic effects, i.e., liver cancer in rats) (NYS, 2002a).

Metolachlor is degraded to metolachlor ESA when the chlorine attached to the terminal carbon atom in the chloroacetyl ($-CH_2Cl$) group, which is a reactive group in biological systems (Ashby and Tennant, 1991), is replaced by a less biologically reactive sulfonic-acid group (see Figure 1). A reduction in the toxic potency of the molecule is associated with this change (Tables 1 and 3). A similar removal of the chlorine during degradation of metolachlor to its oxanilic acid metabolite (known as metolachlor OA) is associated with a reduction in the toxic potency of the resulting molecule (NYS, 2002b). In another chloroacetanilide herbicide (alachlor), the removal and replacement of the chlorine atom by a sulfonic acid group to form alachlor ESA is also associated with a reduction in the toxic potency of the molecule (Heydens et al., 1996, 2000; US EPA, 1998). The reduced toxic potencies of metolachlor ESA, metolachlor OA, and alachlor ESA relative to the parent compound all suggest the removal of the chlorine atom changes the biological fate of the resulting molecule and reduces its toxic potency.

Experimental data on metolachlor ESA and metolachlor show differences in

pharmacokinetics and toxicity (Table 4). The absorption percentage in rats of an oral dose of metolachlor ESA is four- to five-times lower than that of an oral dose of metolachlor. The potency of metolachlor ESA to cause effects also is consistently less than that of metolachlor. Metolachlor ESA did not induce any observable liver effects in rats at a dietary dose of 20,000 ppm for 3 months. This dose is four-times higher than the metolachlor dose (5,000 ppm, diet) that increased serum levels of biomarkers indicative of liver toxicity (e.g., liver enzymes), relative liver weights, and liver hypertrophy in rats exposed for 3 months. Similarly, metolachlor ESA did not induce observable liver or gall bladder lesions in dogs at 1,000 mg/kg/day for 3 months. This dose is five-times higher than the metolachlor dose (200 mg/kg/day) that induced the liver and gall-bladder lesions in dogs exposed for 3 months. Although female dogs at 1,000 mg/kg/day of metolachlor ESA showed increased relative liver weights, the increase was smaller than seen in females and males exposed to 200 mg/kg/day of S-metolachlor, and increased relative liver weights were not seen in male dogs. Similarly, male and female dogs exposed to either metolachlor ESA (500 and 1,000 mg/kg/day) or S-metolachlor (200 mg/kg/day) showed elevated serum levels of liver enzyme (alkaline phosphatase and GGT), but the levels were higher in the dogs exposed to S-metolachlor than in the dogs exposed to the lower doses of metolachlor ESA. These differences are particularly relevant because the liver is the target organ for metolachlor carcinogenesis. In addition, metolachlor ESA was inactive (with and without metabolic activation) in short-term tests indicative of oncogenic potential.

Collectively, the data suggest some differences in pharmacokinetics and toxic effects of metolachlor and metolachlor ESA. The data also suggest that the toxic potency of metolachlor ESA is less than that of metolachlor. These differences are consistent with the hypothesis that the chlorine atom of the metolachlor molecule plays an important role in the molecular events leading to the toxicity of metolachlor. Thus, there are insufficient data to derive a value for metolachlor ESA based on chemical correlation to metolachlor. In addition, there are insufficient data for deriving a value based on chemical correlation to any other chemical.

SELECTION OF VALUE

According to 702.15(a), the selected ambient water quality value shall be the more stringent of the values derived using the procedures found in 702.3 through 702.7 or a general organic guidance value of 50 ug/L. Although a value of 470 ug/L can be derived by applying the procedures of 702.5 to the available non-oncogenic data on metolachlor ESA, the value is based on a limited toxicological data base. In particular, studies on the chronic (non-oncogenic) and reproductive effects of metolachlor ESA were not found. In addition, studies on the oncogenic effects of metolachlor ESA were not found. Accordingly, there are not adequate and sufficient data available to justify a value greater than 50 ug/L as described in 702.15(a)(2). Thus, the general organic guidance value of 50 ug/L is selected as the water quality value for metolachlor ESA.

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SEARCH STRATEGY

Toxline (1966 to June 2003) was searched using the name or CAS Registry Number for metolachlor ESA or the name or CAS Registry Number for metolachlor.

Bureau of Toxic Substance Assessment
New York State Department of Health/KGB02
June 2003

Table 1. Results from Study of SD Rats Given Diets Containing Metolachlor ESA or S-Metolachlor Daily for 3 Months (Novartis, 1999d).

Parameter	Sex	Concentration in Diet (ppm)				
		Metolachlor ESA				S-Metolachlor
		360	1,200	6,000	20,000	5,000
Clinical Signs						
water consumption rates	M	-[1]	-	-	⬆[2]	-
	F	-	-	-	⬆	-
body weights	M	-	-	-	-	⬇
	F	-	-	-	-	⬇
Blood Chemistry						
gamma-glutamyl transpeptidase (GGT)	M	-	-	-	-	⬆
	F	-	-	-	-	⬆
cholesterol	M	-	-	⬇[4]	⬇[4]	-
	F	-	-	-	-	⬆
glucose	M	-	-	-	⬆	⬆
	F	⬆	-	-	-	-
phosphate	M	⬇	-	-	⬇	⬇
	F	-	⬆	⬆	⬆	⬆
total protein (TP)	M	-	-	-	-	⬆
	F	-	-	-	-	-
albumin	M	-	-	-	-	-
	F	-	-	-	-	-
globulin (TP - albumin)	M	-	-	-	-	⬆
	F	-	-	-	-	-
Relative Organs Weights						
liver	M	-	-	⬇[4]	-	⬆
	F	-	-	-	-	⬆
kidney	M	-	-	-	-	⬆
	F	-	-	-	-	⬆
thyroid gland	M	-	-	-	-	-
	F	-	-	-	-	⬆
Histopathology						
liver (hypertrophy of centrilobular hepatocytes	M (0/20)[3]	0/10	0/10	0/10	0/10	0/10
	F (0/20)[3]	1/10	0/10	0/10	0/10	4/10

[1] $p \geq 0.05$.
[2] $p < 0.05$ (⬇ or ⬆).
[3] Incidence in control group.
[4] Results contrary to expected toxicological response to liver toxicant (ATSDR, 1993).

Table 2. Results of Blood Glucose and Phosphate Levels Reported for Rats Fed Diets Containing Metolachlor ESA, Metolachlor OA, S-Metolachlor for 90 Days or Metolachlor for 2 years.

Compound	Rat Strain	Dietary Level (ppm)	Sex	Serum Glucose Level	Serum Phosphate Level
Environmental Degradates of Metolachlor					
ESA[1]	SD	360	M	-*	⬇**
			F	⬆	-
		1,200	M	-	-
			F	-	⬆
		6,000	M	-	-
			F	-	⬆
		20,000	M	⬆	⬇
			F	-	⬆
OA[2]	*Tif:RAIf*	300	M	-	-
			F	-	-
		1,000	M	-	-
			F	-	-
		15,000	M	-	-
			F	-	-
Parent Compound					
metolachlor[3]	CD	3,000 (2 yrs)	M	-	not tested
			F	-	not tested
S-metolachlor[2,4]	SD	3,000[4]	M	-***	-***
			F	-***	-***
		5,000[2]	M	⬆	⬇
			F	-	⬆
		10,000[4]	M	-***	-***
			F	-***	-***

* $p \geq 0.05$.
**$p < 0.05$ (⬆ or ⬇).
*** No treatment-dependent effect on level reported by either Ciba-Geigy (1995b) or US EPA (1997).

[1] Novartis (1999b).
[2] Ciba-Geigy (1992c).
[3] Ciba-Geigy (1983).).
[4] Ciba-Geigy (1995b); US EPA (1997).

Table 3. Results from Study in Dogs Given Gelatin Capsules Containing Metolachlor ESA or S-Metolachlor Daily for 3 Months (Novartis, 1999e).

Parameter	Sex	Daily Dose (mg/kg/day)				
		Metolachlor ESA				S-Metolachlor
		50	200	500	1,000	200
Clinical Signs						
vomiting	M	-[1]	-	-	-	present
	F	-	-	-	present	present
body weight gain	M & F	-	-	-	-	⬇[2]
Blood Chemistry						
alkaline phosphatase	M	-	-	⬆(1.6X)[3]	⬆ (2.1X)[3]	⬆ (4.5X)[3]
	F	-	-	⬆ (1.8X)[3]	- (1.9X)[3]	⬆ (3.6X)[3]
gamma-glutamyl transpeptidase (GGT)	M	-	-	-	⬆ (1.5X)[3]	⬆(3.6X)[3]
	F	-	-	⬆ (3.0X)[3]	- (2.6X)[3]	⬆ (4.7X)[3]
cholesterol	M	-	-	-	-	⬆
	F	-	-	⬆	-	⬆
phospholipids	M	-	-	-	-	-
	F	-	-	-	-	⬆
triglycerides	M & F	-	-	-	-	⬆
glucose & phosphate	M & F	-	-	-	-	-
total protein (TP)	M	-	-	-	-	-
	F	⬇	-	-	-	-
albumin	M	-	-	-	-	⬇
	F	-	-	⬇	⬇	⬇
globulin (TP - albumin)	M	-	-	-	-	⬆
	F	⬇	-	-	-	-
Hematology						
eosinophil count	M	-	⬆	-	⬆	-
	F	-	-	-	⬆	-
prothrombin time	M & F	-	-	-	-	⬆
Relative Organs Weights						
liver	M	-	-	-	-	⬆ (1.3X)[3]
	F	-	-	-	⬆ (1.2)[3]	⬆ (1.5X)[3]
Histopathology						
gall bladder (cystic hyperplasia)	M (0/4)[4]	0/4	0/4	0/4	0/4	2/4
	F (0/4)[4]	0/4	0/4	0/4	0/4	¾
liver (perilobular fatty changes)	M (0/4)[4]	0/4	0/4	0/4	0/4	4/4
	F (0/4)[4]	1/4	0/4	0/4	0/4	2/4
liver (bile duct hyperplasia)	M (1/4)[4]	0/4	0/4	1/4	1/4	4/4
	F (0/4)[4]	1/4	1/4	2/4	0/4	4/4

[1] $p \geq 0.05$.

[2] $p < 0.05$ (⬇ or ⬆).

[3] For comparative purposes, the relative difference between control rats (X) and treated rats is shown.

[4] Incidence in control group.

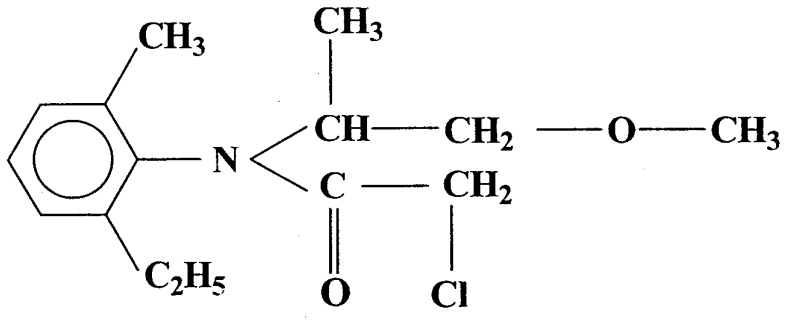
Table 4. Summary of Important Data on the Potential to Base the Ambient Water Quality Value for Metolachlor ESA on the Water Quality Value for Metolachlor under 6 NYCRR 702.7 (Chemical Correlation).

Parameter	Metolachlor	Metolachlor ESA
1. Results of Chronic Dietary Studies in Rats (Basis for Metolachlor AWQ Value)		
liver cancer	yes (3,000 ppm)[1]	not tested
2. Structure		
functional groups	two identified: sole nitrogen (linking aromatic and aliphatic groups) and sole chlorine (attached to the terminal carbon atom in the chloroacetyl group ($-CH_2Cl$))	one: nitrogen still present, but formation of potential mutagenic metabolite by action is unlikely if degradates occurs solely in the sulfonated form in the body, or if minimal cleavage to the unsulfonated form (i.e., metolachlor OA) occurs (US EPA, 1998); the chlorine atom is removed during conversion of chloroacetyl group to an ethanesulfonic acid group
3. Pharmacokinetics		
percent oral dose absorbed by rats	85-99 %	17%
major metabolite of metolachlor	not applicable	no (<0.5% of administered metolachlor dose in rats)
4. Toxicology - Evidence For/Against Common Toxic Effect(s) on Liver (Important Data Because Liver is the Sole Site of Metolachlor Induced Carcinogenesis)		
Subchronic Dietary Study in SD Rats (Novartis, 1999d)		
serum gamma-glutamyl transpeptidase level	⬆[2] (5,000 ppm)	-[2] (20,000 ppm & 6,000 ppm)
serum cholesterol level	⬆ (5,000 ppm)	- (20,000 ppm & 6,000 ppm)
relative weight	⬆ (5,000 ppm)	- (20,000 ppm & 6,000 ppm)
hypertrophy	⬆ (5,000 ppm)	- (20,000 ppm & 6,000 ppm)
Subchronic Oral Study in Dogs (Novartis, 1999e)		
serum alkaline phosphatase level	⬆ (200 mg/kg/day)	⬆ (1,000 & 500 mg/kg/day) - (200 mg/kg/day)
serum gamma-glutamyl transpeptidase level	⬆ (200 mg/kg/day)	⬆ (1,000 & 500 mg/kg/day) - (200 mg/kg/day)
serum albumin level	⬇ (200 mg/kg/day)	⬇ (1,000 & 500 mg/kg/day) - (200 mg/kg/day)
serum globulin level	⬆ (200 mg/kg/day)	- (1,000, 500, & 200 mg/kg/day)
serum cholesterol level	⬆ (200 mg/kg/day)	- (1,000, 500, & 200 mg/kg/day)
serum phospholipids level	⬆ (200 mg/kg/day)	- (1,000, 500, & 200 mg/kg/day)
serum triglycerides level	⬆ (200 mg/kg/day)	- (1,000, 500, & 200 mg/kg/day)
relative weight	⬆ (200 mg/kg/day)	⬆ (1,000 mg/kg/day, females only) - 500 & 200 mg/kg/day)
histopathology (liver)	⬆ (200 mg/kg/day)	- (1,000, 500, & 200 mg/kg/day)
histopathology (gall bladder)	⬆ (200 mg/kg/day)	- (1,000, 500, & 200 mg/kg/day)

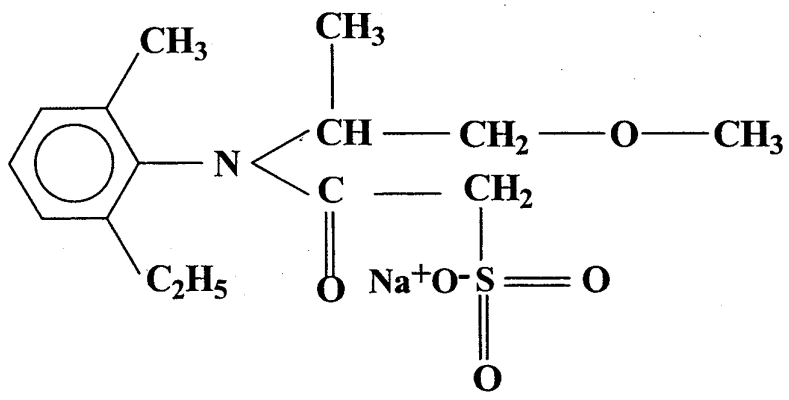
[1] NYS (2002a).

[2] Weight-of-evidence indicates a compound-dependent effect (⬆ or ⬇) or no compound-dependent effect (-).

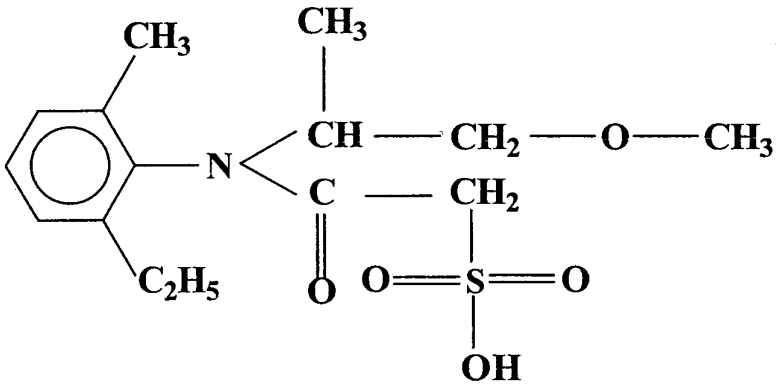
Figure 1. Metolachlor and Environmental Degradate Metolachlor ESA.



METOLACHLOR



METOLACHLOR ESA
(Metolachlor ethanesulfonic acid, sodium salt or CGA-354743)



METOLACHLOR ESA
(Metolachlor ethanesulfonic acid or CGA 376944)