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Office of Prevention, Pesticides
and
Toxic Substances

This document reflects the changes made on pages 2 (summary) and 8 of TXR# 0053495.

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MEMORANDUM

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SUBJECT: Weight of Evidence Comparison of Human and Animal Toxicology Studies and Endpoints for ALDICARB [PC Code: 098301; DP Barcode: D299876]

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Aldicarb is a N-methyl carbamate pesticide that exerts its pesticidal activity and elicits adverse toxic effects by inhibition of cholinesterase activity [ChEI], which has been demonstrated in whole blood, plasma, red blood cells, and brain of rats, mice, and dogs following acute, subchronic, and chronic exposure and in plasma and RBC in humans following acute exposure.

The available data indicate a peak effect within an hour of dosing followed by recovery within 24 hours. As a result, a comparable degree of inhibition occurs whether delivered once or following subchronic or chronic dosing.

There is an acute oral exposure study on aldicarb [MRID 42373001] involving direct dosing of humans in which plasma and RBC cholinesterase activity and clinical signs were monitored. There is also a full database of animal toxicity studies.

OPPTS management has requested that when human studies support a risk assessment, HED should compare the strengths and weaknesses of the human and animal toxicity studies and present how the human studies could be used in endpoint selection, including whether the human data are consistent with animal data in terms of types of effects and effect levels or are there notable differences between animals and humans.

This document focuses on one human acute oral exposure study in which humans were intentionally dosed with aldicarb. The human data are compared with animal data from the available aldicarb animal studies, and recommendations for endpoint selection are made based on the most appropriate studies and uncertainty factors. All of the studies are listed in summary form and then the weight of evidence discussion of endpoint selection follows.

In summary, the aldicarb risk assessment team recommends that the rat subchronic neurotoxicity study [MRID 43829602] and the rat acute neurotoxicity study (MRID 45068601; Moser) be used as co-critical studies for endpoint selection. The results of the acute oral human study [MRID 42373001] suggest that animals and humans have similar toxic responses to aldicarb allowing reduction of the interspecies safety factor to 3X. A factor of 3X was retained for extrapolation from rats to humans because of the limitations of the human study as discussed in detail later in this document. This is summarized in Table 3, column 4, together with two other possible options for endpoint selection in column 2 (use of human study) and column 3 (use of animal data without considering human data).

Toxicity Studies

- Single Dose Oral Studies:

A. Human

In a single oral dose human study with aldicarb (MRID 42373001), following an overnight fast, subjects were dosed with aldicarb or placebo in orange juice at breakfast [consumed over 15-30 minutes]. Cholinesterase [ChE] activity [plasma and RBC] was monitored hourly for the first 6 hours post dose and at 24 hours. Study design and number of subjects/dose are provided in Table 1.

The NOAEL for males for RBC and plasma ChEI and clinical signs is 0.01 mg/kg, based on sweating and plasma [36%] and RBC [12%] ChEI at 0.025 mg/kg. Females were not tested at 0.01 mg/kg and the magnitude of the plasma ChEI [at 0.025 mg/kg (50%)] and RBC ChEI [at 0.025 mg/kg (20%)] was greater in females than males at the two common dose levels. Because of this uncertainty, the lowest dose tested [0.01 mg/kg] is not considered an overall NOAEL for the study. The duration of ChEI was longer in males [at 0.050 mg/kg: plasma (males 1-21 hours) *vs* (females 1-4 hours); RBC (males 1-6 hours) *vs* (females 1-4 hours)] than in females. Additionally, females did not display clinical signs at either dose. Both sexes show effects [ChEI] at 0.025 mg/kg [% inhibition listed above] and at 0.05 mg/kg [plasma (males 52%/females 68%); RBC (males 25%/females 35%)].

Table 1: Summary of Dosing Regimen for Single-Dose Human Oral Toxicity Study for Aldicarb

There were a total of 38 men and 9 women, with 6 men/5 women participating in two sessions [one placebo session and one aldicarb session]. The study consisted of several phases/sessions such that all

subjects were not dosed during the same time frame. However, there were a total of 4 females at each dose level and 4-8 males at each dose level.

Phase/Session		Placebo	0.01 mg/kg	0.025 mg/kg	0.05 mg/kg	0.075 mg/kg
I **males**	a	3	–	4	1	–
	b	5	–	–	3	4*
II **males**	c	4	2	2	2	–
	d	1	3	1	–	–
	e	3	3	1	2	–
III **females**	f	1	–	1	1	–
	g	2	–	1	1	–
	h	3	–	2	2	–

# of subjects; * one subject received a dose of 0.06 mg/kg, due to BW error.

Strengths

- *Double-blind* study design

- *Use of both sexes at mid dose levels.* Both sexes were dosed at 0.025 mg/kg and 0.05 mg/kg thus allowing comparisons between male and female subjects.

- *Administration of multiple dose levels provides quality dose-response information.* There were four dose groups of males [0.01, 0.025, 0.05, 0.075 mg/kg] and two dose groups of females [0.025 and 0.05 mg/kg]. For example, RBC ChE inhibition in males ranges from little to no inhibition at 0.01 mg/kg to 38% at 0.075 mg/kg.

- *Blood sampling at multiple time points.* Cholinesterase activity was monitored at 1, 2, 3, 4, 5, 6, and 24 hours post dose in the human study. These data provide information regarding time to recovery.

Weaknesses

-*Females only tested at mid doses.* Females were dosed only at two dose levels compared to 4 dose levels for males; importantly females were not tested at the lowest dose (0.01 mg/kg). As shown in Table 2 below, females exhibited more plasma and RBC ChE inhibition at 0.05 mg/kg compared to male subjects. The lack of dose-response information for females at the low dose (0.01 mg/kg) provides uncertainty for this study.

- *Blood sampling.* The first measurement of cholinesterase activity post dose was at one hour, which may have been after the peak-effect time. Clinical signs along with cholinesterase inhibition have been observed in rats as early as 0.5 hour and 0.75 hours, respectively.

- *ChEI methodology.* Because ChE inhibition recovers within 24 hours following exposure to N-methyl carbamates, the laboratory protocol used to measure ChE inhibition is an important component of evaluating ChE inhibition data for N-methyl carbamates. Specifically, under certain conditions recovery

can occur prior to analysis and thus underestimating actual ChE inhibition. In the case of the aldicarb human study, some details surrounding the protocol for the modified Ellman were provided. These details suggest that samples were diluted to some degree. It is unknown the degree to which this may have underestimated ChE inhibition. A modified Ellman assay was also used in the guideline acute and subchronic neurotoxicity studies in rats. As noted below and in Table 2, results using a radiometric method (preferred over Ellman) provided more inhibition at common dose levels.

B. Animals

- In an acute [guideline] neurotoxicity study in rats (MRID 43442301), oral doses of 0, 0.05, 0.1, or 0.5 mg/kg of Aldicarb were administered *via* gavage [vehicle water] to both sexes of young adult SD rats [#/sex/group]. Dose-related increase in the inhibition of whole blood [at 0.05 mg/kg: males no change from pre-test; females 23% inhibition from pre-test value], RBC [at 0.05 mg/kg: males no inhibition; females 10% inhibition from pre-test value], and plasma [at 0.05 mg/kg: males56%; females 64%] cholinesterase activities was observed at 0.75 hours after dosing [estimated time of peak effect], although statistical significance was not always attained at the lower dose levels. At termination, brain cholinesterase activity was decreased significantly [males 45%/females 50% of control value] at 0.5 mg/kg [highest dose tested]. In general, females displayed greater inhibition, especially at the higher dose levels than males. At 0.5 mg/kg, clinical signs of ChEI [at 0.5 hours post dose: tremors, lacrimation, salivation, increased respiration, decreased body temperature, arousal, activity, reactivity, fore-/hind limb grip strength] and decreased motor activity [1 hour post dose] were observed. At 0.1 mg/kg, there was decreased fore limb grip strength in females only. Recovery occurred by 8 hours after dosing. The risk assessment team concludes that 0.05 mg/kg can be considered the LOAEL for the guideline acute study. This is an acceptable guideline study.

Strengths:
- Sufficient number of animals used [5 animals/sex/dose]
- Both sexes tested at all dose levels
- Concurrent control
- 3 dose levels provided quality dose-response information
- ChEI and clinical signs measured at peak effect time

Weaknesses:
- Ellman method [modified] used; a radiometric method provides a more appropriate method for measuring cholinesterase inhibition because the factors that promote reversibility are minimized.

- In an acute [non-guideline] neurotoxicity study (MRID 45068601; Moser) in which adult and young (pre-weanling; PND 17) Long-Evans rats [4/sex/group] were directly dosed with aldicarb *via* gavage [vehicle corn oil] at dose levels of 0, 0.05, 0.1, 0.2, and 0.3 mg/kg. At 0.05 mg/kg (lowest dose tested) in PND 17 rats, whole blood ChE inhibition was 75%-81% and brain ChE inhibition was 24-28 %; in adult rats, whole blood ChE inhibition was 84% and brain inhibition was 10-12%. No difference between the sexes was identified in either age group. This study shows an increase in sensitivity only in terms of percent brain ChE inhibition for PND 17 rats in comparison to adults. Both age groups had greater than 75% whole blood ChE inhibition at all dose levels. The LOAEL is 0.05 mg/kg. This study was classified acceptable/non-guideline.

Strengths:
- Both sexes at all doses
- Concurrent control group
- 4 treatment dose levels provided quality dose-response information
- 4 animals/sex/group
- Radiometric method used.
-Adult and juvenile animals evaluated providing information on age-related sensitivity

Weaknesses:
-Fewer animals per group than used in guideline study
-Significant inhibition observed at all dose levels (>75% whole blood inhibition at lowest dose level in adult and juvenile animals.)

- Repeated Dose Oral Studies

A. Human

There is no repeated-dose study on aldicarb in humans. However, based on the reversibility of the effects observed within 24 hours following acute oral exposure of human and following oral exposures of varying lengths to rats, toxicity observed in the acute oral human study is considered representative of all exposure durations.

B. Animal

Subchronic neurotoxicity (90-day rat). In a subchronic neurotoxicity study (MRID 43829602), Crl:CDR(SD)BR rats were dosed *via* **gavage** with 0 [water vehicle], 0.05, 0.20, or 0.40 mg/kg/day of aldicarb (tech., 98.9%) for at least 13 weeks. Twelve animals/sex/group were selected for functional observational battery (FOB) [pre-study and at weeks 4, 8, 13 at approximately 0.5 to 1 hour post dose] and motor activity (MA) testing, and **15** animals/sex/group were selected for serial acetylcholinesterase (ChE) analyses [pre-study and at weeks 4, 8, 13 at approximately 0.75 hour post dose]. Six rats/sex/dose were anesthetized, perfused, and sacrificed for histopathology. CNS sections were embedded in paraffin, while peripheral nerves and spinal ganglia were embedded in plastic.

No treatment-related deaths occurred. Body weight and body-weight gains were decreased in the high-dose males, as was food consumption/efficiency, but these parameters were comparable among the females groups. Dose-related tremors and salivation were observed in both sexes in the mid and high dose group. Treatment-related clinical signs of cholinesterase inhibition/neurotoxicity [home cage and arena tremors, pinpoint pupils, decreased tail pinch response, decreased hindlimb/forelimb grip strength, increased tail flick latency times] were observed in both sexes at various time points during the study, with the severity increasing with dose, and there was some evidence that females were more sensitive. Additionally, motor activity was decreased in both sexes at the mid- and high-dose levels throughout the study. Ophthalmoscopic examination [performed at study termination and not at peak effect time], gross and histopathological evaluations did not show any treatment-related effects.

There was a dose-related inhibition in plasma [61%-90%], whole blood [42%-87%], and RBC [24%-70%] ChE in both sexes and at all doses. Statistical significance was not attained for plasma ChEI for the low-

dose rats of either sex. Whole brain ChE inhibition was observed in both sexes at the mid- and high-dose levels, and in females at the low dose, as well as in cerebellum in low-dose females. The level of whole brain ChE inhibition at the mid- [males 26%-42%; females 33%-46%] and high- [males 58%-64%; females 57%-68%] dose appear to show some increase across weeks 4-13. Ophthalmoscopic examination and gross and histopathological evaluations did not reveal significant aldicarb-related changes. An increased incidence of slight axonal degeneration in the sciatic nerve, described as affecting only individual nerve fibers, were found in 3 high dose males *vs* one control rat, and 2 high dose females *vs* one control rat, but these findings lacked statistical significance.

The LOAEL is 0.05 mg/kg/day, based on the FOB findings (e.g., pinpoint pupils) and ChE inhibition in blood and brain. The NOAEL is <0.05 mg/kg/day.

The available data on the rat indicate a peak effect within an hour of dosing, and the inhibition recovers within 24 hours. Although this study, in which several time periods were investigated, shows an apparent increase in percent ChEI in some sections of the brain at the high dose levels, there was no decrease in the NOAEL or LOAEL for ChEI with time. For aldicarb RBC and/or whole blood ChE inhibition are the most sensitive endpoints. In all available studies RBC and/or whole blood ChE inhibition do not increase with repeated exposures.

Chronic and subchronic (dog). In a 1 year dog feeding study (MRID 40695901), groups of 5 beagle dogs/sex/dose were administered aldicarb technical in the diet daily for 52 weeks at 0, 1, 2, 5, and 10 ppm (0, 0.028, 0.056, 0.13, and 0.25 mg/kg-day). Blood (plasma and red blood cell) cholinesterase determinations were made 3 times prior to exposure and during weeks 5, 13, 26, and 52, two hours after the 2 hour feeding period. Brain measures were made at study termination.

In the one-year study, no effects were seen on mortality, body weight gain, food consumption, clinical signs, clinical chemistry, hematology, urinalysis, organ weights, ophthalmology, gross pathology or histopathology. At the 3 highest dose levels, dogs showed significant dose-related inhibition in plasma ChE activity in both sexes. At the lowest dose, there was significant plasma cholinesterase inhibition in males (18-26%). Significant dose related decreases in RBC Cholinesterase were seen at the 2 highest doses in males and the highest dose in females. Brain cholinesterase was significantly inhibited only at the high dose in males (22%). Based on plasma ChEI, *a NOAEL for ChE inhibition in the study was not established in the one-year study* [LOAEL of 0.028 mg/kg/day].

In a subsequent subchronic study (MRID 41919901), 6 beagle dogs/sex/dose were administered aldicarb *via* the diet at 0, 0.35, 0.7, and 2 ppm [0, 0.01, 0.02, and 0.06 mg/kg/day]. Plasma and RBC cholinesterase determinations were made at -3, -2, -1 weeks prior to dosing and at 2 and 5 weeks, two hours after a limited 2-hour feeding period.

In this subsequent 5-week study in dogs, a **NOAEL for plasma and RBC cholinesterase activity inhibition was established at 0.020 mg/kg/day; LOAEL is 0.06 mg/kg.**

- **Benchmark Dose (BMD) Analysis**

A dose-response analysis and estimation of the BMD_{10s} were performed using the whole blood ChEI data

from the two acute animal studies [guideline and Moser], as well as the whole blood ChEI data from the guideline subchronic neurotoxicity study. An exponential model similar to that used in the OP Cumulative Risk Assessment and supported by the FIFRA SAP was used. The BMD_{10s} for whole blood ranged from 0.0031 to 0.012 in adult animals and 0.0038 to 0.0073 in juvenile animals. The BMD_{10s} for brain ranged from 0.024 to 0.031 in adult animals and 0.014 to 0.020 in juvenile animals. Lack of dose-response data in whole blood (all doses >75% inhibition) provide less confidence in the BMD_{10s} compared to those calculated for brain ChE inhibition. Ratios of the BMD_{10s} for brain ChE inhibition between juvenile and adult animals suggest that juvenile animals are 2X more sensitive than adult rats.

Endpoint Selection.

Acute RfD. The risk assessment team concludes that the similarity of response between humans and rats following acute oral exposure allows for the use of both sets of data in considering toxicity endpoint selection and uncertainty factors (grey column in Table 3). Table 2 provides ChE inhibition observed in rats and humans at dose level common to several studies, 0.05 mg/kg. As shown in Table 2, there is remarkable similarity between the human study and rats studies (subchronic and acute), which used a modified Ellman technique. The Moser study, which considered both adult and juvenile animals, measured ChE inhibition using a preferred methodology, the radiometric method. It is also important to note that the Moser study used corn oil as the gavage vehicle, which may promote more absorption compared to water used as the gavage vehicle in the subchronic and acute rat studies performed by the pesticide registrant.

Table 2. Comparison of % ChEI at 0.05 mg/kg

compartment/sex/study	subchronic rat [week 4]	rat acute	human acute	rat acute [Moser]
males				
RBC	32%	-	25%	not measured
plasma	61%	56%	52%	not measured
whole blood	42%	-	N/A	84%
females				
RBC	24%	10%	39%	not measured
plasma	65%	64%	68%	not measured
whole blood	47%	77%	N/A	81%

The risk assessment team considered the rat subchronic neurotoxicity study and the non-guideline acute neurotoxicity study (Moser) to be co-critical for assessment of the acute exposure scenarios. Due to the fact that reversibility of ChEI occurs within 24 hours following aldicarb exposure, the use of this subchronic neurotoxicity study in rats for endpoint selection is considered appropriate (repeated dosing is considered a series of acute exposures). The cholinesterase inhibition in the acute human study and rat subchronic study were comparable at the 0.05 mg/kg dose level. As noted above there is uncertainty regarding the human study due to the lack of female subjects at the lowest dose (0.01 mg/kg) as females exhibited more ChE inhibition at the 0.025 and 0.05 mg/kg levels compared to male subjects. Although no rat studies have established a NOAEL for brain, RBC and/or whole blood ChE inhibition, the database of rat studies includes studies where animals of both sexes were tested at each dose level, studies comparing adult and juvenile animals,

measurement of clinical signs at < 1 hour, and evaluation using both Ellman and radiometric methods. Thus, the rat database provides a solid basis for developing the point of departure for aldicarb. The similarity in response between humans and rats at 0.05 (Table 2), however, allows for the reduction of the interspecies factor [Table 3, Column 4] from 10X to 3X A factor of 3X was retained for extrapolation from rats to humans because of the limitations of the human study. These limitations include:

- Use of the Ellman method for human ChEI measurements rather than the more sensitive radiometric method which was used in the co-critical Moser study;
- Human females were not dosed at the lowest dose level, and females appear to be slightly more sensitive than males; therefore, an adequate comparison of human and rat females could not be made;
- Only adult human data are available so that a comparison of young humans relative to young rats can not be made; this is important because young rats appear to be more sensitive to ChEI than adult rats;
- Increased sensitivity of young animals have been seen in the brain ChEI for which no human data are available; it is unknown whether the brain ChEI in young humans would show the same or a greater sensitivity as that seen in the young rats.

An additional 10X uncertainty factor is needed to account for extrapolating from a LOAEL to NOAEL. It is notable that greater than 75% **whole blood** ChEI was observed in both age groups at the LOAEL. The 10X LOAEL to NOAEL factor is supported by the estimated whole blood BMD10s [0.003-0.012]. In addition, female human subjects at the lowest dose (0.025 mg/kg) had 20% RBC inhibition. Given these uncertainties, an additional 10X is appropriate to extrapolate to a NOAEL of 0.005 mg/kg. Therefore, a total uncertainty factor of 300 (10X for intraspecies variations, 3X for interspecies differences, and 10X LOAEL to NOAEL) is appropriate.

FQPA Safety Factor Considerations

For the recommended endpoints selected from animals studies, a Special Hazard Based FQPA safety factor is not needed. As shown by the BMD analysis, juvenile animals are approximately 2X more sensitive than adult rats. Using the recommended approach, this sensitivity is accounted for in the point of departure of 0.005 mg/kg/day as the BMDs for the young were estimated to be 0.0038-0.0073 for whole blood ChE inhibition. The extrapolated NOAEL of 0.005 mg/kg/day incorporates this potential sensitivity since the point of departure risks are not likely to be under-estimated based on the NOAEL = 0.005 mg/kg/day. The database for aldicarb is complete, including both rat [MRID 41004501] and rabbit [MRID 00132668] developmental toxicity studies, a rat 2-generation reproduction study [MRID 42148401], acute and subchronic rat neurotoxicity studies, a rat developmental neurotoxicity study [MRID43829601], as well as a special acute neurotoxicity study (Moser). Therefore, an FQPA **database** UF is also not required. There is no evidence of increased sensitivity in any of the guideline studies.

However, as the human study only evaluated adult subjects, if the endpoint from the human study were to be selected for risk assessment, the increased pup sensitivity would not be directly reflected, and an FQPA factor would be required (see Table 2, column 2). These effects are considered insufficient as a basis for retaining the full 10X FQPA safety factor. The magnitude of the brain ChEI in the PND 17 pups was 2X greater than that of the adult rat. Therefore, a FQPA safety factor of 2X would be required [see Table 2; column 2].

NOTE: There are no residential uses of aldicarb.

Short and intermediate term residential & occupational exposure.

Based on the fact that reversibility of effects within 24 hours is seen in both the human and animal studies and on the fact that dosing in the subchronic neurotoxicity study in rats and special acute neurotoxicity study are considered a series of acute exposures, the same co-critical studies are considered appropriate for endpoint selection.

Chronic RfD and long term residential & occupational exposure.

The risk assessment team recommends the use of the same co-critical studies for establishing a chronic RfD and to assess long-term occupational or residential risk. However, the team has determined that a chronic risk assessment is not needed, since risks resulting from aldicarb exposure are better described as a series of acute risks.

Furthermore, any chronic risks would necessarily be lower than those estimated for acute exposure since long-term average exposure levels rather than daily high-end exposure estimates would be used to calculate chronic risks.

Short, intermediate and long-term inhalation exposure.

same as above

Table 3. Comparison of Endpoint Selection Possibilities

Parameter	Human study[1]	Rat study[2]	Rat (human)[3] (recommended)
LOAEL	0.01 mg/kg	0.05 mg/kg	**0.05 mg/kg**
UF LOAEL-to-NOAEL	3X	10X	**10X**
NOAEL	0.0033 mg/kg	0.005 mg/kg	**0.005 mg/kg**
UF (intraspecies)	10X	10X	**10X**
UF (interspecies)	1X	10X	**3X**
FQPA SF	**2X**	**1X**	**1X**
acute RfD	0.00033 mg/kg	0.00005 mg/kg	**0.00017 mg/kg**
acute PAD	0.00017 mg/kg	0.00005 mg/kg	**0.00017 mg/kg**
chronic RfD	0.00033 mg/kg/day	0.00005 mg/kg/day	**0.00017 mg/kg/day**
chronic PAD	0.00017 mg/kg/day	0.00005 mg/kg/day	**0.00017 mg/kg/day**
endpoint	RBC/plasma ChEI	whole blood/brain ChEI	**whole blood/brain ChEI**

[1]Human study = Endpoints and Points of Departure using human study
[2]Rat Study = Endpoints and Points of Departure using animal studies without consideration of human study
[3]Rat (human) = Endpoints and Points of Departure using animal data for endpoint selection, comparing animal data to human data to reduce interspecies safety factor, both considered as part of weight-of-evidence determination

Aldicarb Toxicology Endpoint Selection.

Exposure Scenario	Dose Used in Risk Assessment, UF[1]	Hazard-Based FQPA SF and Endpoint for Risk Assessment	Study and Toxicological Effects
DIETARY EXPOSURES			
Acute Dietary: General US Population [MRID No. 43829602, 45068601 & 42373001	LOAEL= 0.05 mg/kg/day UF = 300 Acute RfD = 0.00017 mg/kg/day	FQPA SF = 1X aPAD=acute RfD / FQPA SF = 0.00017 mg/kg/day	Rat subchronic/acute neurotoxicity LOAEL=0.05 mg/kg/day based on whole blood and brain ChEI and FOB findings (pinpoint pupils) *human study [reduction of interspecies factor to 3X]*
Chronic Dietary: General US Population [MRID No. 43829602, 45068601 & 42373001]	LOAEL = 0.05 mg/kg/day UF = 300 Chronic RfD = 0.00017 mg/kg/day	FQPA SF = 1X cPAD =chronic RfD / FQPA SF =0.00017 mg/kg/day	Rat subchronic/acute neurotoxicity LOAEL=0.05 mg/kg/day based on whole blood and brain ChEI and FOB findings (pinpoint pupils) *human study [reduction of interspecies factor to 3X]*
DERMAL EXPOSURES[2]			
Short-Term (1-30 days); Intermediate-Term (30 days to several months) [MRID No. 43829602, 45068601 & 42373001]	Oral study LOAEL = 0.05 mg/kg/day Absorption factor = 100%	LOC for MOE = 300[1]	Rat subchronic/acute neurotoxicity LOAEL=0.05 mg/kg/day based on whole blood and brain ChEI and FOB findings (pinpoint pupils) *human study [reduction of interspecies factor to 3X]*
INHALATION EXPOSURES[2]			
Any Duration [MRID No. 43829602, 45068601 & 42373001]	Oral study LOAEL = 0.05 mg/kg/day Absorption factor = 100%	LOC for MOE = 300[1]	Rat subchronic/acute neurotoxicity LOAEL=0.05 mg/kg/day based on whole blood and brain ChEI and FOB findings (pinpoint pupils) *human study [reduction of interspecies factor to 3X]*

[1] The combined UF of 300 includes 3X for interspecies extrapolation, 10X is for intraspecies variability, and a database UF of 10X for extrapolation from the LOAEL to the NOAEL.

[2] Appropriate route-to-route extrapolation should be performed for these risk assessments. For both dermal and inhalation risks, a 100% absorption factor should be used to convert relevant exposure estimates to equivalent oral doses and compared to the oral LOAEL.

Guideline No./ Study Type	MRID No. (year)/ Classification	Results
870.3150 90-Day oral toxicity in non-rodents (dogs) 2 hours post dose	41919901 (1991) Acceptable	NOAEL = 0.02 mg/kg/day LOAEL = 0.06 mg/kg/day based on plasma, RBC Cholinesterase Inhibition in male and female dogs
870.3700a Prenatal developmental in rodents (rats)	41004501 (1988) Acceptable ~~Guideline~~	**Maternal** NOAEL = 0.125 mg/kg/day LOAEL = 0.25 mg/kg/day based on decreased body weight gain and food consumption. **Developmental** NOAEL = 0.125 mg/kg/day LOAEL = 0.25 mg/kg/day based on ecchymosis of the trunk.
870.3700b Prenatal developmental in non-rodents (rabbits)	00132668 (1983) Acceptable	**Maternal** NOAEL = 0.1 mg/kg/day LOAEL = 0.25 mg/kg/day based on decreased body weight, pale kidneys, hydroceles on the oviducts. **Developmental** NOAEL = > 0.5 mg/kg/day
870.3800 Reproduction and fertility effects at termination	42148401 (1991) Acceptable	**Parental/Systemic** NOAEL = 0.4 mg/kg/day LOAEL = 0.7-0.9 mg/kg/day based on decreased body weight gains and RBC ChEI (♀); plasma ChEI (♂). **Reproductive** NOAEL = 0.7-0.9 mg/kg/day LOAEL = 1.4-1.7 mg/kg/day based on decreased viability and body weights, and signs of debilitation.
870.4100a Chronic toxicity rodents am sample	43045401 (1993) Acceptable	NOAEL = 0.047 mg/kg/day LOAEL = 0.47 mg/kg/day based on plasma, RBC, cholinesterase inhibition (♂).
870.4100b Chronic toxicity dogs beagle 2 hours after feeding	40695901, 42191501 (1988) Acceptable	NOAEL < 0.028 mg/kg/day LOAEL = 0.028 mg/kg/day based on plasma ChEI.
870.6200a Acute neurotoxicity screening battery Sprague-Dawley Crl:CD(SD)BR rat peak effect time 0.75 hour	43442301 (1994) Acceptable	NOAEL = 0.05 mg/kg/day LOAEL = 0.1 mg/kg/day based on behavioral changes; plasma ChEI. at 0.05 mg/kg
870.6200b Subchronic neurotoxicity screening battery Sprague-Dawley Crl:CD(SD)BR rat peak effect time 0.75 hour	43829602 (1995) Acceptable	NOAEL < 0.05 mg/kg/day LOAEL = 0.05 mg/kg/day based on pinpoint pupils and blood and brain ChEI.

Guideline No./ Study Type	MRID No. (year)/ Classification	Results
870.6300 Developmental neurotoxicity Sprague-Dawley Crl:CD(SD)BR rat ChE activity monitored 2 hours post dose	43829601 (1995) Acceptable	**Maternal** NOAEL = 0.05 mg/kg/day LOAEL = 0.1 mg/kg/day based on plasma ChEI. **Offspring** NOAEL = 0.05 mg/kg/day LOAEL = 0.1 mg/kg/day based on reduced body weights and decreased motor activity.
Acute neurotoxicity Special studies Moser VC Long-Evans rat peak effect time 1 hour	45068601 (1999) TAP 157 94-106 Acceptable	NOAEL < 0.05 mg/kg. PND 17 day pups 2x as sensitive as adults in brain ChEI. LOAEL = 0.05 mg/kg pups blood (♂,♀), brain ChEI (♂)
Acute oral - human ChE activity monitored at 1, 2, 3, 4, 5, 6, 24 hours post dose	42373001 (1992) Acceptable	NOAEL for males 0.01 mg/kg, based on RBC and plasma ChEI and sweating at LOAEL of 0.025 mg/kg NOAEL not determined in females; LOAEL = 0.025 mg/kg, based on RBC and plasma ChEI

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Chemical:	**Methamidophos**
PC Code:	**101201**
HED File Code	**61200 SRRD CDC**
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