UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

Date: **19-MAR-2020**

SUBJECT: **Formetanate:** Response to Comments on the Draft Human Health Risk Assessment for Registration Review.

PC Code: 097301
Decision No.: 549183
Petition No.: NA
Risk Assessment Type: Human Health Risk Assessment
TXR No.: NA
MRID No.: NA

DP Barcode: D451174
Registration No.: NA
Regulatory Action: Registration Review
Case No.: 0091
CAS No.: 23422-53-9
40 CFR: §180.276

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Background

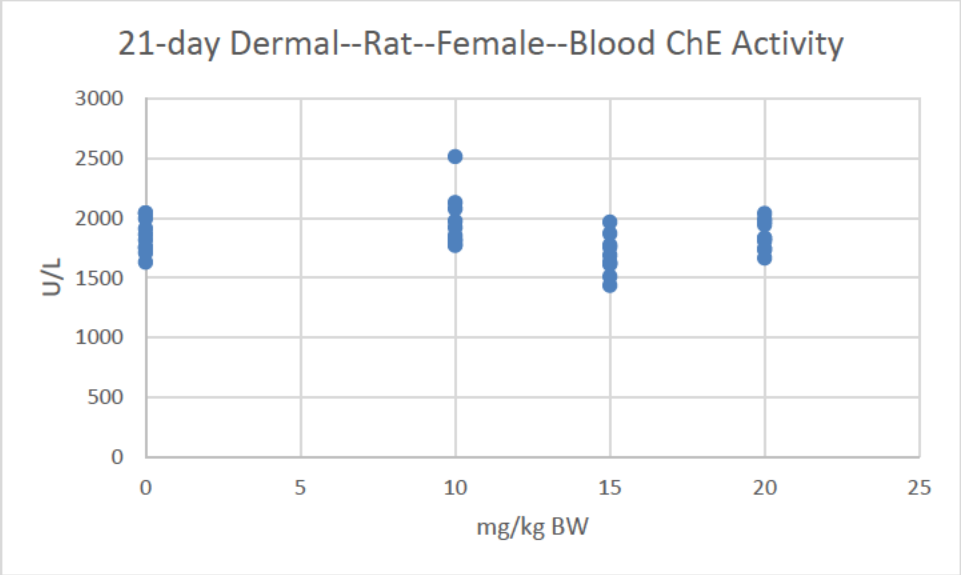
Formetanate HCl is an *N*-methyl carbamate (NMC) miticide/insecticide used on orchard crops (nectarines, oranges, grapefruit, lemons, limes, tangelos, and tangerines) and alfalfa grown for seed. The Health Effects Division (HED) prepared a draft human health risk assessment which was published in September of 2018 (S. Shelat. et al., D445040, 26-SEP-2018). The agency received multiple public comments on the 2018 draft risk assessment and the responses to these public comments are provided below.

Submission 1: Gowan, February 28, 2019, Re: Formetanate Hydrochloride Docket Number: EPA-HQ-OPP-2010-0939

Comment from Gowan in Feb 28, 2019 Letter Regarding Short- and Intermediate-term Dermal

"Short- and Intermediate-Term Dermal: A route-specific 21-day dermal study in rats was selected with a NOAEL of 10 mg/kg/day and LOAEL of 20 mg/kg/day based on RBC cholinesterase inhibition in female rats. This study is appropriate for the route and duration of exposure."

We disagree with the selection of the NOAEL. From the graph below, it is evident that there is no dose-response. The linear regression slope of units per liter (U/L) vs mg/kg is -3.32 (-0.179% of the control mean of 1851 U/L) and is not significantly different from zero (p = 0.42).



Blood ChE activity (U/L).

mg/kg	Mean	SD
0	1851	144
10	1964	229
15	1686	160
20	1854	124

10 female rats per dose.

The ChE activity at the low dose and the high dose was greater than the controls (no inhibition).

Clearly, the high dose of 20 mg/kg BW/day was a NOAEL dose, not a LOAEL dose. We concluded that 21 days of dermal dosing with formetanate had no adverse effect on ChE activity. The dermal point of departure (POD) for risk assessment should be the highest dose tested:

20 mg/kg BW/day.

This will double the dermal MOEs in the EPA assessment.

We urge the EPA to accept this scientific assessment of the data. The dermal MOEs impact the ARIs. This is important in any scenario with dermal exposure.

Response from HED:

There are two available dermal toxicity studies with formetanate. A 21-day study (1999, MRID: 44948501), with dose levels of 0, 10, 15 and 20 mg/kg/day (as cited by Gowan above), was determined by HED to have problems related to optimal time for assessment of ChE activity as well as problems with the assessment of motor activity, and the time of assays relative to blood sample collection was not reported. Because of these deficiencies, this study was classified by HED as supplemental. In response to HED's concerns with this study, a second study (2000, MRID: 45311901) designed to determine the time to peak effect for ChE inhibition following dermal applications of 0, 10, 20 or 500 mg/kg of formetanate was submitted. This study is appropriate for the route and duration of exposure (with a NOAEL of 10 mg/kg/day and LOAEL of 20 mg/kg/day based on RBC cholinesterase inhibition in female rats). The dermal risk assessment was therefore based on this study. HED does not concur with Gowan's request to revise the dermal point of departure (POD).

Comment from Gowan in February 28, 2019 Letter Regarding the Level of Detection (LOD) for citrus and nectarine:

Page 23. *"In field trials, residues in citrus and nectarines residues were non-detectable with a limit of quantitation (LOQ) of 0.02 ppm. EPA did not report the LOD. May be an issue requiring further quantification, especially when considered with drinking water exposures."*

Response from HED:

For the citrus field trials, the LOQ (determined as the lowest limit of method validation (LLMV)) was 0.01 ppm in each citrus matrix and the LOD was 0.0037 ppm (MRID 49098501). For the nectarine field trials, the LOQ (determined as the LLMV) was 0.02 ppm and the LOD was 0.007 ppm (MRID 49098502).

Since residues in nectarines in the submitted field trials were non-detectable, HED has recommended for a tolerance level of 0.02 ppm in nectarines based on the LOQ. The tolerance revision was previously recommended; however, 40 CFR §180.276 was not revised (Memo, I. Negrón-Encarnación, D411374, 08-SEP-2013; Memo, I. Negrón-Encarnación, D423120, 07-JAN-2015).

Comment from Gowan in February 28, 2019 Letter Regarding the Dietary Exposure Assessment:

> *HED notes that there were 39 detectable residues (N=1802) in the most recent PDP (2013, 2014, and 2015) monitoring data for nectarines. The detects occurred in 2014 and 2015 and range from 0.0028-0.059 ppm; 17 of the detects were >0.02 ppm.*
>
> *These residues should be disregarded in the dietary risk assessment. Based on the label directions for* ***"no applications after petal fall,"*** *there is no reasonable expectation of residues in fruit at harvest. The PDP residues probably represent* ***misapplications, not a label use.***
>
> *As noted in section 5.4.3 at page 26, Acute Dietary Risk Assessment, "Nectarine was a driver in the assessment." Since exposures at the 99.9th percentile are the policy standard, the positive results likely skew the dietary risk assessment and affect the subsequent assessment that includes drinking water. This assessment needs to be refined.*

Response from HED:

It is HED's general practice to use the distribution of residues, as reported, from the Pesticide Data Program (PDP). At the time the samples were collected by PDP, they were not over-tolerance residues; therefore, it is appropriate to include them in the Registration Review assessment. For food only, children 3-5 years old were the most highly-exposed population subgroup and utilized 25% of the acute Population Adjusted Dose (aPAD). Although nectarine is a driver in the food only assessment, when food and drinking water exposures are estimated together, drinking water is the driver.

The results of the drinking water exposure and risk assessment are dependent on the pH of the soil. Both the acute total daily intake and eating occasion dietary assessments for water alone based on applications in acidic environments (Ground Water 19.32 ppb Scenario) resulted in exposure and risk estimates that exceed HED's level of concern at the 95th and 99.9th percentiles of exposure for all population subgroups. A food and drinking water exposure and risk assessment was not conducted for this drinking water scenario since the water alone assessments resulted in risks of concern.

Total daily intake and eating occasion analyses were conducted for food and drinking water based on applications in neutral/alkaline environments (MN Alfalfa Distribution) for characterization purposes. The most highly-exposed population subgroup was all infants <1-year old with an upper-bound exposure estimate that was 100% of the aPAD (total daily intake) and a lower-bound exposure estimate that was 63% of the aPAD (eating occasion analysis) at the 99.9th percentile of exposure. Drinking water was the driver in the assessments.

Comment from Gowan in February 28, 2019 Letter Regarding Drift Assessment and Buffer Zones

> *The registrant provided information that citrus orchards are not deciduous and do not have "Sparse" foliage. A full foliage scenario needs to be developed for citrus airblast applications. Nectarines do have sparse foliage when sprayed with formetanate. The*

registrant has also provided recalculations of the drift assessment taking adjustments to the dermal point of departure into account.

Response from HED:

HED acknowledges that foliage density has a direct impact on the predicted potential for drift to occur. The exposure and risk assessment does report the Tier 1 assessment but the agency is supportive of the variability in agricultural practices between citrus orchards and nectarines and will assess the appropriate information to accurately reflect this difference. The values, however, provided by the registrant (Gowan) also incorporate the adjustment of the dermal POD, with which HED does not concur.

Comment from Gowan in February 28, 2019 Letter Regarding Occupational Exposure and Risk Assessments: Handlers

Table 8.1 is provided with refinements of the dermal points of departure as proposed by the registrant with no other discussion to changes to the exposure and risk assessment. However, upon further review, the registrant (Gowan) has incorporated additional personal protective equipment to the assessment that was not including in the original exposure and risk assessment.

Response from HED:

HED has not concurred with the proposed changes to the dermal PODs and therefore has not adjusted the current exposure and risk assessment table as provided in the Registration Review Assessment. HED notes the registrant's comment that handheld spray equipment is not used in citrus, nectarines, or alfalfa. HED also notes that the registrant, Gowan, has listed Personal Protective Equipment (PPE) that is in addition to the engineering controls provided by the water soluble packaging for the mixer/loader scenarios. It is not standard to assess PPE in addition to engineering controls due to the structure of the Worker Protection Standard and accompanying policy and practice.

Comment from Gowan in February 28, 2019 Letter Regarding Occupational Post-application Non-Cancer Exposure and Risk Estimates for Formetanate Hydrochloride

Upon the premise that the dermal POD will be adjusted. The registrant notes that nectarine thinning will be require an REI of 12 days rather than 18 days with the new dermal point of departure and all other scenarios will result in no REI past 0 days.

Response from HED:

HED has not concurred with the proposed changes to the dermal PODs and therefore has not adjusted the current exposure and risk assessment table.

Submission 2: Gowan, July 21, 2019, A few comments on the cited EPA formetanate risk assessments by Gowan Company: Supplemented 21 July 2019

Comment from Gowan in July 21, 2019 Letter Regarding Short- and Intermediate-term Dermal

This comment is the same as the comment provided in the February 28, 2019 letter regarding the dermal point of departure.

Response from HED:

The registrant did not provide **s**ufficient justification for revising the dermal POD. See answer above.

Comment from Gowan in July 21, 2019 Letter Regarding the Inhalation POD

"Inhalation POD:

- *Based on the BMDL-10 from the female rat RBC inhibition inhalation study (mg/m^3). High dose (8 mg/m^3) excluded as the exponential model did not fit the data with that dose. The subsequent model fit the data very well: output attached.*
  - *BMDL-10 analyses are often used in cholinesterase inhibition studies and was used by EPA in this draft human health risk assessment (see page 14, oral CCA study).*
- *Human equivalent dose (HED) was computed from the BMDL-10 concentration with EPA spreadsheet.*
- *BMDL-10 = 0.1747 mg/m^3.*
- *HED=0.057 mg/kg BW*

Aggregate Risk Index (ARI) = 1÷ [(Dermal LOC ÷ Dermal MOE) + (Inhalation LOC ÷ Inhalation MOE)]. ARIs =>1.0 are considered acceptable.

- *Dermal uncertainty factor (UF)=100 (10 intra- and 10 interspecies).*
- *Inhalation UF=30 (10 intraspecies and 3 interspecies based on HED and EPA standard practice). No need for a 10X UF due to lack of NOAEL as the BMDL-10 analysis identifies the point of departure (POD) for 10% RBC inhibition."*

Response from HED:

The registrant's analysis of the inhalation data is inconsistent with the human health risk assessment. HED has previously (see below) outlined the rationale for the POD and human-equivalent dose (0.078 mg/kg/day). It is unclear from the above commentary what the registrant's justification is for the proposed change in the human-equivalent dose to 0.057 mg/kg/day. Without such justification, HED stands by its original rationale.

HED's rationale is as follows. A LOAEL of 0.00081 mg/kg/day was identified in female rats for red blood cell (RBC) cholinesterase inhibition in the acute rate inhalation study. The human-equivalent dose was calculated using the LOAEL and the regional deposited-dose ratio (RDDR). A systemic RDDR was estimated at 2.709 based on extra respiratory effects, a mass median aerodynamic diameter (MMAD) of 3.0 µm, and geometric standard deviation (GSD) of 2.93 µm from the lowest dose tested (0.00081 mg/L).

The POD from the route-specific inhalation study was adjusted for expected human exposure duration. Duration adjustment is performed based on Haber's law, which assumes that a

toxicological effect is proportional to the product of exposure level and duration. A daily duration adjustment (from 3 hours/day exposure in the acute rat inhalation study) was applied when appropriate; however, no weekly adjustment was made since the study only evaluated acute (1 day) exposure. The RDDR of 2.709 was applied to the duration-adjusted POD to obtain human equivalent concentrations, which were then used to calculate subsequent human equivalent doses[1].

Summary of HEC/HED Values for Formetanate						
Population	Scenario	Tox duration adjustment[a]		HEC[b]		HED (mg/kg-day)
		Daily	Weekly	mg/L	mg/m3	
Occupational	Handler	0.375	1	0.001	0.823	0.078

a. Toxicity duration adjustment from 3 hours/day exposure in the acute rat inhalation study. No weekly adjustment was made since the study only evaluated acute (1 day) exposure.
b. Human equivalent concentrations calculated using duration adjustments, when applicable, and a systemic regional deposited dose ratio (RDDR) of 2.709, which was obtained with a mass median aerodynamic diameter (MMAD) of 3.00 µm and a geometric standard deviation (GSD) of 2.93 µm from the lowest dose tested (0.08 mg/m3), as well as the female body weight of 205 g from the acute rat inhalation study.

Comment from Gowan in July 21, 2019: "*Occupational Exposure and Risk Assessments: Handlers*":

Table 11.1 is provided with refinements of the dermal and inhalation points of departure as proposed by the registrant with no other change to the exposure and risk assessment.

Response from HED:

HED has not concurred with the proposed changes to the dermal and inhalation PODs and therefore has not adjusted the current exposure and risk assessment table provided in the Registration Review Assessment. HED also notes that the registrant, Gowan, has listed PPE that is in addition to the engineering controls provided by the water soluble packaging for the mixer/loader scenarios. It is not standard to assess PPE in addition to engineering controls due to the structure of the Worker Protection Standard and accompanying policy and practice. HED notes the registrant's comment that handheld spray equipment is not used in citrus, nectarines, or alfalfa.

[1] Human equivalent dose (mg/kg/day) = human equivalent concentration (mg/L) x human-specific conversion factor (11.8 L/hr-kg) x respiratory tract to oral absorption ratio (assume 1) x duration of daily exposure for activity (occupational handler = 8 hrs/day, residential handler and indoor post-application = 2 hrs/day, residential outdoor post-application = 2.3 hrs/day)