Public Health Concentration

Metolachlor and Metolachlor Degradates Ethanesulfonic Acid and Oxanilic Acid in Groundwater

Pesticide and Environmental Toxicology Branch
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

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Prepared by

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I. SUMMARY

This report describes the Office of Environmental Health Hazard Assessment (OEHHA) derivation of the public health concentrations (PHC) in water for metolachlor and its environmental degradates metolachlor ethanesulfonic acid (MESA) and metolachlor oxanilic acid (MOXA). The PHCs derived are 1300 parts per billion (ppb) for MESA, 3200 ppb for MOXA, and 7 ppb for metolachlor. This report includes the risk characterization of human consumption of drinking water at the detected levels for a lifetime. OEHHA conducts this evaluation under the California Pesticide Contamination Prevention Act (PCPA) (DPR, 2017a). The California Department of Pesticide Regulation (DPR) initiated the evaluation process to determine if the detected levels of MESA and MOXA at concentrations from 0.059 to 20.2 ppb would "pollute" the groundwater. The term pollute is defined in Food and Agriculture Code Section 13142(j)[1] as "to introduce a pesticide product into the groundwaters of the state resulting in an active ingredient, other specified ingredient, or a degradation product of a pesticide above a level that does not cause adverse health effects, accounting for an adequate margin of safety."

OEHHA relied in part upon reviews of the toxicology database conducted by the US Environmental Protection Agency (US EPA) and DPR. While the current concern is with MESA and MOXA, OEHHA's evaluation includes metolachlor because it is the parent compound of the degradates and has a more comprehensive toxicity database.

For metolachlor, subchronic oral toxicity studies showed mainly lower body weight, lower body weight gain, and increased absolute/relative organ weights (liver and kidney). Metolachlor was not toxic to the developing fetus in animal studies at doses lower than those causing maternal toxicity. There is no evidence of neurotoxicity in any of the available studies. With chronic exposure, the liver is the target organ with preneoplastic foci and tumors in rats and increased alkaline phosphate level in dogs. Metolachlor showed limited positive results in genotoxicity assays. US EPA classified metolachlor as Group C - possible human carcinogen, based on liver tumors in rats at the highest dose tested.

Based on the available toxicity information, MESA and MOXA are generally less toxic than metolachlor. The target organ is also the liver, with dogs being the more sensitive species than rats. In a subchronic oral study with dogs, MESA at ≥ 500 milligrams per kilogram of body weight per day (mg/kg-day) treatment resulted in increased alkaline phosphatase and ɣ-glutamyl transpeptidase levels, and increased liver organ weight. MOXA caused increased alkaline phosphatase level reported at a higher dose of 1000 mg/kg-day, also in a subchronic dog study. For this enzyme effect, S-metolachlor

[1] http://leginfo.legislature.ca.gov/faces/codes_displaySection.xhtml?sectionNum=13142.&lawCode=FAC

caused significant effect at 200 mg/kg-day in dogs. There is no evidence of MOXA or MESA causing developmental toxicity in rats, the only species studied. There is also no evidence of neurotoxicity in the limited number of studies conducted with either chemical. Genotoxicity studies of MOXA or MESA both showed negative results in the *in vivo* studies and all but one of the *in vitro* genotoxicity studies. The only positive result was increased DNA damage in spermatozoa and embryos of Pacific oysters detected by the comet assay (Mai et al., 2014). For both MESA and MOXA, there are no chronic or carcinogenicity studies available and thus potential carcinogenicity cannot be evaluated at this time. Overall, the available data do not suggest that MESA or MOXA poses carcinogenic activity, although the data are limited.

OEHHA develops the PHCs using the general approach of the Public Health Goal (PHG) program for exposure to chemicals in drinking water for a lifetime. The critical studies for MESA and MOXA are the subchronic oral toxicity studies conducted with dogs (Altmann, 1999 and Lees, 2004). The points of departure (PODs) are a No-Observed-Effect Level (NOEL) of 200 mg/kg-day for MESA and a NOEL of 500 mg/kg-day for MOXA. Benchmark dose modeling was not conducted for because of low number of animals tested, variability in enzyme changes, and uncertainty regarding the appropriate response level to set the benchmark dose for the enzymes. The PHC is calculated using the POD and applying applicable uncertainty factors (UFs), relative source contribution (RSC), and drinking water intake (DWI). For these chemicals, the total UF is 3,000: 10 for interspecies extrapolation, 30 for intraspecies variability, and 10 for additional uncertainty (for duration extrapolation since PHCs are to cover lifetime exposure and there are no available studies that adequately cover long exposure periods). The DWI is the upper 95th percentile drinking water consumption rate of 0.053 L/kg-day, which represents a time- and age-adjusted average. Since MESA and MOXA exposures are only from drinking water, a RSC of 100 percent is applied and the PHCs are 1300 ppb and 3200 ppb for MESA and MOXA, respectively. The detected levels (up to 20.2 ppb) of MESA and MOXA are far below the PHCs and thus adverse effects are not expected for the population from lifetime exposure in the drinking water.

OEHHA also derives a PHC of 7 ppb for metolachlor, in case metolachlor is detected in groundwater in the future. The POD is a lower confidence limit on the benchmark dose at 5% response ($BMDL_{05}$) of 5.8 mg/kg-day for increased incidence of cellular alterations (foci) in the liver of female rats (Tisdel, 1983). The total UF is 3,000: 10 for interspecies extrapolation, 30 for intraspecies variability, and 10 for carcinogenicity potential. The RSC applied is 20 percent since water is only one of the exposure sources.

II. INTRODUCTION

A. Background

Since 2001, the California Department of Pesticide Regulation (DPR) has detected metolachlor ethanesulfonic acid (MESA) and metolachlor oxanilic acid (MOXA) in groundwater in about 20% of the wells tested in California. MESA and MOXA are two environmental degradates of metolachlor. DPR did not detect metolachlor in any of the well water samples tested. DPR determined that the presence of MESA and MOXA in the well water samples was the result of legal uses of metolachlor-containing herbicide products. Under the California Pesticide Contamination Protection Act (PCPA) mandate (DPR, 2017a), these detections have to be evaluated by a subcommittee of the Pesticide Registration and Evaluation Committee (PREC), consisting of one member each from DPR, Office of Environmental Health Hazard Assessment (OEHHA), and the State Water Resources Control Board (SWRCB). The subcommittee is tasked to review reports submitted by the registrant and any other information or data necessary to make the finding whether or not the detected chemicals "pollute" the groundwater – defined by PCPA as a concentration "above a level that does not cause adverse health effects, accounting for an adequate margin of safety." OEHHA's primary responsibility is to derive public health concentrations (PHCs) to evaluate the detected groundwater levels.

Metolachlor and S-metolachlor are broad spectrum pre-emergent herbicides used for general weed control in many agricultural food and feed crops (DPR, 2016). From 1990 to 2014, the crops comprising about 89% of the total use in California were processing tomatoes, corn, cotton, and beans. Metolachlor was first registered in the US in 1976 for general weed control on turf.

B. Physical and Chemical Properties, Environmental Fate and Transport

Metolachlor is a member of the chloroacetanilide class of herbicides. Metolachlor, referred to as alpha metolachlor, is a racemic mixture of 50% each of R-enantiomer and S-enantiomer (US EPA, 2001). S-Metolachlor contains a higher ratio (88:12) of S- to R-enantiomer. The mechanism of action is inhibition of plant protein synthesis and interfering with plant growth. Metolachlor, MESA, and MOXA are water soluble ranging from 530 to 212,461 parts per million (ppm) (US EPA, 2008; The Metolachlor Task Force, 2017), and their physical and chemical properties are listed in Table 1.

Metolachlor is persistent in the environment. It is stable to hydrolysis under normal environmental conditions (US EPA, 1995). In surface soil, the field dissipation half-life is estimated to be 114 days (DPR, 2016). Metolachlor degradation in soil occurs mainly via microbial metabolism through different enzymatic pathways (DPR, 2016). Five

major degradants have been identified but the two predominant metabolites are MESA and MOXA (Figure 1; Adapted from Roberts, 1998).

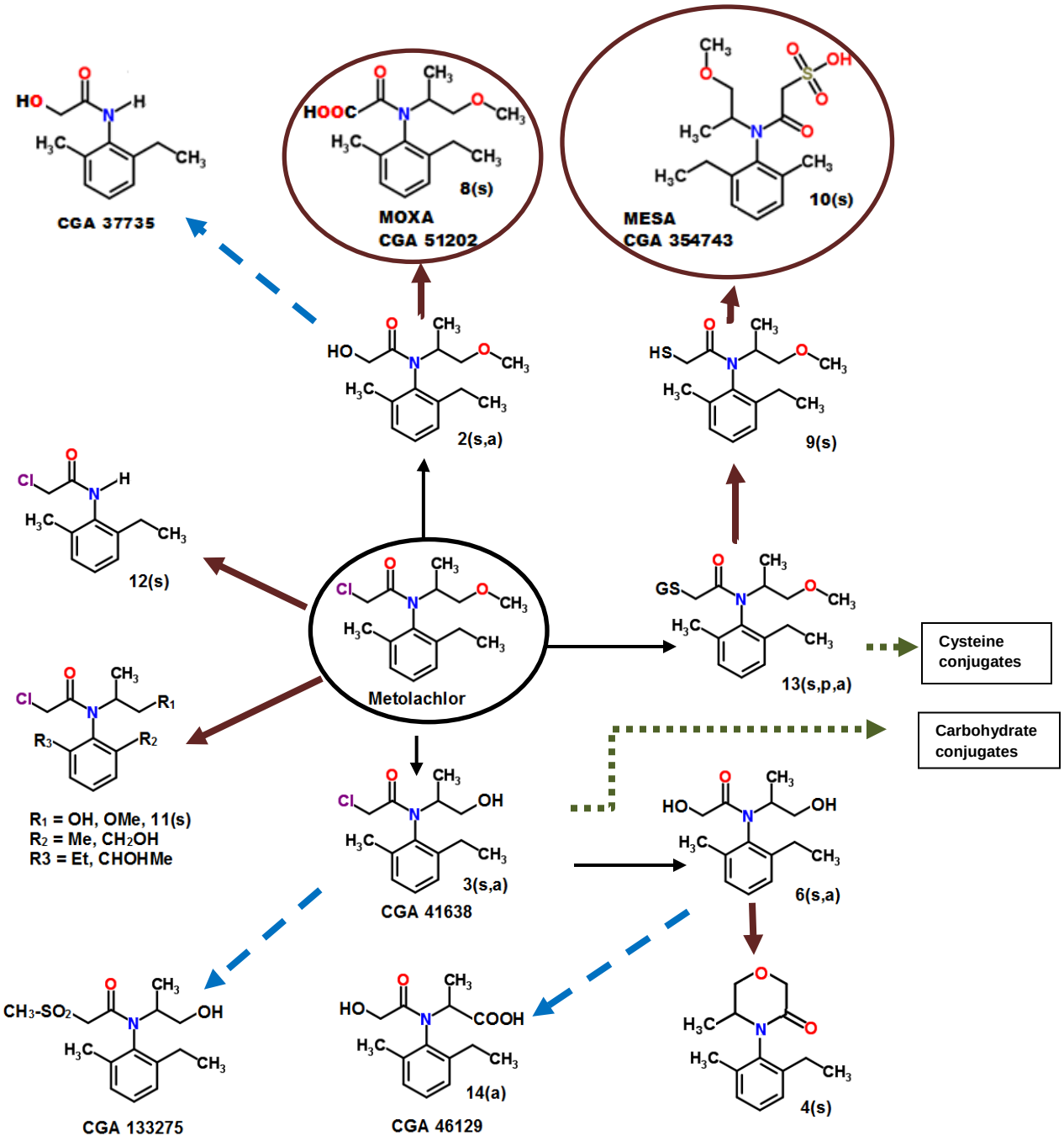
Table 1. Physical and chemical properties of metolachlor, MESA, and MOXA.

	Metolachlor[a]	S-Metolachlor[b]	MESA[b]	MOXA[b]
CAS	51218-45-2	87392-12-9	171118-09-5	152019-73-3
CGA ID	CGA-24705	CGA-77102	CGA-354743	CGA-51202
Formula	$C_{15}H_{22}ClNO_2$	$C_{15}H_{22}ClNO_2$	$C_{15}H_{23}NO_5S$	$C_{15}H_{21}NO_4$
Molecular weight (g/mole)	283.8	283.8	329	279.3
Log K_{ow}	3.13	3.05	NA	NA
Water solubility (mg/L, ppm)	530 at 20°C	480 at 20°C	212,461	238
Vapor Pressure (mm Hg)	3.14×10^{-5} at 25°C	NA	NA	NA
	1.3×10^{-5} at 20°C	NA	NA	NA
Henry's Law Constant (atm-m^3/mole)	9.0×10^{-9} at 20°C	NA	NA	NA
	2.44×10^{-8} at 25°C	NA	NA	NA

a/ US EPA (2008) and DPR (2003).
b/ The Metolachlor Task Force (2017). NA=not available from the report.

Metolachlor is moderate to highly mobile in different types of soil. Leaching of metolachlor from soil by run-off is likely and has a potential for downward movement to groundwater. The parent compound and major environmental degradates of metolachlor are monitored in California by DPR as part of the DPR's Groundwater Protection Program, and they are included on its Groundwater Protection List (GWPL). Since the late 1980s, DPR has analyzed 433 samples from 282 wells for metolachlor. Metolachlor was not detected in any of these samples (DPR, 2016). Starting in 2001, DPR added two metolachlor/S-metolachlor degradates to the analytical screen, MESA and MOXA, in response to groundwater detections in other states. In total, DPR has detected MESA/MOXA using an unequivocal analytical method at concentrations ranging from 0.05 to 20.2 ppb in 62 of 282 wells tested. The 62 positive wells were located in the following counties: Kings, Sacramento, San Joaquin, Solano, Stanislaus, Tulare, and Yolo.

Figure 1. Metabolic pathways of metolachlor



Adapted from Roberts, 1998: a, animal specific route dash →; p, plant specific route dotted →; s, soil metabolic route thickened → ; and **black** → for any route.

According to DPR (2016), the SWRCB, in conjunction with the US Geological Survey (USGS), sampled 1845 wells in 54 counties in California from 2004 through 2010 for metolachlor as part of their Groundwater Ambient Monitoring and Assessment (GAMA) Priority Basin Project. In this project, metolachlor was detected in 43 wells in 18 counties at concentrations ranging from 0.002 to 0.16 ppb. The USGS did not analyze for metolachlor degradates in this study. DPR conducted sampling to confirm the GAMA detections but did not detect the parent compound. DPR stated that this difference could be due to the lower GAMA reporting limit (0.006–0.13 ppb) for SWRCB compared to that (0.05 ppb) for DPR, and that DPR did not sample the same wells. OEHHA accessed the SWRCB's GAMA database for more current results (last 10 years) which showed that metolachlor detections were found in a total of 20 wells in 6 out 9 Regional Water Quality Control Board (RWQCB) regions covering 18 counties, and the concentrations ranged from 0.002 to 0.16 ppb. These detections need to be evaluated by DPR.

III. TOXICITY PROFILE

The toxicity of metolachlor and S-metolachlor has been reviewed in the United States Environmental Protection Agency (US EPA) Registration Eligibility Document (RED; US EPA, 1995), in the Tolerance Reassessment Eligibility Document (TRED) toxicology chapter (US EPA, 2001), in DPR's Toxicological Summary (DPR, 2017b), and in published scientific literature. The database for metolachlor is comprehensive, while it is incomplete for S-metolachlor, MESA, and MOXA. Almost all of the toxicity studies were conducted by the oral route. US EPA determined that metolachlor and S-metolachlor have comparable toxicity profiles; thus, studies from either chemical can be used interchangeably for endpoint selection (US EPA, 2001). The following presentation of the available toxicological data discusses in detail repeated-dosing studies considered for PHC derivation while summarizing other studies based on information in the US EPA (2001) and DPR (2017b) reviews.

A. Pharmacokinetics and Metabolism

Based on animal studies, both metolachlor and S-metolachlor were extensively absorbed and metabolized following oral administration, and eliminated via urine and feces (as reviewed in US EPA 2001). Residues were highest in red blood cells for metolachlor and whole blood for S-metolachlor. Metabolism of metolachlor in the rat was complex, with up to 32 metabolites identified in urine and feces. Figure 1 shows the major metabolic pathways for metolachlor in rats, plants, and soil. Biliary excretion and enterohepatic circulation play a significant role in the elimination of metolachlor.

MESA has only been detected at 0.28% of total metabolites in rats given metolachlor (Mewes, 1998 in DPR, 2017b). When MESA was given to rats, it was not well absorbed by the oral route (as reviewed in US EPA, 2001 and DPR, 2017b). It mostly passed through the gastrointestinal tract without being absorbed and was recovered in the feces. There is no pharmacokinetic information on MOXA.

B. Metolachlor and S-Metolachlor

1. Acute Toxicity

A summary of the acute toxicity profile for metolachlor and S-metolachlor is presented in Appendix 1. The acute toxicity studies are high dose, short-term studies, with toxicity characterized by the concentration (LC_{50}) or dose (LD_{50}) of the chemical exposure that caused a 50 percent increase in mortality. In acute toxicity tests, metolachlor is slightly toxic by the oral, dermal, and inhalation routes (US EPA, 1995, 2001; DPR, 2017b). It is slightly irritating to the eye and non-irritating to the skin in rabbits, but is positive for skin sensitization in guinea pigs. S-metolachlor is also only slightly acutely toxic by the oral and dermal route and relatively non-toxic by the inhalation route. It causes slight

eye irritation and is non-irritating dermally in rabbits, but is positive for skin sensitization in guinea pigs (US EPA, 2001).

2. Subchronic Toxicity

Oral

In the subchronic dietary toxicity studies, the only evidence of toxicity from metolachlor was a decrease in body weight or body weight gain in female rats at 259 milligrams per kilogram of body weight per day (mg/kg-day) and in male and female dogs at 29 mg/kg-day (See Appendix II). The lowest No-Observed-(Adverse)-Effect Levels (NOAELs) for these studies were 23.4 mg/kg-day in rats (Fankhauser, 1999a; reviewed in US EPA, 2001) and 9.7 mg/kg-day in dogs (Estes, 1980; reviewed by US EPA, 2001 and DPR, 2017b). Note that US EPA uses the term "NOAEL", while DPR uses mostly the term "NOEL" for No-Observed-Effect Level. For simplicity, the term NO(A)EL is used when the NOAEL and NOEL are the same from both sources. The Lowest-(Adverse)-Observed-Effect Level is indicated as LO(A)EL.

Also shown in Appendix II are subchronic toxicity studies conducted with S-metolachlor (US EPA, 2001). In one subchronic dietary toxicity study, no effects were observed in male and female rats at the highest dose tested of approximately 208 or 236 mg/kg-day, respectively (Fankhauser, 1999b; reviewed by US EPA, 2001). In another subchronic dietary toxicity study in rats, decreased body weight and body weight gain, reduced food consumption and food efficiency as well as increased absolute and relative kidney weights in males were observed at 150 mg/kg-day (180.3 mg/kg-day as calculated by DPR reviewers). The NO(A)EL was 15 mg/kg-day (US EPA) or 17.5 mg/kg-day (DPR) (Chang, 1995a; reviewed by US EPA, 2001 and DPR, 2017b). No effects were reported in a 90-day dog study at the highest dose (74 mg/kg-day) tested (Chang, 1995b; reviewed by US EPA, 2001 and DPR, 2017b).

Dermal

For dermal exposure, DPR established a systemic NOEL of 100 mg/kg-day for increased relative liver and kidney weights after metolachlor was applied topically to the skin of rabbits up to 1000 mg/kg-day for 21 days (Mastrocco et al., 1987; reviewed by US EPA, 2001 and DPR, 2017b). In contrast, USEPA determined that there was no evidence of systemic toxicity at the highest dose tested (1000 mg/kg-day) for this study and no NOAEL was established. Both DPR and US EPA noted that dermal irritation was observed at 10 mg/kg-day and above. This is in contrast to the acute toxicity studies, where dermal irritation was not observed.

3. Chronic Toxicity

The oral chronic toxicity database for metolachlor consisted of a one-year study in dogs (Hazelette and Arthur, 1989) and two-year toxicity studies in rats (Tisdel, 1983) and mice (Tisdel, 1982). Note that according to US EPA Federal Insecticide Fungicide and Rodenticide Act (FIFRA) guidelines, a one year study in dogs is categorized as a chronic study. This is different from the OEHHA guidance where exposure duration of ≤78 weeks is considered subchronic based on the average lifespan of dogs of 15 years (OEHHA, 2008). These studies are listed in Table 2. An earlier study with rats conducted in 1979 by Industrial BioTest Laboratory was not considered in this evaluation because US EPA dismissed the study due to inadequate clinical chemistry determinations and lack of dietary preparation records. In response, the chronic dietary rat and mouse studies were conducted (Tisdel, 1982, 1983). There are no chronic toxicity studies of S-metolachlor.

Rat- Tisdel, 1983

In the rat study, metolachlor (95.4% active ingredient) was administered in the diet to 60 CD-Crl:CD albino rats/sex/group at dose levels of 0, 30, 300 or 3000 ppm (0, 1.5, 15 or 150 mg/kg-day calculated by OEHHA, assuming 1 ppm = 0.05 mg/kg-day since the report did not provide the dosages) for two years. The mean body weight gain and food consumption were slightly decreased in the 3000 ppm females throughout the study; these changes were not statistically significant. Absolute liver weight, liver weight to body weight ratio, and liver weight to brain weight ratio were greater (7%, 13% and 5%, respectively) in 3000 ppm males. These changes were not statistically significant as calculated by the study authors. Both US EPA and DPR established the NO(A)EL at 300 ppm (15 mg/kg-day) for the above effects.

US EPA used this NOAEL and applied an uncertainty factor (UF) of 100 to derive the reference dose (RfD) of 0.15 mg/kg-day for the Integrated Risk Information System (IRIS) (IRIS, 1990).

OEHHA examined the data for liver foci of cellular alterations in female and male rats in this study. There were statistically significant increases in the high dose group for eosinophilic type foci (females), the combined total incidence of foci (either eosinophilic, clear, or basophilic; males and females), and in the total number of animals with any type of foci (females). The alteration shown as liver foci is generally considered to be a precursor to carcinogenicity (William, 1989; Thoolen et al., 2010). The females were more sensitive for this endpoint with statistical significance for trend and pair-wise comparison (Table 3).

Table 2. Chronic toxicity studies for metolachlor.

Species Route Duration	Dose (ppm) or mg/kg-day)	NO(A)EL (mg/kg-day)	LO(A)EL (mg/kg-day) and Endpoint	Reference[a,b]
Rat Diet 2-years	0, 30, 300, 3000 ppm M/F: 0, 1.5, 15, or 150 mg/kg-day	15 (NOAEL)[a]	150 Slight↓ BW and food consumption (F)	a,b,c Tisdel, 1983
		15 (NOEL)[b]	150 ↓ BW (F), ↑ liver and testes weight (M); ↑ cholesterol (M,F), ↑ liver alteration (foci) (M and F), ↑ neoplastic liver adenoma and carcinoma (M,F)	
		5.8[c] ($BMDL_{05}$)	Increased foci of cellular alterations in F	
Mouse Diet 2-years	0, 300, 1000, or 3000 ppm M/F: 0, 45, 150, or 450 mg/kg-day	150 (NOAEL)[a] (NOEL)[b]	450 Possible ↑ mortality[a], ↓ BW (M and F); ↑ AST, ALT and alkaline phosphatase levels and urine protein (M); ↓spleen and seminal vesicle weights (M); ↓ uterus weight (F)	a,b Tisdel, 1982
Dog Diet 1-year	0, 100, 300, 1000 ppm M: 0, 3.5, 9.7, or 32.7 mg/kg-day F: 0, 3.6, 9.7, or 33.0 mg/kg-day	9.7 (NOAEL)[a] (NOEL)[b]	33.0 ↓ BW gain, ↑mean alkaline phosphatase (F)[b]	a,b Hazelette and Arthur, 1989
		33.0 (NOAEL)[b]	No significant effect	

a/ From US EPA (2001).
b/ From DPR (2017b).
c/ Determined by OEHHA for this assessment. $BMDL_{05}$=lower limit on the benchmark dose at 5% response (Appendix III).
Abbreviations: AST=aspartate aminotransferase, ALT=alanine aminotransferase, BW= body weight, F=female, M=male

Table 3. Pre-neoplastic foci in the liver of female rats administered metolachlor in diet for two years (Tisdel, 1983).

	Incidences[a]			
Dose (mg/kg-day)	**0**	**1.5**	**15**	**150**
Eosinophilic	4/60***	7/60	5/60	23/60***
Clear	4/60	6/60	9/60	12/60*
Basophilic	7/60*	5/60	10/60	11/60
Animal with at least one type of liver foci	13/60***	15/60	18/60	34/60***

a/ Number of animal affected, from the study report.
Statistical significance by Cochran-Armitage test for trend (indicated on control group) or Fisher Exact test for pair-wise comparison (indicated on significant dose group when compared to control) with * p<0.05, ** p<0.01, *** p<0.001.

Liver tumors were also found in male and female rats of the same study (Table 4). The first liver carcinoma was found at 74 weeks (males) and 90 weeks (females) whereas the first adenoma (or neoplastic nodules in the report) was found at 82 weeks (males) and 104 weeks (females). The increases of adenomas and carcinomas observed in the females were statistically significant by trend and by pair-wise comparison at the high dose. For males, only the trend for adenomas was statistically significant. After the original histopathological examination by the conducting laboratory, an independent pathologist reviewed selected slides prior to the 3rd carcinogenicity peer review (US EPA, 1993). Because of the limited scope of the slide re-read and individual animal data for the re-read were not available, OEHHA relied on the original data to determine the effective number of animals at risk for statistical analysis of liver tumors (Table 4).

Table 4. Incidences of treatment-related liver tumors in rats administered metolachlor in diet for two years (Tisdel, 1983).

	Male				Female			
Dose (mg/kg-day)	**0**	**1.5**	**15**	**150**	**0**	**1.5**	**15**	**150**
Adenoma[a]	0/51***	0/53	0/57	4/55	0/45***	0/43	1/43	4/51*
Carcinoma[a]	2/52	1/53	3/57	2/55	0/45*	0/43	0/43	2/51
Combined adenoma or carcinoma	2/52*	1/53	3/57	6/55	0/45***	0/43	1/43	6/51*

a/ Incidences were for effective number of animals at risk- animals which were alive when the first tumor was found (74 weeks for males, 90 weeks for females). Statistical significance by Cochran-Armitage test for trend (indicated on control group) or Fisher Exact test for pair-wise comparison (indicated on significant dose group when compared to control) with * p<0.05, ** p<0.01, *** p<0.001.

OEHHA also examined the data for thyroid and nasal tumors, which had been associated with compounds (acetochlor, alachlor, butachlor) that are structurally similar to metolachlor. For metolachlor, these tumors were found at low incidences, and not considered treatment-related as none was statistically significant by trend or pair-wise comparison. The US EPA noted that the dosing for this study may not be sufficiently high enough (US EPA, 1993). Although the body weights of the female rats at the highest dose were approximately 10% lower than that of the controls, there was no difference between the male treated groups and the control. A reduction of 10% in body weight is a general indicator that the maximally tolerated dose has been reached.

Mouse- Tisdel, 1982

In the chronic mouse study (Tisdel, 1982), metolachlor (95% active ingredient) in the diet was fed to 52 CD-1 mice/sex/group at doses of 0, 300, 1000, or 3000 ppm (0, 45, 150, or 450 mg/kg-day, based on 1 ppm being equal to 0.150 mg/kg-day; US EPA, 2001) for two years. Sixteen additional mice/sex/group were sacrificed at 12 and 18 months. Decreases in body weight gain were observed in both sexes at the high dose tested. There were some treatment-related effects on clinical chemistry as noted in Table 2. There was a dose-related decrease in absolute and relative weight of the seminal vesicles, which were statistically significant only in high dose males. There were no effects on testes weight or accompanying histological changes and therefore, the toxicological significance of this finding in the seminal vesicles is unknown. US EPA noted that the significantly increased mortality in the high dose group could be due to treatment or viral infection.

While US EPA reported no treatment-related microscopic changes in any organs, DPR noted an increase of nodular hyperplasia (adenoma) in the male livers. The total incidences were: 7/63 (control), 8/64 (45 mg/kg-day), 12/65 (150 mg/kg-day), and 8/64 (450 mg/kg-day). Hepatocellular carcinoma incidences were: 2/63, 0/64, 4/65, and 1/64 from control to the highest dose tested. OEHHA analyzed these datasets individually and combined tumors, and found the increased incidence was mainly at the mid-dose and all incidences were not statistically significant by trend or pair-wise comparison. There was no increase in adenoma or carcinoma in female mice.

Both US EPA and DPR found there were no treatment-related tumors, and established the same NO(A)EL at 1000 ppm, or 150 mg/kg-day for endpoints shown in Table 2. OEHHA concurs with these conclusions.

Dog- Hazelette and Arthur, 1989

In the chronic dog study, beagles (6/sex/group for control and high dose; 4/sex/group for mid-dose) were fed a diet containing metolachlor (97% active ingredient) at 0, 100,

300, or 1000 ppm (male: 0, 3.5, 9.7, or 32.7 mg/kg-day; female: 0, 3.6, 9.7, or 33.0 mg/kg-day) for one-year (Hazelette and Arthur, 1989). This report noted transient reduced mean food consumption and body weight gain during the study. WHO (1996) cited an apparent decrease in kidney weight at the two highest doses. However, this effect was not statistically significant. Alkaline phosphatase level in blood was significantly increased in the 1000-ppm females at weeks 12, 26, and 40, but not at 51 weeks. The study authors considered the finding of minimal toxicological significance because the effect was not reported in males and was not associated with any gross or microscopic organ changes. US EPA and DPR established a NO(A)EL of 300 ppm (9.7 mg/kg-day) for reduced body weight gain and increased alkaline phosphate level in females. OEHHA agrees with a NO(A)EL of 9.7 mg/kg-day for this study. Increases in alkaline phosphatase levels were also reported in dogs during the 6-month oral (dietary) study with metolachlor (Estes, 1980), the 13 week oral (capsule) study with MESA (Altmann, 1999), and the 13-week oral (capsule) study with MOXA (Lees, 2004). Taken together, it is OEHHA's opinion that the change in alkaline phosphatase levels was treatment related and an indicator of liver toxicity.

4. Genotoxicity

OEHHA reviewed the genotoxicity studies of metolachlor cited in US EPA (US EPA, 2001) and DPR (DPR, 2017b) reviews and those in the published literature (Table 5). Some of the guideline studies, while showing negative results, were not considered acceptable by DPR. Reports in the published literature demonstrated positive results for genotoxicity of metolachlor in a limited number of *in vitro* studies. A review by Dearfield et al. (1999) indicated that there were positive genotoxicity tests from commercial grade metolachlor including positive mutation assay in *Salmonella* strain TA100 and *Saccharomyces cerevisiae* strain D4 with metabolic activation. Metolachlor identified as technical grade was not genotoxic in the same assays (Plewa et al., 1984). Metolachlor, MESA, and MOXA were all positive in comet assays using sperm cells and embryos of Pacific oyster (*Crassostrea gigas*; Mai et al., 2014). Osano et al. (2002) found that metolachlor was genotoxic in an *in vitro* genotoxicity test, the Mutatox® assay, which is conducted with a dark mutant of *Vibro fischeri*, a marine photobacterium. The Mutatox® assay is reported to be sensitive and responsive to chemicals that are DNA damaging agents, DNA intercalating agents, DNA synthesis inhibitors, and direct mutagens (Kwan et al., 1990). A metolachlor formulation, Dual®, caused *in vitro* cell transformations in baby hamster kidney (BHK21) cells (Slamenova et al., 1992). The amount of metolachlor in Dual® was not specified in the study. Finally, Roloff et al. (1992) demonstrated a dose-dependent increase in chromosomal damage (break frequency, percentage of cells with aberrations, and mean mitotic index) following *in vitro* exposure of metolachlor in isolated human lymphocytes.

Table 5. Genotoxicity profile of metolachlor and S-metolachlor.

Assay type and end point	Test systems	Results		Reference[a,b]
		-S9	+S9	
Metolachlor (CGA24705)				
***in vitro* Gene Mutation**				
Bacterial cells	*S. typhimurium* multiple strains (including TA 100)	NA	(-)	a (A), b (UA)
	TA 1538	NA	(-)	Plewa et al, 1984
	TA 100	NA	(+)	
	S.cerevisiae	NA	(+)	
	Vibrio fischeri Mutatox®	(+)	(-)	Osano et al., 2012
Mammalian cells	Mouse lymphoma cells L5178Y/TK$^{+/-}$	(-)		a (A), b (A)
***In vitro* Cell Transformation**				
Anchorage independent colonies	BHK21 cells (baby hamster kidney) (Dual®)	(+)	(-)	Slamenova et al, 1992
Morphological changes	Syrian hamster embryo cells (Dual®)	(-)	NA	Slamenova et al, 1992
***In vitro* Chromosomal Damage**				
Sister chromatid exchange	Human lymphocytes	(-)		Hill et al., 1997
Chromosomal aberration	Human lymphocytes	(+)		Roloff et al., 1992
***in vivo* Chromosomal Damage**				
Dominant lethal assay	Albino male mice/gavage 0 to 300 mg/kg	(-) germinal cells		a (A), b (UA)
Micronucleus formation	Chinese hamsters/gavage 0 to 5000 mg/kg	(-) bone marrow		a (A), b (A)
***In vitro and In vivo* DNA Damage**				
in vitro comet assay	Oyster embryos	(+)		Mai et al., 2014
	Oyster spermatozoa	(+)		
in vitro UDS	Human fibroblasts	(-)	NA	a (A), b (UA)
	Rat hepatocytes	(-)		a (A), b (A)
In vivo/in vitro UDS	Rats/gavage 0 to 1500 mg/kg	(-) hepatocytes		a (A)
	Sprague Dawley rats/gavage 0 to 450 mg/kg	(-) hepatocytes		b (A)

S-Metolachlor (CGA 77102)			
In vitro Gene mutation	*S. typhimurium* strains, and *E. coli* WP2uvrA	(-)	a (A), b (A)
In vivo Chromosomal damage (micronucleus formation assay)	Tif:MAGf mice/gavage 0 to 2000 mg/kg	(-) bone marrow	a (A), b (A)
	NMRI mice/gavage 0 to 800 mg/kg	(-) bone marrow	b (A)
In vivo/in vitro UDS	Tif:Ralf rats/gavage 0 to 3200 mg/kg	(-) hepatocytes	a (A), b (A)

a/ From US EPA (2001).
b/ From DPR (2017b).
Abbreviations: A=Acceptable under FIFRA Guidelines, Dual®=metolachlor formulation was tested, NA=not available, P=published paper, S9= rat liver fraction for metabolic activation, UA=Unacceptable under FIFRA Guidelines, UDS=unscheduled DNA synthesis and repair, (+)= positive result, (-) = negative result.

5. Reproductive and Development Toxicity

Reproductive Toxicity

There are no reproductive toxicity studies conducted with S-metolachlor.

In a two-generation reproductive study, rats were given metolachlor in the diet at doses of 0, 30, 300, and 1000 ppm (males [F_0-F_1], 0, 2.3-2.4, 23.5-23.7, and 75.8-76.6 mg/kg-day; females [F_0-F_1], 0, 2.5-2.6, 26.0-25.7, and 85.7-84.5 mg/kg-day). There was no evidence of parental or reproductive toxicity at approximately 80 mg/kg-day, the highest dose tested (Page, 1981; reviewed by US EPA, 2001 and DPR, 2017b). However, small but statistically significant decreases in fetal body weight were observed in the high dose groups of the F1 offspring on lactation days 14 and 21, and F2 offspring on lactation days 4, 7, 14, and 21. This finding was determined to be toxicologically significant and the NO(A)EL for developmental effects was approximately 25 mg/kg-day.

Development Toxicity

In the animal toxicity studies, developmental effects were only present at doses equal to or higher than those causing maternal toxicity. A developmental toxicity study of metolachlor was conducted with pregnant New Zealand white rabbits treated by gavage at 0, 36, 120, or 360 mg/kg-day on gestation days 6 to 18 (Lightkep, 1980; reviewed by US EPA, 2001 and DPR, 2017b). DPR established a maternal NOEL of 36 mg/kg-day for reduced food consumption and body weight gain, and miosis at 120 mg/kg-day. The developmental NOEL was 360 mg/kg-day, the highest dose tested, and no fetotoxicity or teratogenicity was observed.

In another developmental toxicity study, metolachlor was administered by gavage at doses of 0, 30, 100, 300, and 1000 mg/kg-day to 25 pregnant rats/group from gestational days 6 through 15 (Lochry, 1985, reviewed by US EPA, 2001 and DPR, 2017b). There was an increased incidence of death and clinical signs of toxicity (such as convulsions, excess salivation, urine-stained abdominal fur) in the dam at 1000 mg/kg-day, the highest dose tested. There were also developmental effects at 1000 mg/kg-day (slight decrease in the number of implantations per dam, decreased number of live fetuses/dam, increased number of resorptions/dam and significant decrease in mean fetal body weight). The developmental and maternal NO(A)EL was 300 mg/kg-day.

For S-metolachlor, developmental toxicity studies were also conducted in rats and rabbits. In the rat study, S-metolachlor was administered at 0, 5, 50, 500, or 1000 mg/kg-day to 24 mated rats on days 6-15 of gestation (Khalil, 1995; reviewed by US EPA, 2001 and DPR, 2017b). Maternal effects were limited to effects on reduced food

consumption and body weight gain. There were no treatment-related effects on pregnancy outcomes or fetal abnormalities. The maternal NO(A)EL was 50 mg/kg-day and the developmental NO(A)EL was 1000 mg/kg-day, the highest dose tested.

In the rabbit study, 19 mated New Zealand white rabbits were dosed with 0, 20, 100, or 500 mg/kg-day S-metolachlor on days 7-19 of gestation (Gilles and Giknis, 1995; reviewed by US EPA, 1997; US EPA, 2001; DPR, 2017b). Maternal effects were mainly limited to reduced food consumption and body weight (US EPA described these as pronounced) in the high dose group. DPR determined that malformed fetuses were found in 1/16 mid-dose litters and 2/18 high-dose litters; in one high-dose litter, all five fetuses were malformed (malformations reported included cleft palate, hydrocephaly, reduced trachea size, curled tongue, and abnormal limb; based on data in US EPA, 1997). US EPA concluded that most of the severe effects were observed in one high dose litter and were unlikely due to treatment. DPR assigned a maternal NOEL of 100 mg/kg-day and a developmental NOEL of 500 mg/kg-day for no effects observed. US EPA (1997) assigned a maternal NOAEL of 20 mg/kg-day, and a developmental NOAEL of ≥ 500 mg/kg-day.

6. Neurotoxicity/Immunotoxicity/Endocrine Disruption Studies

There is no evidence of neurotoxicity or neuropathology in any of the studies available in the database. Therefore, US EPA has not required developmental neurotoxicity studies for metolachlor and S-metolachlor. There are no guideline immunotoxicity studies; they are not currently required by US EPA. US EPA reviewed the results of the Endocrine Disruptor Screening Program (EDSP) Tier 1 assay for metolachlor (US EPA, 2015). There was no convincing evidence for a potential interaction of metolachlor with the estrogen or androgen pathways. There are some evidence for potential interaction of metolachlor with thyroid pathways in mammals; however, amphibian metamorphosis assay did not support this finding. There are no data to support potential thyroid toxicity in the young animals.

7. Human Epidemiology Studies

The Agricultural Health Study (AHS) is a prospective cancer and health outcome study of licensed pesticide applicators and their spouses from North Carolina and Iowa, who were enrolled from 1993-1997. More than 89,000 individuals have participated in the study (https://aghealth.nih.gov/about/). Several publications (Silver et al., 2015; Hou et al., 2013; Alavanja et al., 2004; Rusiecki et al., 2006) using the AHS data found there may be an association between metolachlor exposure in pesticide applicators and cancer.

Hou et al. (2013) examined the data for male applicators with no cancer and found a statistically significant association between increasing lifetime day use of metolachlor and shortened relative telomere length, which may or may not be associated with increased cancer risk. Alavanja et al. (2004) examined 46 lung cancer cases and found an increasing risk of lung cancer risk with increasing lifetime exposure days to metolachlor. However, this trend was not significant when analyzed using intensity-weighted days of pesticide exposure.

Using the same dataset for lung cancer, Rusiecki et al. (2006) also found a non-significant increased relative risk of lung cancer with lifetime exposure days in the highest exposure category but not with intensity-weighted lifetime days.

Silver et al. (2015) in a subsequent publication, or follow-up analysis of the same cohort, did not confirm significant association between metolachlor use and lung cancer incidences. No associations were found between increased risk associated with metolachlor exposure and incidence of all cancers combined in the same study. In a cohort of 26,505 workers who had ever reported using metolachlor, investigators did identify positive associations (statistically significant trend) between metolachlor use and incidence of liver cancer (total 25 cases) and follicular cell lymphoma (total 32 cases) when the number of cases for workers with highest reported use was compared to that for workers who do not handle metolachlor. The trend was not significant when risk for the high use worker cases were compared to those for low use metolachlor workers. The authors concluded that follow-up studies were needed to better differentiate the effects of metolachlor exposure and other factors, including co-exposure of other pesticides, associated with these tumors.

C. MESA and MOXA

A limited series of acute and subchronic toxicity, developmental toxicity and genotoxicity studies were conducted for MESA and MOXA (US EPA, 2001; DPR, 2017b). The acute toxicity of these soil degradates was essentially comparable to metolachlor, except for causing greater eye irritation (Tables 6 and 8). Relevant toxicity studies are discussed below.

1. MESA

There was no evidence of developmental toxicity up to 1000 mg/kg-day, based on a single study in rats (Doubovetzky, 1999; reviewed by US EPA, 2001 and DPR, 2017b).

There are two subchronic oral toxicity studies, one with rats and one with dogs. The 90-day dietary rat study (Bachmann, 1999; reviewed by US EPA, 2001 and DPR, 2017b) showed no treatment-related effect at the high dose of 1,685 mg/kg-day.

In the dog study (Altmann, 1999), 4 beagle dogs/sex/group were dosed orally with 0, 50, 200, 500, or 1000 mg/kg-day MESA (98.5% purity) in capsules for 13 weeks. This study also included an S-metolachlor dosed group (200 mg/kg-day). The results showed more significant effects for S-metolachlor than those treated with MESA (the effects are included under Section IV.B; Table 8).

For the MESA treatment, significant effects were mostly limited to the high dose groups. They included: increased total bilirubin levels, increased alkaline phosphatase levels, increased mean ɣ-glutamyl transpeptidase levels, and increased absolute liver weight. US EPA noted that there were mild treatment-related effects but questioned the toxicological significance of the findings and established a NOAEL of 1000 mg/kg-day at the highest dose tested. DPR's evaluation differed from that of US EPA and assigned a NOEL of 200 mg/kg-day for the study based on the clinical chemistry data. After evaluating the data from the study, OEHHA concurs with the NOEL of 200 mg/kg-day. OEHHA recognizes that relatively small changes of liver enzyme and bilirubin levels in blood alone may not be sufficient for the determination of a NOAEL. However, in this case, these changes are consistent with the toxic effect of metolachlor with liver as the target organ. Furthermore, since the dogs in the study were dosed for only 13 weeks, OEHHA considers that more severe effects of liver are possible and may be observed with longer exposure duration.

Since there is no chronic toxicity study for MESA, OEHHA chose this subchronic dog study as the critical study for PHC derivation. The subchronic rat study showed no treatment-related effect at the highest dose tested.

Due to lack of lifetime toxicity studies, the carcinogenicity of MESA cannot be evaluated in this assessment. There are four *in vitro* and one *in vivo* genotoxicity studies on MESA. The only positive result was increased DNA damage in sperm and embryos of Pacific oysters *in vitro* (Table 6; Mai et al., 2014).

Table 6. Toxicity profile for MESA.

Duration Route Species	**Dose/test system**	**Result[a,b]**	**Toxicity Category[c] or NO(A)EL**	**Reference[a,b]**
Acute Toxicity				
Acute oral/gavage Hanlbm:WIST rat	5000 mg/kg	LD_{50} > 5000 mg/kg	IV	a,b
Acute oral/gavage Tif:RAIf rat	2000 mg/kg	LD_{50} > 2000 mg/kg	III	a,b
Acute dermal Hanlbm:WIST rat	2000 mg/kg, 24-hour semi-occlusive	LD_{50} > 2000 mg/kg	III	a,b
Primary eye irritation rabbit	0.1 mL/eye (0.66 mg/eye)	Moderate irritant	II	a,b
Primary dermal irritation rabbit	0.5 g/site for 4 hour, occlusive	Non-irritating	IV	a,b
Dermal Sensitization guinea pig	6 hours, 1/week, for 3-week induction	Weak dermal sensitizer	Positive	a,b
Subchronic Toxicity				
Subchronic 90-day/diet Sprague-Dawley rat	0, 360, 1200, 6000, 20,000 ppm; M: 0 to 1545 mg/kg-day; F: 0 to 1685 mg/kg-day	NO(A)EL[a,b]: 1685 mg/kg-day No treatment-related effect at the highest dose tested		a,b
Subchronic 13-week/capsule dog	**0, 50, 200, 500, 1000 mg/kg-day**	NOAEL[a]: >1000 mg/kg-day **NOEL[b]: 200 mg/kg-day Clinical chemistry (alkaline phosphatase, total bilirubin) changes**		**a,b Altmann, 1999**
Developmental Toxicity				
Gestation days 6-15/ oral gavage Mated female Wistar rat	0, 250, 500, 1000 mg/kg-day	Maternal and develop-mental NO(A)EL[a,b]: >1,000 mg/kg-day No adverse effect		a,b
Genotoxicity				
Test System	**Dose**	**Result**		**Reference**
In vitro Gene Mutation	312.5-5000 µg/plate ± activation	(-) *Salmonella* and *Escherichia* strains		a,b
In vitro Gene mutation	185.2-5000 µg/mL ± activation	(-) Chinese hamster V79		a,b
In vitro Unscheduled DNA synthesis	9.77 to 5000 µg/mL	(-) primary rat hepatocytes		a,b
In vitro DNA damage (comet assay)	0-10 µg/mL	(+) Pacific oyster spermatozoa and embryos		Mai et al., 2014
In vivo Chromosome aberration/micronucleus	0, 1250, 2500, 5000 mg/kg by gavage	(-) no ↑ micro-nucleated polychromatic erythrocytes in bone marrow of rats		a,b

a/ From US EPA (2001). b/ From DPR (2017b).

c/ US EPA established the toxicity categories with the highest toxicity is Category I.

2. MOXA

There was no evidence of developmental toxicity up to 1000 mg/kg-day based on a single study in rats (Marty, 1992; reviewed by US EPA, 2001 and DPR, 2017b) (Table 7).

There are two subchronic oral toxicity studies, one with rats (Schneider, 1992; reviewed by US EPA, 2001 and DPR, 2017b) and one with dogs (Lees, 2004). The three-month dietary rat study (Schneider, 1992) showed no treatment-related effect at the high dose of 1020 mg/kg-day.

In the dog study, beagle dogs (4/sex/group) were given capsules with 0, 50, 500, or 1000 mg/kg-day MOXA for 90 days (Lee, 2004). MOXA was generally well tolerated and there were no treatment related effects on survival, body weights, or food consumption. Treatment-related effects were limited to increases in salivation in males at 500 and 1000 mg/kg-day, and hematological and clinical chemistry measurements (including alkaline phosphatase levels), mostly in the high dose group. These effects are included in Section IV.B. Table 8. DPR established a NOAEL at 1000 mg/kg-day for no adverse effect observed at the highest dose tested. OEHHA set a lower NOEL of 500 mg/kg-day based on statistically significant increases in alkaline phosphatase levels in the 1000 mg/kg-day dose group (180% of control levels; $p<0.01$) and clinical signs (increased salvation in males).

Since there is no chronic toxicity study for MOXA, OEHHA chose this subchronic dog study as the critical study for PHC derivation. The other subchronic rat study showed no treatment-related effect at the highest dose tested.

Due to lack of lifetime toxicity studies, the carcinogenicity of MOXA cannot be evaluated in this document. There are three *in vitro* and one *in vivo* genotoxicity studies. The only positive result was from increased DNA damage in sperm and embryos of Pacific oysters *in vitro* (Table 7; Mai et al., 2014).

Table 7. Toxicity profile for MOXA.

Duration Route Species	Dose	Result[a,b]	Toxicity Category[c] or NO(A)EL	Reference[a,b,d]
Acute Toxicity				
Acute oral/gavage Tif:RAIf rat	2000 mg/kg	LD_{50} (M/F) >2000 mg/kg	III	a,b
Acute dermal Tif:RAIf rat	1333 mg/kg, 24-hour semi-occlusive	LD_{50} >1333 mg/kg	II	a,b
Primary eye irritation rabbit	38 mg/eye	Severe irritant	II I	a,b
Primary dermal irritation rabbit	0.5 g/site, 4-hour semi-occlusive	Non-irritating	IV	a,b
Dermal sensitization guinea pig	intradermal injection	Sensitizer	Positive	a,b
Subchronic Toxicity				
Subchronic 3 months/diet Tif:RAIf rat	0, 300, 1000, 15000 ppm; M: 0 to 1002 mg/kg-day; F: 0 to 1020 mg/kg-day	NOAEL[a]: > 1020 mg/kg-day NOEL[b]: 1020 mg/kg-day No treatment-related effect at the highest dose tested		a,b
Subchronic 90 days/capsule Dog	**0, 50, 500, 1000 mg/kg-day**	**NOAEL: 1000 mg/kg-day[b] NOEL: 500 mg/kg-day[d] Clinical signs and clinical chemistry changes**		**b,d Lees, 2004**
Developmental Toxicity				
Gestation days 6-15/ oral gavage Mated female Tif:RAIf rat	0, 10, 100, 1000 mg/kg-day	Maternal and developmental NOAEL[a]: ≥1000 mg/kg-day NOEL[b]: 1000 mg/kg-day		a,b
Genotoxicity				
Test System	**Dose**	**Result**		**Reference[a,b]**
In vitro Gene Mutation	312.5-5000 µg/plate ± activation	(-) *Salmonella* and *Escherichia* strains		a,b
In vitro Gene Mutation	375 to 4000 µg/mL ± activation	(-) Chinese hamster V79		a,b
In vitro DNA damage (comet assay)	0-10 µg/mL	(+) Pacific oyster spermatozoa and embryos		Mai et al., 2014
In vivo Micronucleus test	0 to 2400 mg/kg gavage	(-) no ↑ micronucleated polychromatic erythrocytes in bone marrow of rats		a,b

a/ From US EPA, 2001.
b/ From DPR 2007.
c/ US EPA established the categories with the highest toxicity is Category I.
d/ Established by OEHHA in this report.

IV. HAZARD IDENTIFICATION AND DOSE-RESPONSE ASSESSMENT

The critical toxicity endpoints and point of departure (POD) determinations are discussed in this section. The POD is the critical dose level of a chemical from a study in animals or humans that is used for risk assessment as a starting point for the calculation of the acceptable daily dose (ADD). The POD is typically determined by fitting a dose-response model to the toxicity data using the Benchmark Dose Software (US EPA, 2017). In order to account for the uncertainty of the data, OEHHA selects the 95% lower confidence limit of the benchmark dose (BMD), called the BMDL (L stands for the lower confidence limit). The $BMDL_{05}$ is the BMDL with the response level set at 5% for quantal data. When data are not amenable to BMD modeling, OEHHA uses the traditional NO(A)EL/LO(A)EL approach in identifying a POD. This approach is used for the increased alkaline phosphatase levels in the dog studies with metolachlor, MESA, and MOXA. The datasets in these studies were not modeled because of the low number of animals tested and variability in the data. Furthermore, it is not known what level of change would be appropriate to set the benchmark response.

A. Metolachlor

1. Non-carcinogenic Effects

OEHHA selected the dog study (Hazelette and Arthur, 1989) as the most sensitive study with a NO(A)EL of 9.7 mg/kg-day for increased alkaline phosphatase levels and decreased body weight gain in females (Table 2). The chronic rat study (Tisdel, 1983) had the next lowest NO(A)EL of 15 mg/kg-day for non-cancer effects including decreased body weight gain and food consumption.

2. Carcinogenicity Weight of Evidence

OEHHA conducted a weight of the evidence analysis, which considered results from lifetime carcinogenicity studies in rodents, human epidemiology studies, genotoxicity studies, a mode of action evaluation, and high-throughput cell-based assays. In our evaluation, we also considered carcinogenicity determinations by US EPA.

The findings included:

- Male and female mice cancer bioassays: No treatment-related increase in tumors found.
- Male rat cancer bioassay: Hepatocellular adenomas were statistically significant only by trend test (Table 4).
- Female rat cancer bioassay:

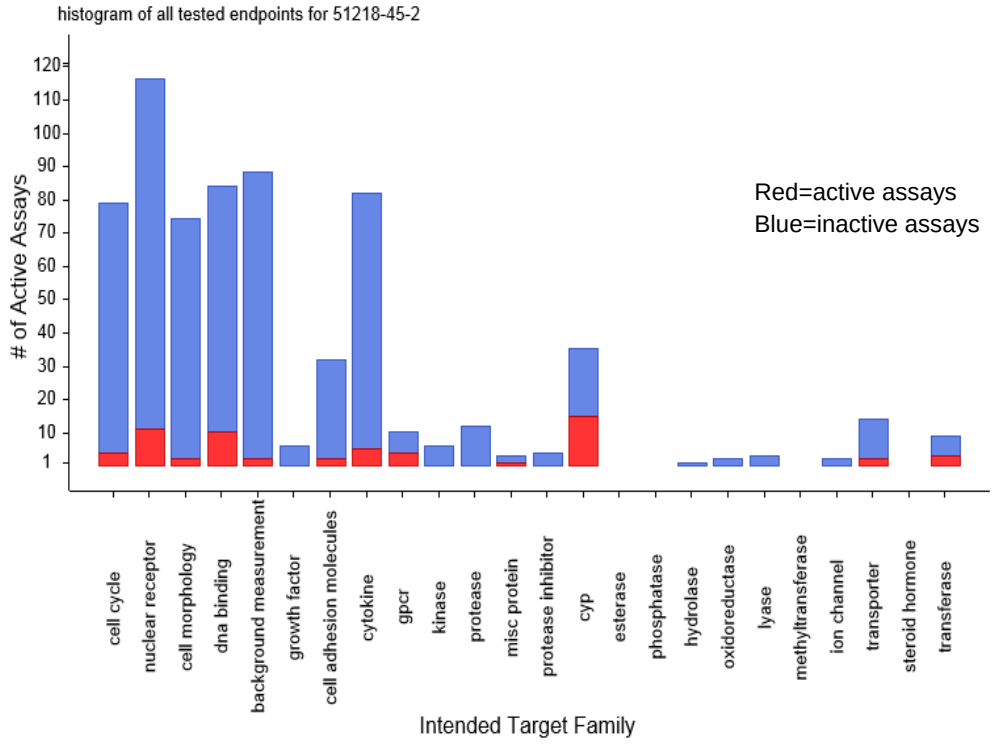
- Preneoplastic liver foci of cellular alterations were statistically significant by trend and pair-wise comparison (high-dose) (Table 3).
- Liver adenomas were statistically significant by trend and pair-wise comparison, liver carcinomas were significant by trend, and combined liver tumors were significant by trend and pair-wise comparison (Table 4).

- Using the data in the AHS, researchers found a positive association between occupational exposure to metolachlor and certain types of cancer, including liver cancer. However, the results were limited by small number of cases and confounding factors, such as co-exposure to other pesticides, which were not ruled out.
- The mode of action for liver toxicity and oncogenicity remains unknown. The guideline genotoxicity studies were negative. All *in vivo* genotoxicity studies were negative. There are several positive *in vitro* genotoxicity studies for metolachlor in the literature.
- Metolachlor is "active" in ToxCast™ assays for a variety of intended target families[2]. The most active was assays for cytochromes P450, nuclear receptors, and DNA binding[3]. There were four active assays for cell cycle and morphology including positive effects on oxidative stress and mitotic arrest in human hepatic G2 liver cells and tumor suppressor p53 in a human colon carcinoma cell line. A histogram of the active versus inactive endpoints grouped by intended target family is presented in Figure 2. S-Metolachlor was tested less extensively and was only active in some assays, predominantly in the nuclear receptor and DNA binding families of assays[4]. These results need further analysis for use in mode of action determination.

OEHHA also considered US EPA's structure-activity relationship analysis and carcinogenicity determination. In 1993, US EPA determined that metolachlor should be classified as Group C - "possible human carcinogen, based on liver tumors in rats at the highest dose tested" and used low-dose linear extrapolation to estimate cancer risk (US EPA, 1993; US EPA, 2015). US EPA also considered compounds, which are structurally similarity to metolachlor. The most widely used chloroacetanilides in the US in addition to metolachlor include alachlor, acetochlor, butachlor, and propachlor. Compared to metolachlor, the other four chloroacetanilides are more potent carcinogens and have been classified as likely human carcinogens (Group B) by US EPA (2004). Alachlor, acetochlor, and propachlor are also listed on the current Proposition 65 list, as chemicals known to the state of California to cause cancer.

[2] Targets (such as receptors or DNA) or processes and pathways (such as oxidative stress) which are linked to an apical toxicity endpoint.
[3] https://actor.epa.gov/dashboard/#chemical/51218-45-2
[4] https://actor.epa.gov/dashboard/#chemical/87392-12-9

Figure 2. Active assays for metolachlor in ToxCast™, grouped by intended target family[5]



In 1995, US EPA retained the cancer classification of metolachlor as a possible human carcinogen, but revised their recommendation from linear to non-linear approach based on the lack of genotoxicity and structure-activity analysis with structurally similar compounds (US EPA, 1995). They concluded that metolachlor does not have a common mechanism of carcinogenicity with acetochlor and alachlor due to the type of tumors found and chemical structure considerations (Federal Register, 2015). According to US EPA (2004), chloroacetanilide herbicides that are structurally related (*i.e.*, acetochlor, alachlor, and butachlor) induce nasal epithelial and thyroid follicular cell tumors, but the incidences for these tumor types were low in metolachlor-treated animals. The target organ for the carcinogenicity of metolachlor is the liver (Table 4; Tisdel, 1983).

For chloroacetanilides, such as alachlor and acetochlor, the quinone imine that is formed from their 2,6-alkylaniline base structure is presumed to be the ultimate precursor for their carcinogenicity. According to US EPA for metolachlor, “Because of

[5] https://actor.epa.gov/dashboard2/#chemical/51218-45-2

the steric hindrance (provided by the additional alkyl group around the nitrogen atom) the nitrogen atom [in metolachlor] is significantly less susceptible to amide dealkylation and extremely stable to metabolic hydrolysis of the amide so that formation of the disubstituted aniline is presumably very low (if any)" (US EPA,1995). In other words, US EPA determined that metolachlor does not form a quinone, which could react with nasal epithelial tissues. Coleman et al. (2002) found that human liver microsomes *in vitro* did not metabolize metolachlor into the quinone, which is the necessary precursor to form the carcinogenic intermediate quinonimines, indicating a lower genotoxic potential for metolachlor in humans. However, these conclusions are inconsistent with the studies reported by Dearfield et al. (1999) and Jefferies et al. (1998). They found evidence of formation of quinonimines *in vivo* following administration of metolachlor to rats. In addition, the potential contribution of extrahepatic metabolism of metolachlor to carcinogenic intermediates cannot be determined from the available data.

In conclusion, OEHHA determined that there is suggestive evidence that metolachlor is a carcinogen. Among the cancer bioassays available, metolachlor was negative in male and female mice, equivocal in male rats, and positive, but in low incidence at the highest dose tested, in female rats. It was negative in all *in vivo* genotoxicity tests but was positive in a limited number of *in vitro* genotoxicity tests. The association of metolachlor use and certain types of cancer, including liver cancer, in metolachlor applicators was based on a very small number of cases, and confounding factors such as co-exposure to other pesticides were not ruled out. Thus, OEHHA concluded that while the overall evidence on the carcinogenicity of metolachlor was suggestive, it did not support conducting a quantitative risk assessment of the liver tumor data using the linear low-dose extrapolation approach.

Instead, OEHHA decided to evaluate the carcinogenicity concern of metolachlor based on a preneoplastic endpoint - liver foci in rats (Tisdel, 1983), and later factored in the uncertainty associated with carcinogenicity potential. OEHHA modeled the total number of female rats with any type of liver foci of cellular alterations and calculated a $BMDL_{05}$ of 5.8 mg/kg-day for this endpoint (Table 3; Appendix III).

B. MESA and MOXA

The data from animal toxicity studies are limited for MESA and MOXA as presented in previous sections (Sections III.C.1 and 2). Subchronic toxicity studies in dogs were chosen to calculate the PHCs for MESA and MOXA.

OEHHA compared the relative toxicity to the liver for metolachlor or S-metolachlor, MESA, and MOXA to determine if the metolachlor database can be used as the surrogate for these degradates. The data used for this comparison are those from the subchronic toxicity studies with dogs (Table 8; Altmann, 1999; Lees, 2004). S-

metolachlor and these degradates both showed liver toxicity as observed changes in clinical chemistry data (total bilirubin, alkaline phosphatase, and ɣ-glutamyl transpeptidase) and absolute liver weight. At 200 mg/kg-day, S-metolachlor showed greater liver toxicity than MESA at the same and higher doses. S-metolachlor was also much more toxic than MOXA, which did not have any effect until the dose was increased to 1000 mg/kg-day.

OEHHA determined that based on the large differences in relative toxicity of metolachlor and its degradates, separate PODs and PHCs should be determined for metolachlor, MESA, and MOXA. The PODs derived for MESA and MOXA were the NOELs of 200 mg/kg-day and 500 mg/kg-day, respectively, mainly based on clinical chemistry data.

Table 8. Comparison of liver toxicity in dogs.

Parameter (% change from control)	**Sex**	**Altmann (1999)**						**Lees (2004)**	
		Control	**S-Meto-lachlor**	**MESA**				**MOXA**	
		mg/kg-day							
		0	**200**	50	**200**	500	1000	500	1000
Total bilirubin	M	100	171*	127	145*	171**	230**	86	80
	F	100	115	101	128	154**	177**	76	74*
Alkaline phosphatase	M	100	452*	121	142	161*	207**	127	180**
	F	100	413*	128	127	182**	193	117	122
ɣ-Glutamyl transpeptidase	M	100	364*	117	122	122	147**	100	107
	F	100	474*	219	208	303**	258	100	93
Liver-absolute weight	M	100	137*	91	100	108	109**	104	107
	F	100	149*	108	105	117	115	103	108

Statistical significance from the reports at * p<0.05, ** p<0.01.
Abbreviations: F=female, M=male.

V. PUBLIC HEALTH CONCENTRATION DETERMINATION

A. General Approaches

OEHHA develops the PHCs using the general approach of the Public Health Goal (PHG) program for exposure to chemicals in the drinking water for a lifetime. For non-carcinogenic and carcinogenic effects, the derivation of a PHC starts with the PODs derived from the animal studies. This dose is converted to an acceptable daily dose (ADD), which is then back calculated to an acceptable level in the drinking water.

1. Acceptable Daily Dose

The ADD is the estimated maximum average daily dose of a chemical (in mg/kg-day) that can be consumed by a human for an entire lifetime without adverse effects. To determine the ADD, the POD is adjusted by factors to account for uncertainties in the risk assessment, such as differences between animals and humans (interspecies extrapolation), and differences among humans in response to a chemical exposure (intraspecies variation, including sensitive individuals). This combined factor is referred to as a total uncertainty factor (UF).

When developing health-protective levels for non-carcinogenic effects based on animal toxicity studies, OEHHA generally applies a total UF of 300 (OEHHA, 2008).

These UFs are:

- 10 for interspecies extrapolation consisting of
  √10 for pharmacodynamics and √10 for pharmacokinetics.
- 30 for intraspecies variability consisting of
  √10 for pharmacodynamics and 10 for pharmacokinetics.

A table of default UFs for ADD derivation is presented in Appendix IV. Additional adjustments may be included depending on the limitations of the database.

The ADD is calculated using the following equation:

$$ADD = \frac{POD}{UF}$$

2. Drinking Water Concentration

To calculate the PHC for a chemical, the ADD is converted to a concentration in drinking water that accounts for the total exposure to the chemical that people receive from using tap water. Since metolachlor, MESA, and MOXA are very soluble in water,

they are not likely to be volatilized into the air for inhalation exposure, and dermal exposure is considered negligible. Consumption of drinking water was determined to be the major exposure pathway in the PHC calculation.

The PHC (in milligrams/liter, mg/L or in microgram/liter, µg/L) is derived by the following equation:

$$PHC = \frac{ADD \times RSC}{DWI}$$

OEHHA applied a daily water intake (DWI) of 0.053 L/kg-day, which is the time-weighted lifetime average drinking water consumption rate based on lifestage-specific water consumption rates, and is a value for lifetime exposure (OEHHA, 2012).

The PHC calculation also includes consideration of the relative source contribution (RSC) - the proportion of exposures to a chemical attributed to tap water, as part of total exposure from all sources (including food and air). The RSC values typically range from 20 to 100% (expressed as 0.20 to 1.0 in the equation), where the default RSC is 100% (1.0) when tap water is the only source of the chemical, and 0.2 when there are multiple sources.

B. Metolachlor

For non-carcinogenic effects, OEHHA used the NO(A)EL of 9.7 mg/kg-day from the dog study (Hazelette and Arthur, 1989) as the POD to estimate the ADD. A total UF=1000 was applied. It included the default inter- and intra-species UF of 300, plus an additional UF of 3 to extrapolate subchronic exposure to lifetime exposure. The dogs were exposed to metolachlor for only one year, which is less than 12% of lifetime (see Appendix IV).

$$\text{Metolachlor ADD} = \frac{9.7 \text{ mg/kg-day}}{1000} = 0.0097 \text{ mg/kg-day}$$

A default RSC value of 0.2 was applied because there are other potential sources of metolachlor, such as the diet. The PHC based on non-carcinogenic effect is:

$$\text{Metolachlor PHC} = \frac{0.0097 \text{ mg/kg-day} \times 0.2}{0.053 \text{ L/kg-day}} = 0.037 \text{ mg/L}$$

$$= 37 \text{ µg/L or } \textbf{40 ppb} \text{ (rounded)}$$

OEHHA also considered the $BMDL_{05}$ of POD of 5.8 mg/kg-day for liver foci in female rats (Tisdel, 1983) as the POD for carcinogenicity concern. Since this is an upstream

effect and the liver carcinogenicity is not evaluated directly, OEHHA included an additional UF of 10 to ensure that the PHC based on liver foci would be sufficiently protective against the carcinogenic potential of metolachlor. The ADD was calculated with a total UF=3000. Thus, the PHC for this endpoint is:

$$\text{Metolachlor PHC} = \frac{(5.8 \text{ mg/kg-day}/3000) \times 0.2}{0.053 \text{ L/kg-day}}$$

$$= 0.007 \text{ mg/L} = 7 \text{ µg/L or } \mathbf{7 \text{ ppb}}$$

The lower PHC of 7 ppb is more health protective and could be selected to evaluate metolachlor if it were detected in the groundwater.

C. MESA

The POD for MESA was the NOEL of 200 mg/kg-day in the subchronic dog study based on percent changes in clinical chemistry data and absolute liver weight (Altmann, 1999). A total UF=3000 was applied. This accounted for OEHHAs default inter- and intra-species UF of 300, plus an additional 10-fold factor because a 3-month study in dogs is subchronic in duration, and is a less than 8% of lifetime exposure (see Appendix IV).

$$\text{MESA ADD} = \frac{200 \text{ mg/kg-day}}{3000} = 0.07 \text{ mg/kg-day}$$

The default RSC value of 1.0 was applied because the exposure to MESA is primarily found in drinking water only. The PHC is:

$$\text{MESA PHC} = \frac{0.07 \text{ mg/kg-day} \times 1}{0.053 \text{ L/kg-day}} = 1{,}321 \text{ µg/L or } \mathbf{1300 \text{ ppb}} \text{ (rounded)}$$

D. MOXA

The POD for MOXA was the NOEL of 500 mg/kg-day in the subchronic dog study based on percent changes in clinical chemistry data (Lees, 2004). Using the same equations, UF, DWI, and RSC described for MESA:

$$\text{MOXA ADD} = \frac{500 \text{ mg/kg-day}}{3000} = 0.17 \text{ mg/kg-day}$$

$$\text{MOXA PHC} = \frac{0.17 \text{ mg/kg-day} \times 1}{0.053 \text{ L/kg-day}} = 3{,}208 \text{ µg/L or } \mathbf{3200 \text{ ppb}} \text{ (rounded)}$$

E. Existing Levels

There are no established drinking water guidance levels for MESA or MOXA. The existing levels for metolachlor are based on non-carcinogenic effects. The World Health Organization (WHO) set a guideline level of 10 µg/L, or 10 ppb, for metolachlor in drinking water. This value was calculated using a NOAEL of 3.5 mg/kg-day from the one-year dog dietary study for non-statistically significant decrease in kidney weight at the two higher doses (WHO, 1996; Hazelette and Arthur, 1989; Section III.B.3). US EPA in 1987 established a lifetime health advisory level (HAL) of 10 µg/L for metolachlor in drinking water based on a NOAEL of 1.5 mg/kg-day for increased liver foci from the chronic rat study (US EPA, 1987; Tisdel, 1983). In a subsequent assessment, US EPA used a NOAEL of 9.7 mg/kg-day for decreased body weight gain in the one-year chronic dog study to derive a chronic oral RfD of 0.10 mg/kg-day (US EPA, 1995). The lifetime HAL was revised to 700 ppb, calculated from the chronic RfD, assuming a 70 kg adult consuming 2 L/day water (0.029 L/kg-day) and a 20% RSC (US EPA, 2012b). US EPA also established the Drinking Water Equivalent Level (DWEL) at 3500 ppb when 100% RSC is from water. A comparison of the US EPA and OEHHA calculations is shown in Table 9.

Table 9. Factors in the derivation of lifetime drinking water levels for metolachlor and degradates.

Chemical Source	POD mg/kg-day	Uncertainty factors				RSC	DWI	HAL, PHC
		Inter-species	Intra-species	Addit-ional	Total		L/kg-day	ppb
Metolachlor								
US EPA	9.7	10	10	1	100	0.2	0.029[a]	700
OEHHA	5.8	10	30	10[b]	3000	0.2	0.053	7
MESA OEHHA	200	10	30	10[c]	3000	1.0	0.053	1300
MOXA OEHHA	500	10	30	10[c]	3000	1.0	0.053	3200

a/ Drinking water rate of 2 L/day and 70 kg body weight.
b/ UF for carcinogenicity concern.
c/ UF for extrapolation from subchronic to lifetime POD (study duration <8% of estimated lifetime; see Appendix IV).
Abbreviations: DWI=drinking water intake, POD= point of departure, RSC=Relative Source Contribution, HAL=health advisory level.

VI. RISK CHARACTERIZATION

OEHHA recommends that chemical-specific PHCs be applied in the evaluation of detected levels of MESA and MOXA because: (1) they are produced by microbes in soil and are not metabolites from metolachlor metabolism in animals, and (2) there is sufficient evidence to show that they are less toxic than metolachlor. There are two equivalent margin of safety approaches to characterize the risk associated with the exposure to the detected levels (expressed as ppb or as exposure in term of mg/kg-day) in the drinking water:

1) **% PHC = Detected level in ppb ÷ PHC in ppb x 100%**

2) **Margin of Exposure (MOE) = POD in mg/kg-day ÷ Exposure in mg/kg-day**

   Exposure = detected level (in mg/L) x drinking water rate L/kg-day

When the % PHC is ≤ 100% or MOE is ≥ the total UF, human exposure to the detected levels in the drinking water would not be expected to cause adverse health effects.

Table 10 shows the risk calculated using both methods. OEHHA used the average detected level of the two degradates of 0.3 ppb (The Metolachlor Task Force, 2017) as well as the highest degradate detection of 20.2 ppm (DPR, 2016) to calculate the margin of safety. Using the PHCs developed in this document, the detected MESA and MOXA levels are not expected to cause adverse health effects. If metolachlor is detected in the future, a similar comparison could be made for metolachlor using the PHC value developed in this report.

Table 10. Comparison of detected level to PHCs and MOEs for MESA and MOXA.

Chemicals	% PHC method			MOE method		
	Detected levels (ppb)	**PHC (ppb)**	**% PHC** (Target ≤100%)[a]	**POD (mg/kg-day)**	**Exposure (mg/kg-day)**	**Calculated MOE** (Target MOE ≥3000)[a]
MESA	0.3 20.2	1300 1300	0.02% 1.6%	200 200	0.000016 0.0011	$1.3x10^7$ $1.8x10^5$
MOXA	0.3 20.2	3200 3200	0.01% 0.6%	500 500	0.000016 0.0011	$3.1x10^7$ $4.5x10^5$

a/ Target for no adverse effect expected from lifetime exposure to the detected level in the drinking water.

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APPENDIX I. ACUTE TOXICITY PROFILE FOR METOLACHLOR AND S-METOLACHLOR

Study Type	Species	Result[a,b]	Toxicity Category[c]	Reference
Metolachlor (CGA 24705)				
Acute oral	Rat	LD_{50}= 2780 mg/kg	III	a
		LD_{50}= M: 3302 mg/kg, F: 2000 mg/kg	III	b
Acute dermal	Rabbit	LD_{50} >10,000 mg/kg	III	a
		LD_{50} >2000 mg/kg	III	b
Acute inhalation	Rat	LC_{50} > 1.75 mg/L	III	a
		LC_{50} >4.33 mg/L or 4102 mg/kg[d]	IV	b
Eye irritation	Rabbit	No irritation	IV	a
		Corneal opacity, iritis, conjunctival redness	III	b
Dermal Irritation	Rabbit	Non-irritating, mild edema	IV	a,b
Skin sensitization	Guinea pig	Sensitizer	Positive	a,b
S-Metolachlor (CGA 77102)				
Acute oral	Rat	LD_{50}= 2672 mg/kg (M,F) 2515 mg/kg (F)	III III	a b
Acute dermal	Rabbit	LD_{50} >2000 mg/kg	III	a
Acute inhalation	Rat	LC_{50} > 2.91 mg/L	IV	a
Dermal Irritation	Rabbit	Non-irritating	IV	a
Eye irritation	Rabbit	Slight to moderate conjunctival irritation	III	a
Skin sensitization	Guinea pig	Sensitizer	Positive	a

a/ From US EPA (2001).

b/ From DPR (2017).

c/ US EPA established the toxicity categories for the use to develop precautionary and personal protective equipment statements on the pesticide product labels and regulatory purposes. The highest toxicity is Category I. See: http://www.ecfr.gov/cgi-bin/text-idx?SID=ec376f296cd00252877e3fce3a447ff5&mc=true&node=se40.26.156_162&rgn=div8

d/ Using a rat default inhalation rate of 0.25 L/min and 0.38 kg body weight from USEPA (2012a, Table 2-5), the dose is estimated to be 4102 mg/kg-day.

Abbreviations: F=female, M=male.

APPENDIX II. SUBCHRONIC TOXICITY STUDIES FOR METOLACHLOR AND S-METOLACHLOR

Species/Route/ Duration	Dose (ppm or mg/kg-day)	NO(A)EL (mg/kg-day)	LO(A)EL (mg/kg-day) and Endpoint	Reference [a,b]
Metolachlor (CGA 24705)				
Sprague-Dawley rat/diet/ 3 months	0, 30, 300, 3000 ppm M: 0, 2.00, 20.2, 210 mg/kg-day F: 0, 2.32, 23.4, 259 mg/kg-day	F: 23.4	259 ↓ BW and BW gain (F)	a
Dog/diet/ 3 months	Metolachlor: 0, 50 (weeks 1-9), 150, 500 and 1000 ppm (weeks 9-15)	>1000 ppm	No adverse effect	b
Dog/diet/ 6 months	0, 100, 300, 1000 ppm M: 0, 2.9, 9.7, 29.6 mg/kg-day F: 0, 3.0, 8.8, 29.4 mg/kg-day	M/F: 9.7/8.8	29 ↓ BW gain	a
		9.7/8.8	↑ Alkaline phosphatase level and liver weight	b
New Zealand rabbit/dermal/ 21 days	0, 10, 100, 1000 mg/kg-day (applied 6 hours/day to intact skin)	NE[a]	No systemic effect	a
		100[b]	↑ Relative liver and kidney weights	b
S-Metolachlor (CGA 77102)				
Sprague-Dawley rat/diet/ 90 days	0, 30, 300, 3000 ppm M: 0, 1.9, 20.4, 208.0 mg/kg-day F: 0, 2.13, 23.9, 236.0 mg/kg-day	M/F: 208/236	No adverse effect	a
Sprague-Dawley rat/diet/ 13 weeks	0, 30, 300, 3000, 10,000 ppm M: 0, 1.81, 17.5, 180.3, 592.8 mg/kg-day F: 0, 2.24, 23.0, 230.2, 730.5 mg/kg-day [c]	M: 15 [a] M: 17.5[b]	150[a] (180.3)[b] ↓ BW and BW gain, food consumption, and food efficiency; ↑ kidney relative and absolute weights	a,b
Dog/diet/ 90 days	0, 300, 500, 1000, 2000 ppm M: 0 to 62 mg/kg-day F: 0 to 74 mg/kg-day	M: 62 F: 74	Highest dose had no effect	a,b

a/ From US EPA (2001).
b/ From DPR (2017).
Abbreviations: BW=body weight, M=male, F=female, NE=NOAEL not established.

APPENDIX III. BENCHMARK DOSE MODELING RESULTS

Benchmark dose modeling was conducted using female rats with incidence of liver foci of cellular alteration Table 3 (Tisdel, 1983).

Model[a]	Goodness of fit		BMD_{5Pct} (mg/kg-day)	$BMDL_{5Pct}$ (mg-kg-day)	Basis for model selection
	p-value	AIC			
Gamma[b]	0.867	289.90	13.4	8.97	Significant *p*-value, low AIC, scaled residuals <2, best visual fit
Dichotomous-Hill	0.744	291.72	7.27	1.57	
Logistic	0.777	290.12	20.8	15.9	
LogLogistic	**0.919**	**289.78**	**10.1**	**5.78**	
Probit	0.785	290.10	20.0	15.3	
Weibull[c] Quantal-Linear[d]	0.867	289.90	13.4	8.97	
Multistage 3°[e] Multistage 2°[f]	0.867	289.90	13.4	8.97	

[a] Selected model in bold; scaled residuals for selected model for doses 0, 1.5, 15, and 150 were -0.31, 0.19, 0.18, -0.06, respectively.

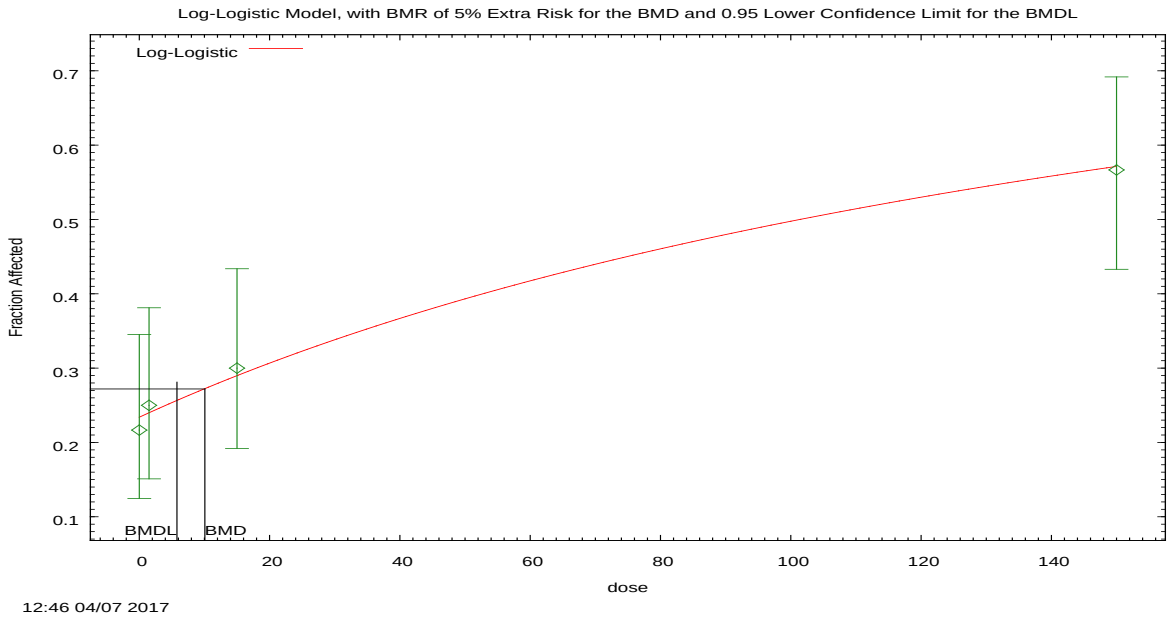

Figure 3. Plot of incidence rate by dose with fitted curve for LogLogistic model for foci in liver of female rats; dose shown in mg/kg-dag.

Logistic Model. (Version: 2.14; Date: 2/28/2013)

The form of the probability function is: P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]

Slope parameter is restricted as slope >= 1

Benchmark Dose Computation.

BMR = 5% Extra risk

BMD = 10.065

BMDL at the 95% confidence level = **5.77981**

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	0.233699	0.216667
intercept	-5.2535E+00	-5.1224E+00
slope	1	1

Analysis of Deviance Table

Model	Log(likelihood)	# Parameters	Deviance	Test d.f.	p-value
Full model	-142.8	4			
Fitted model	-142.89	2	0.169782	2	0.92
Reduced model	-152.76	1	19.9163	3	0

AIC: = 289.78

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Residual
0	0.2337	14.022	13	60	-0.31
1.5	0.2397	14.38	15	60	0.19
15	0.2894	17.366	18	60	0.18
150	0.5705	34.233	34	60	-0.06

Chi^2 = 0.17 d.f = 2 P-value = 0.9191

APPENDIX IV. DEFAULT UNCERTAINTY FACTORS FOR PHG DERIVATION

The table describes the default uncertainty factors OEHHA generally uses to calculate the Acceptable Daily Dose (OEHHA, 2008).

LOAEL uncertainty factor (UF_L)		
Values used:	10	LOAEL, any effect
	1	NOAEL or benchmark used
Interspecies uncertainty factor (UF_A)		
Combined interspecies uncertainty factor (UF_A):	1	human observation
	√10	animal observation in nonhuman primates
	10	where no data are available on toxicokinetic or toxicodynamic differences between humans and a non-primate test species
Toxicokinetic component (UF_{A-k}) of UF_A:	1	where animal and human PBPK models are used to describe interspecies differences
	√10	non-primate studies with no chemical- or species-specific kinetic data
Toxicodynamic component (UF_{A-d}) of UF_A:	1	where animal and human mechanistic data fully describe interspecies differences. (*This is unlikely to be the case.)*
	2	for residual susceptibility differences where there are some toxicodynamic data
	√10	non-primate studies with no data on toxicodynamic interspecies differences
Intraspecies uncertainty factor (UF_H)		
Toxicokinetic component (UF_{H-k}) of UF_H:	1	human study including sensitive subpopulations (e.g., infants and children), or where a PBPK model is used and accounts for measured inter-individual variability
	√10	for residual susceptibility differences where there are some toxicokinetic data (e.g., PBPK models for adults only)
	10	to allow for diversity, including infants and children, with no human kinetic data
Toxicodynamic component (UF_{H-d}) of UF_H:	1	Human study including sensitive subpopulations (e.g., infants and children)
	√10	Studies including human studies with normal adult subjects only, but no reason to suspect additional susceptibility of children
	10	Suspect additional susceptibility of children (e.g., exacerbation of asthma, neurotoxicity)
Subchronic uncertainty factor (UF_S)[a]		
Values used:	1	Study duration >12% of estimated lifetime
	√10	Study duration 8-12% of estimated lifetime
	10	Study duration <8% of estimated lifetime
Database deficiency factor (UF_D)		
Values used:	1	No substantial data gaps
	√10	Substantial data gaps including, but not limited to, developmental toxicity

[a] Exposure durations of 13 weeks or less are subchronic regardless of species (OEHHA, 2008)