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SUBJECT: UPDATED CRITICAL POINTS OF DEPARTURE (POD) AND TARGET MARGINS OF EXPOSURE (MOE) FOR ACEPHATE AND METHAMIDOPHOS

On June 12, 2025, the Human Health Assessment Branch's (HHA) Risk Assessment Section (RAS) was asked by management to provide updated critical points of departure (PODs) and target margins of exposure (MOEs) for acephate and methamidophos to be used for calculating health risks from short-term occupational exposures to these organophosphate (OP) pesticides. This memorandum is in response to that request.

I. Background

Acephate is an insecticide registered in California for use on a variety of agricultural crops, seed treatments, for use in outdoor and indoor non-agricultural settings and for use in greenhouses. Methamidophos, the major metabolite and degradate of acephate, was previously registered separately as insecticide and acaricide, however, all its uses in the US were canceled in 2009. Because methamidophos is a metabolite and degradate of acephate, both state and federal agencies make an effort to update and maintain current toxicity, exposure and risk data on methamidophos regardless of its registration status as an active ingredient. The toxicity of acephate and its metabolite methamidophos is related to their ability to inhibit the enzyme acetylcholinesterase (AChE) in the central and the peripheral nervous system.

DPR has evaluated all required toxicity data submitted for acephate, and methamidophos as part of registration in California and conducted human health risk assessments in 2005 and 2008 ((DPR, 2005; DPR, 2008). In the past, the US Environmental Protection Agency (US EPA) also published human health risk assessments for both acephate and methamidophos separately. US EPA published its most recent human health risk assessment for acephate in 2023, which established PODs based on inhibition of brain AChE in oral, dermal and inhalation studies in rats (US EPA, 2023).

Methamidophos is a more potent cholinesterase inhibitor and has a greater toxicity potency than acephate. After cancelation, US EPA began to evaluate this metabolite by converting the detected residues or calculated exposures of methamidophos into acephate equivalents. In the 2023

HHRA, US EPA did not establish separate PODs for methamidophos, instead used Toxicity Adjustment Factors (TAF) to convert methamidophos residues and exposure to acephate equivalents and express risks in terms of acephate. US EPA set a target MOE of 100, which included 10 for interspecies extrapolation (UF_A) and 10 for intraspecies variation (UF_H) (US EPA, 2023).

II. DPR Evaluations of Acephate: History and Updates

From 2008 to 2023:

In its 2008 risk characterization document (RCD) for acephate, DPR established a critical acute oral POD of 1.0 mg/kg/day (DPR, 2008). This POD was a no-observed-effect level (NOEL) based on inhibition of plasma and RBC cholinesterase activities at the lowest-observed-effect level (LOEL) of 1.25 mg/kg/day in an oral study with human volunteers. At the time, the target MOE, equal to the total uncertainty factor (UF_{TOTAL}), was set at 10 to account for intraspecies variability (UF_H).

For methamidophos, DPR selected an acute oral POD of 0.3 mg/kg/day, which was a NOEL based on brain AChE inhibition and functional observational signs in an acute neurotoxicity study in rats (DPR, 2005). The target MOE for methamidophos was 100 (10 for interspecies extrapolation and 10 for intraspecies variation).

The acute oral NOEL of 1.0 mg/kg/day was used by HHA's Exposure Assessment Section (EAS) to estimate risks from short-term occupational exposures to acephate by dermal and inhalation routes (DPR, 2013; Zhao and Formoli, 2009). Until 2023, RAS also used this NOEL to evaluate illegal residues found in fresh produce for the California Pesticide Residue Monitoring Program (CPRMP), as well as for derivation of health-based action levels for acephate in edible cannabis products (DPR, 2024). When illegal methamidophos residues were detected on fruits and vegetables, RAS evaluated the risk using the acute oral NOEL of 0.3 mg/kg/day from DPR's 2005 methamidophos RCD (DPR, 2005). RAS also added an additional UF_{DB} of 10 for gaps in the database on potential developmental neurotoxicity (DNT) that increased UF_{TOTAL} for acephate and methamidophos to 100 and 1000, respectively (Rubin *et al.*, 2018). This was consistent with US EPA's 2015 white paper that imposed an additional Food Quality Protection Act (FQPA) Safety Factor of 10 for potential DNT effects for all OP pesticides (US EPA, 2015).

Since 2023:

In 2023, RAS reviewed the recently published US EPA's human health risk assessment for acephate and its implications for evaluating methamidophos residues (US EPA, 2023). Unlike DPR's 2008 RCD that used inhibition of plasma and RBC AChE in humans as the critical acute endpoint, US EPA relied on brain AChE inhibition rats for its assessment. While human studies are preferred for risk assessment, RAS concluded that the studies in rats provided toxicological data not available in the limited human study, such as measurements of the most sensitive target

of acephate, the brain AChE, and the enzyme inhibition by methamidophos, included extensive dose-response and duration evaluations, as well as dermal and inhalation route-specific data. In addition, several of US EPA's critical studies in rats were not submitted to DPR or reviewed in the 2008 RCD. These included acute and steady-state comparative cholinesterase assays (CCA) and 21-day dermal and inhalation studies with methamidophos that established route-specific TAFs for this metabolite, and the 5-day critical dermal study with acephate. US EPA also used updated risk assessment methodologies, such as benchmark dose modeling (BMD) and inhalation dosimetry, which were not employed in the older DPR's RCD. Furthermore, US EPA evaluated the DNT potential for acephate and methamidophos using chemical-specific data and new approach methodologies (NAMs) *in vitro* assays and reduced the previous FQPA Safety Factor from 10 to 1.

Based on these considerations, RAS adopted US EPA's latest critical acute oral POD for acephate for use in its CPRMP evaluations and the cannabis program in 2024 (DPR, 2024). RAS also adopted US EPA's oral TAF for methamidophos and uses it to derive methamidophos-specific acute oral POD for these programs. Finally, RAS established target MOEs based on US EPA's UF_{TOTAL}, which was 100 for both acephate and methamidophos for exposures via oral and dermal routes. The use of inhalation dosimetry adjustment factor allowed for reduction of UF_A from 10 to 3 thus reducing the inhalation UF_{TOTAL} to 30. US EPA's critical studies and endpoints are described below and summarized in Tables 1 and 2.

1. Acephate

(a) Oral POD:

US EPA selected the critical POD of 0.272 mg/kg/day to characterize all oral exposure scenarios for acephate (acute and repeated dietary exposures, and incidental oral exposures). This POD was calculated using BMD modeling. It was the benchmark dose lower limit ($BMDL_{10}$) for brain AChE inhibition measured in an acute CCA in male rat pups on PND11, with a BMD_{10} of 0.5128 mg/kg/day. OP pesticides can exhibit steady state inhibition of AChE in which the degree of inhibition is in equilibrium with the production of an uninhibited enzyme. For most OPs the steady state inhibition is reached within 2–3 weeks of repeated doses. However, comparing oral acute, subchronic and chronic BMDs for acephate shows that steady-state inhibition of brain AChE was achieved in a single day, with the level of inhibition remaining the same with increasing exposure duration. Therefore, US EPA concluded that the acute and steady-state oral PODs are the equivalent (US EPA, 2023).

(b) Dermal POD

For dermal exposures, US EPA established a steady-state dermal POD of 150 mg/kg/day, which was a no-observed adverse-effect level (NOAEL) based on brain AChE inhibition at the lowest-observed adverse-effect level (LOAEL) of 300 mg/kg/day in 5-day and 21-day (6 hours/day, 5 days/week) repeated-dose dermal toxicity studies in rats (US EPA, 2023). Similar to the oral route, there was no difference in brain AChE inhibition after 5 or 15 dermal doses in the rat

studies an US EPA concluded that the short-term and steady-state dermal PODs were the same (US EPA, 2023).

(c) Inhalation POD

For inhalation exposures, US EPA established a steady-state POD of 1.205 mg/m^3 for acephate, which was a $BMDL_{10}$ based on brain AChE inhibition in a 4-week inhalation toxicity study in rats, with a BMD_{10} of 1.581 mg/m^3. The inhalation POD was adjusted for duration and converted to human equivalent concentration (HEC) by applying a regional deposited dose ratio (RDDR) of 2.881 (US EPA, 2023).

DPR converted this HEC to a human equivalent dose (HED) of 0.243 mg/kg/day by applying its default human breathing rate for adults of 0.28 m^3/kg/day (Andrews and Patterson, 2000).

2. Methamidophos

US EPA calculated route-specific methamidophos TAFs to account for the higher toxicity of this metabolite when compared to acephate. The oral TAF of 2.76 was derived from the ratio of the BMD_{10} values of 0.513 and 0.186 mg/kg/day for acephate and methamidophos, respectively, based on brain AChE inhibition in an acute oral CCA study in rats. The dermal TAF of 400 was derived from the ratio of comparative effect level (CEL) values of acephate (300 mg/kg/day) and methamidophos (0.75 mg/kg/day) that caused 15% brain AChE inhibition in dermal studies in rats. The inhalation TAF of 4.81 was the ratio between CEL values of acephate (1.492 mg/kg/day) and methamidophos (0.310 mg/kg/day) that caused 15% brain AChE inhibition in inhalation studies in rats. The route-specific TAFs were used to convert methamidophos residues, and exposures to acephate equivalents and express risks in terms of acephate (US EPA, 2023).

III. Conclusions and Recommendations

For calculating acute risks from occupational exposures to acephate and methamidophos, RAS recommends the following updated PODs and target MOEs that were adopted from US EPA's most recent human health risk assessment for acephate (US EPA, 2023):

<u>Acephate</u>

1. The acute or steady-state oral POD of 0.272 mg/kg/day based on inhibition of brain AChE inhibition in acute oral studies in rats is appropriate for characterizing human risk from short-term incidental oral exposures (Table 1). The calculated risks should be compared to a target MOE of 100. This consistent with HHA's evaluations of acephate in CPRMP and the cannabis programs (DPR, 2024).
2. The steady-state dermal POD of 150 mg/kg/day based on inhibition of brain AChE in repeated-dose dermal studies in rats is appropriate for characterizing human risk from short-term dermal exposures (Table 1). Dermal studies in rats showed that brain AChE inhibition levels were similar after 5 or 15 dose exposures indicating that short-term and

steady-state dermal PODs were the same. Calculated risks should be compared to a target MOE of 100.

3. The steady-state inhalation POD_{HED}, a human equivalent dose, of 0.243 mg/kg/day based on inhibition of brain AChE in repeated-dose inhalation studies in rats is appropriate for characterizing human risk from short-term inhalation exposures (Table 1). The calculated risks should be compared to a target MOE of 30.

Methamidophos

1. RAS also established separate oral, dermal and inhalation PODs for methamidophos based on the above PODs for acephate and route specific TAFs accounting for the higher toxicity of methamidophos (Table 1, Table 2). The TAF of 2.76 (oral), 400 (dermal) and 4.81 (inhalation) were calculated by US EPA as ratio between acephate and methamidophos doses causing 10% or 15% brain AChE inhibition in the respective route route-specific studies (Table 2).
2. Calculated risks from oral and dermal exposure to methamidophos should be compared to a target MOE of 100, and risks from inhalation route to a target MOE of 30. Alternatively, calculated exposures to methamidophos could be adjusted by the appropriate TAF to convert to acephate equivalents and express risks in terms of acephate.

NOTE: Currently, US EPA and DPR use different default assumptions for body weight and breathing rates. These differences may result in different quantitative risk estimates. In its 2023 acephate risk assessment, US EPA used a default adult body weight of 80 kg which the agency considers to be most appropriate for evaluating adult occupational and residential exposure scenarios. In contrast, DPR uses a default body weight of 71.8 kg, which also dictates the default adult breathing rate used in assessments (Andrews and Patterson, 2000). HHA is in the process of evaluating whether updates to default values are warranted based on current data. However, for purposes of this memorandum, the established default values have been applied.

Table 1. Updated Points of Departure (POD), Uncertainty Factors (UF), and Target Margin of Exposure (MOE) for Acephate and Methamidophos

Short-term Exposure Scenario	Acephate	Methamidophos		Target MOE[h] (UF_{TOTAL})
	POD_{ace} (mg/kg/day)	**TAF[d]**	**POD_{met} = POD_{ace} ÷ TAF** (mg/kg/day)	
Oral (Incidental or dietary)	0.272[a]	2.76[e]	0.0986	100 (UF_A=10; UF_H=10)
Dermal	150[b]	400[f]	0.375	100 (UF_A=10; UF_H=10)
Inhalation (occupational – 8 h/day)	0.243[c]	4.81[g]	0.0505	30 (UF_A=3; UF_H=10)

MOE – margin of exposure; PODace – acephate point of departure; PODmet – methamidophos point of departure; UF_A – uncertainty factor (10x) for interspecies extrapolation; UF_H – uncertainty factor (10x) for intraspecies (human) variability; UF_{TOTAL} – product of UF_A x UF_H; TAF – toxicity adjustment factor

Source: Second Revised Draft Human Health Risk Assessment (DRA) in Support of Registration Review (US EPA, 2023). PODs for acephate, (toxicity adjustment factors) TAFs, and total UFs were established by US EPA (2023). Methamidophos is a metabolite and degradate of acephate. DPR calculated PODs for methamidophos based on US EPA's PODs for acephate and route-specific TAFs for methamidophos.

[a]Oral acute and steady-state POD for acephate. This POD was calculated using Benchmark Dose (BMD) modeling (US EPA, 2023). It was the benchmark dose lower limit ($BMDL_{10}$) for brain acetyl cholinesterase (AChE) inhibition in an acute comparative cholinesterase inhibition assay (CCA) in male rat pups on PND11, with a BMD_{10} of 0.5128 mg/kg/day.

[b]Dermal steady-state POD for acephate was a no-observed adverse-effect level (NOAEL) based on brain AChE inhibition at the lowest-observed adverse-effect level (LOAEL) of 300 mg/kg/day in 5 and 21-day (6 h/day, 5 days/week) repeated-dose dermal toxicity studies in rats (US EPA, 2023).

[c]Inhalation steady-state POD for acephate was 1.205 mg/m^3, a $BMDL_{10}$, for brain AChE inhibition in a 4-week (6 h/day) inhalation toxicity study in female adult rats on Day 29, with a BMD_{10} of 1.581 mg/m^3 (US EPA 2023). The POD was adjusted for duration and converted to occupational human equivalent concentration (HEC) of 2.604 mg/m^3/kg/day by applying a regional deposited dose ratio (RDDR) [2.604 mg/m^3/kg/day = 1.205 mg/m^3 × 6/8 h × 5/5 day × 2.881 RDDR]. RAS converted the HEC to a human equivalent dose (HED) of 0.243 mg/kg/day by using 0.28 m^3/kg/day adult human breathing rate [0.243 mg/kg/day = 2.604 mg/m^3× 0.28 m^3/kg/day × 8/24 h]. ***Sources***: RDDR was from US EPA's acephate risk assessment (US EPA, 2023). Adult human breathing rate is from DPR's guideline for selecting default inhalation rates (Andrews and Patterson, 2000).

[edfg]Toxicity adjustment factors (TAF) for methamidophos (US EPA, 2023). DPR used acephate POD_{ace} to derive POD_{met} for methamidophos by applying route-specific toxicity adjustment factors (TAF); 2.76 (oral), 400 (dermal), and 4.81 (inhalation, see Table 2).

[h]Target Margin of Exposure (MOE) is equivalent to the total uncertainty factor (UF_{TOTAL}), which is a product of interspecies (UF_A), and intraspecies (UF_H) uncertainty factors (DPR, 2018).

Table 2. Toxicity-Adjustment Factors (TAF) established by US EPA to account for the greater methamidophos toxicity compared to the parent acephate (US EPA, 2023)

Route of Exposure	Acephate (mg/kg/day) BMD_{10} or CEL	Methamidophos (mg/kg/day) BMD_{10} or CEL	TAF (Acephate ÷ Methamidophos)	Toxicity Endpoint
Oral	0.513	0.186	2.76	Acephate: BMD_{10} for brain AChE inhibition in an acute CCA study in rats. Methamidophos: BMD_{10} for brain AChE inhibition in male pups in a repeat CCA study in rats.
Dermal	300	0.75	400	Comparative effect level (CEL) values, defined as the experimental dose causing a maximum of 15% brain AChE inhibition (US EPA (2006) Cumulative Risk Assessment, Table I.B-2 and I.B-3)
Inhalation	1.492	0.31	4.81	

AChE – acetyl cholinesterase; BMD – benchmark dose; CCA – comparative cholinesterase assay; CEL – comparative effect level; TAF = Toxicity Adjustment Factor

IV. References

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