



**OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION**

WASHINGTON, D.C. 20460

July 10, 2025

**MEMORANDUM**

**SUBJECT:** **Dicamba and Dicamba BAPMA Salt.** Human-Health Risk Assessment for Proposed Section 3 Registration on Dicamba-tolerant Cotton and Dicamba-tolerant Soybean.

**PC Code:** 029801, 128931, 100094

**CAS No.:** 1918-00-9, 104040-79-1, 105-83-9

**Petition No.:** NA

**Risk Assessment Type:** Single Chemical Aggregate

**TXR No.:** NA

**MRID No.:** NA

**Task Group No.:** 00619469, 00621217, 00624275

**Parent Case No.:** 00557700, 00561415, 00615474

**Registration No.:** 264-REUR, 7969-LNT, 100-RTLG

**Regulatory Action:** Section 3

**Case No.:** 0065

**40 CFR:** §180.227

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**Introduction**

The Registration Division (RD) has requested that the Health Effects Division (HED) conduct human health risk assessments, as needed, for the proposed uses of dicamba diglycolamine (DGA) and dicamba N, N-Bis-(3-aminopropyl) methylamine (BAPMA) salt formulations on dicamba-tolerant cotton and soybean. The following registration requests are combined for this assessment:

- Bayer Crop Science is requesting the registration of a dicamba DGA salt end-use product KHNPO090 HERBICIDE [File Symbol: 264-REUR] for restricted use on dicamba-tolerant cotton and soybean [TG00619469].
- Syngenta Crop Protection LLC is requesting the registration of a dicamba DGA salt end-use product Tavium® Plus VaporGrip® Technology [File Symbol: 100-RTLG] for restricted use on dicamba-tolerant cotton and soybean [TG00621217].
- BASF is requesting the registration of dicamba BAPMA salt end-use product Engenia Herbicide [File Symbol: 7969-LNT] for restricted use on dicamba-tolerant cotton and soybean [TG00624275].

HED notes that previously registered end-use products<sup>1</sup> containing similar dicamba formulations for use on dicamba-tolerant cotton and soybean were assessed previously in (A. Gavelek & K. Lowe, D429870, 2016-03-29) and most recently in (P. Savoia *et al.*, D461765, 2021-04-21) in support of registration review. However, since this time, those end-use products have been vacated.<sup>2</sup> HED has also updated its data assumptions for assessing occupational exposures. Furthermore, the use profiles, application restrictions, and personal protective equipment (PPE) requirements for the proposed dicamba DGA salt and dicamba BAPMA salt end-use products listed above are not consistent with those assessed previously. Based on these considerations, HED has conducted dietary, occupational, residential, and aggregate human health exposure assessments as needed for these proposed uses.

The conclusions conveyed in this assessment were developed in full compliance with *EPA Scientific Integrity Policy for Transparent and Objective Science*, and EPA Scientific Integrity Program's *Approaches for Expressing and Resolving Differing Scientific Opinions*. The full text of *EPA Scientific Integrity Policy for Transparent and Objective Science*, as updated and approved by the Scientific Integrity Committee and EPA Science Advisor can be found here: [https://www.epa.gov/system/files/documents/2023-12/scientific\\_integrity\\_policy\\_2012\\_accessible.pdf](https://www.epa.gov/system/files/documents/2023-12/scientific_integrity_policy_2012_accessible.pdf). The full text of the EPA Scientific Integrity Program's *Approaches for Expressing and Resolving Differing Scientific Opinions* can be found here: <https://www.epa.gov/scientific-integrity/approaches-expressing-and-resolving-differing-scientific-opinions>.

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1 The proposed end-use products are based on previously registered products 264-1210, 100-1623, and 7969-472.

2 See <https://www.epa.gov/pesticides/epa-provides-update-over-top-uses-dicamba>.

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## 1.0 Executive Summary

Dicamba (3,6-Dichloro-*o*-anisic acid) is a selective benzoic acid herbicide currently registered in various acid and salt formulations on a variety of agricultural and non-agricultural use sites. Dicamba is an auxin agonist that induces abnormal and uncontrollable growth to disrupt normal plant functions at high concentrations. For dicamba-tolerant varieties, the dicamba mono-oxygenase (DMO) gene is introduced into seeds to encode the enzyme dicamba *O*-demethylase to convert dicamba into the non-herbicide metabolite 3,6-dichlorosalicylic acid (DCSA), thus causing the plant to tolerate the herbicidal effect of dicamba. Dicamba-tolerant varieties demonstrate further hydroxylation of DCSA to form the 2,5-dichloro-3,6-dihydroxybenzoic acid (DCGA) metabolite.

HED considers available study data for the dicamba acid, dicamba salt forms [isopropylamine (IPA) and diglycolamine (DGA), and N, N-Bis-(3-aminopropyl) methylamine (BAPMA)], and metabolites [DCSA, DCGA, and 5-hydroxydicamba (5-OH dicamba)] when assessing human health risks from exposures to dicamba. Based on available toxicity studies and structural similarities, the various forms of dicamba are considered to be of comparable toxicity and are assessed concurrently.

RD has requested that HED conduct human health exposure assessments as needed for the Section 3 registration of two dicamba DGA salt formulation end-use products [264-REUR and 100-RTLG] and one dicamba BAPMA salt formulation end-use product [7969-LNT] for restricted use on dicamba-tolerant cotton and soybean. Because the use patterns, restrictions, and application rates across these proposed use sites are similar, these actions are evaluated concurrently.

This memorandum serves as HED's human health exposure and risk assessment for the proposed uses of dicamba associated with Task Groups 00619469, 00621217, and 00624275.

*Use Profile:* KHNP0090 HERBICIDE [264-REUR] and Tavium® Plus VaporGrip® Technology [100-RTLG] are restricted use pesticide products formulated as a liquid concentrate and capsule suspension, containing 42.8% and 17.7% of the active ingredient (ai) dicamba DGA salt, respectively. Engenia Herbicide [7969-LNT] is also a restricted use pesticide product and is formulated as a liquid concentrate containing 60.8% of the ai dicamba BAPMA salt. For dicamba-tolerant cotton and soybean, broadcast, banded, or spot treatment applications are permitted via ground equipment only at a single use maximum application rate of 0.5 lb acid equivalents (ae)/acre (A). These applications are permitted during preplant, at-plant, preemergence, and/or postemergence, where specified. Aerial and chemigation applications of these products are not permitted. For broadcast applications, a minimum of 15 gallons of spray solution/A is recommended. No more than two applications are permitted per growing season for a maximum annual application rate of 1.0 lb ae/A. A minimum retreatment interval of 7 days is specified on the proposed KHNP0090 HERBICIDE [264-REUR] and Engenia Herbicide [7969-LNT] product labels.

All proposed product labels require workers to wear baseline attire (i.e., long-sleeve shirt, long pants and shoes plus socks) along with personal protective equipment (PPE) including chemical resistant gloves when handling these products. A NIOSH-approved dust/mist filtering respirator with any oil-resistant(R), oil-proof (P), or high efficiency (HE) filter is also required for all handlers of the BAPMA salt formulated product. A restricted entry interval (REI) of 24 hours is listed on all labels.

*Exposure Profile:* Humans may be exposed to dicamba in food and drinking water since dicamba may be applied directly to growing crops, and application may result in dicamba reaching surface and ground sources of drinking water. In an occupational setting, applicators may be exposed while handling the pesticide prior to application as well as during application. There is also potential for post-application exposure for workers re-entering treated fields. The proposed restricted end-use products are intended for professional use applications to agricultural use sites only, therefore, residential handler and post-application exposures are not anticipated. Adult short-term dermal and children's short-term dermal and incidental oral (post-application) exposures may occur from residues resulting from spray drift following applications to the proposed agricultural use sites.

*Hazard Characterization & Dose Response Assessment:* The toxicology database for dicamba is complete for assessing potential exposures to the proposed dicamba DGA salt and dicamba BAPMA salt formulations. No additional data are required, nor are additional updates required at this time.

The dietary, incidental oral, and dermal endpoint determinations for dicamba acid are protective for assessing anticipated exposures from the dicamba DGA salt and dicamba BAPMA salt formulations. However, due to differences in the toxicological inhalation endpoints between the dicamba acid (which is protective of the DGA salt form) and BAPMA salt forms, separate inhalation points of departure (PODs) have been selected for these assessments. The toxicological endpoints and PODs for assessing human health risks from exposures to the dicamba DGA salt and the BAPMA salt formulations are summarized below.

The acute dietary POD for dicamba is based on ataxia, unsteady gait, and convulsions in the dams (considered a single-dose effect since the signs occurred within 3 hours after dosing) observed at the lowest observed effects level (LOAEL) of 86 mg/kg/day in a rat developmental study for the dicamba BAPMA salt. The no observed adverse effects level (NOAEL) of 29 mg/kg/day is selected for deriving the acute reference dose (RfD). An uncertainty factor of 100X (which includes a 10X to account for interspecies extrapolation, 10X for intraspecies variation, and a Food Quality Protection Act (FQPA) Safety Factor (SF) of 1X) is applied to the NOAEL to obtain an acute RfD of 0.29 mg/kg/day. A separate acute dietary risk assessment was not conducted for females since developmental toxicity endpoints of concern attributable to a single dose (exposure) were not identified in the database.

The chronic dietary POD for dicamba is based on decreased pup body weights observed at 37 mg/kg/day (LOAEL) in a two-generation reproduction toxicity study with the DCSA metabolite. The NOAEL of 4 mg/kg/day is selected for deriving the chronic RfD. An uncertainty factor of 100X (10X to account for interspecies extrapolation, 10X for intraspecies variation, and 1X for FQPA SF) is applied to the NOAEL to obtain a chronic RfD of 0.04 mg/kg/day.

The incidental oral POD is selected from the two-generation reproductive toxicity study in rats dosed with parent compound (dicamba acid) and based on impaired pup growth observed at the LOAEL of 450 mg/kg/day; the NOAEL of 136 mg/kg/day was selected as the POD for this scenario. The Level of Concern (LOC) for incidental oral exposures is 100, which includes the 10X factor to account for interspecies extrapolation, a 10X factor to account for intraspecies variation, and a 1X FQPA SF.

Dermal endpoints were not selected for dicamba acid or its salts, as there are no adverse systemic effects in the database from dermal exposure at the limit dose (1000 mg/kg/day) and no evidence of susceptibility in available developmental and reproductive studies.

Route-specific inhalation studies are currently available for the dicamba acid and dicamba BAPMA salt formulations. However, since the dicamba BAPMA salt demonstrated to be more toxic than the dicamba acid, separate inhalation PODs have been selected for assessing risk from inhalation exposures to the dicamba DGA salt and dicamba BAPMA salt formulations. For the dicamba DGA salt, the inhalation POD was based on the route-specific dicamba acid inhalation toxicity study in Wistar rats with a lowest observed adverse effect concentration (LOAEC) of 0.050 mg/L based on local effects of hyperplasia in the lungs and lymph nodes (no observed adverse effect concentration (NOAEC) = 0.005 mg/L, non-systemic, pulmonary regional deposited dose ratio (RDDR) = 0.590). For the dicamba BAPMA salt, the inhalation POD is based on the dicamba BAPMA salt inhalation toxicity study in rats with a LOAEC of 0.0014 mg/L based on local effects of hyperplasia and ulceration of the larynx (no NOAEC, non-systemic, extra-thoracic RDDR = 0.190). The standard interspecies extrapolation uncertainty factor (UF) is reduced from 10X to 3X for dicamba acid (and DGA salt) and BAPMA salt due to the calculation of human equivalent concentrations (HECs) accounting for pharmacokinetic (not pharmacodynamic) interspecies differences. The LOC for dicamba BAPMA salt inhalation exposures is 300 (3X for interspecies extrapolation, 10X for intraspecies variation, and a 10X UF<sub>L</sub> is applied due to lack of a NOAEC). For all other forms of dicamba, the inhalation exposure LOC is 30 (3X for interspecies extrapolation, 10X for intraspecies variation, and 1X for FQPA SF when applicable).

Dicamba is classified as “*Not Likely to be Carcinogenic to Humans*” based on an absence of treatment-related tumors in mice and rats.

*Residue Chemistry:* The residue chemistry data in support of the dicamba-tolerant registration requests have been previously reviewed and found to be acceptable (M. Jackson, 029801\_TG00619469\_CHEMR, 2025-07-10). The nature of residues for dicamba-tolerant cotton and dicamba-tolerant soybean is understood (P. Savoia *et al.*, D461765, 2021-04-21; P. Savoia, D408384, 2016-03-29; A. Kamel, D384422, 2013-04-17). Bridging data to demonstrate equivalency of residues resulting from the dicamba BAPMA salt formulation with respect to the dicamba DGA salt were previously submitted by BASF and have been reviewed by HED (P. Savoia, D429868 & D429964, 2016-03-29). These data demonstrate that the average combined residues of dicamba are protective for potential residues resulting from the use of dicamba BAPMA salt formulations, which fall below established tolerance limits. No proposed tolerances or changes to the established tolerances for soybean seed (10 ppm), soybean forage (60 ppm), soybean hay (100 ppm), soybean hull (30 ppm), cotton undelinted seed (3 ppm), and cotton gin byproducts (70 ppm) have been requested by the petitioners. No revised tolerances on livestock commodities are required to support the current registrations requests.

*Dietary Exposure Assessment:* Acute and chronic aggregate dietary (food and drinking water) risk assessments were conducted to include all registered and proposed uses of dicamba. These assessments assume a 100 percent crop treated (PCT) and HED default processing factors, where applicable. Estimated drinking water concentrations (EDWCs) were modeled by the Environmental Fate

and Effects Division (EFED) and incorporated directly into these dietary assessments.<sup>3</sup> An unrefined acute dietary assessment was conducted using tolerance level residues. Acute dietary risk estimates are not of concern for the general U.S. population and all population subgroups assessed (<100% acute population-adjusted dose (aPAD)) at the 95<sup>th</sup> percentile; with the most highly exposed population subgroup being all infants (<1 year old) at 39% of the aPAD. A refined chronic dietary assessment was conducted using average field trial residues for crops, and tolerance level residues for livestock commodities. Chronic dietary risk estimates are not of concern for the general U.S. population and all population subgroups assessed (<100% chronic population-adjusted dose (cPAD)); with the most highly exposed population subgroup being children ages 1-2 at 51% of the cPAD.

*Residential Exposure and Risk Assessment:* The proposed end-use products are labeled as restricted use pesticides intended for professional use only applications to agricultural use sites. Since there are no residential uses and/or use sites proposed as part of these registration requests, quantitative residential handler and/or post-application assessments are not conducted at this time. However, there are existing residential uses of dicamba that have been assessed previously in (A. Gavelek & K. Lowe, D429870, 2016-03-29) and most recently evaluated in (P. Savoia *et al.*, D461765, 2021-04-21). There were no residential handler and/or post application risk estimates of concern (i.e., all inhalation margins of exposure (MOEs)  $\geq$  inhalation LOC of 30; and all incidental oral MOEs  $\geq$  incidental oral LOC of 100) identified for currently registered uses of dicamba. Since no dermal hazard was identified for dicamba, quantitative residential handler and/or post-application dermal risk assessments were not conducted.

*Aggregate Risk Assessment:* The acute and chronic aggregate risk estimates for dicamba includes food and drinking water only and are equivalent to the acute and chronic dietary risk estimates, which are not of concern. Since there are short-term residential uses, short-term aggregate risks were assessed which include contributions from food, drinking water, and residential exposure. No dermal hazard has been identified for dicamba, and the inhalation and incidental oral endpoints are selected based on different toxicological effects, therefore, the short-term aggregate risk assessment only includes applicable oral exposures (e.g., food, water and incidental oral). As a result, a short-term aggregate assessment was not conducted for adults (only residential inhalation exposures assessed for adults). For children, the short-term aggregate [(food, water, and residential (incidental oral))] MOE is above the LOC of 100 and not of concern.

*Non-Occupational Spray Drift Assessment:* Because the toxicological profile for dicamba acid is protective for the dicamba DGA salt formulation, the spray drift assessment for the proposed agricultural uses for the dicamba DGA salt form considers all currently registered uses of dicamba, including uses on residential turf. However, because there are no registered turf uses for the dicamba BAPMA salt formulation, the potential for spray drift from these proposed uses are assessed independently from the proposed uses of the dicamba DGA salt formulation.

Dicamba DGA salt: The need for a quantitative spray drift assessment for the dicamba DGA salt has been evaluated by HED. However, since dicamba is currently registered for use on turf, it was considered whether the risk assessment for the turf use would be considered protective of any type of

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3 D460422. Peck, C. 04-MAR-2021. Drinking Water Memo for the Registration Review of Dicamba Acid, Salts, and Degradate 3,6-dichlorosalicylic acid (DCSA).

exposure expected to result from spray drift. The maximum crop application rate (0.5 lb ae/A), adjusted for maximum anticipated spray drift deposition potential (0.26), was found to be less than or equal to the existing turf application rate (1 lb ae/A). Therefore, the conducted post-application exposure assessment for turf is considered protective of anticipated spray drift exposures from the proposed agricultural/non-agricultural uses of dicamba DGA salt and a quantitative spray drift assessment is not conducted at this time. As determined, there were no residential post-application risks of concern identified for the registered use on turf.

**Dicamba BAPMA salt:** A quantitative non-occupational spray drift assessment was conducted for dicamba BAPMA salt. Adult dermal and children (1 to <2 years old) dermal exposures were not assessed since there were no adverse effects observed in the route specific dermal toxicity study up to and including the limit dose. Therefore, only incidental oral exposures for children (1 to <2 years old) are quantitatively assessed. Using default turf transferable residues (TTR) assumptions, children (1 to <2 years old) incidental oral risk estimates from exposure to dicamba BAPMA salt associated with spray drift residues results in no risks of concern (i.e., MOEs  $\geq$  LOC of 100) at the field edge for groundboom applications.

**Non-occupational Bystander Inhalation Exposure and Risk:** The potential for non-occupational exposures to vapor phase dicamba residues emitted from treated fields for application rates up to 2.0 lb ae/A were evaluated previously in (A. Gavelek & K. Lowe, D429870, 2016-03-29) and most recently in (P. Savoia *et al.*, D461765, 2021-04-21) in support of registration review. The volatilization modeling was completed using the Probabilistic Exposure and Risk model for FUMigants (PERFUM) and chemical/formulation-specific flux data. HED concluded that while volatilization of dicamba from treated crops (at rates up to 2.0 lb ae/A) does occur and could result in bystander exposure, airborne concentrations, even at the edge of the treated fields, were not of concern. HED notes that the volatilization assessment SOP's, methodologies, and data assumptions remain current. Since the proposed agricultural uses of dicamba DGA salt and dicamba BAPMA salt are at application rates lower (0.5 lb ae/A) than those previously assessed (2.0 lb ae/A), these assessments are considered protective for the proposed agricultural uses. Therefore, there are no non-occupational bystander inhalation risks of concern anticipated from these proposed uses.

**Occupational Exposure and Risk Assessment:** Since no dermal hazard has been identified for dicamba, quantitative occupational handler and/or post-application dermal risk assessments were not conducted at this time. Only occupational handler inhalation exposures are assessed. All occupational handler inhalation risk estimates are not of concern (i.e., MOEs  $\geq$  inhalation LOC of 30 for the DGA salt; and  $\geq$  inhalation LOC of 300 for the BAPMA salt) assuming baseline attire and label required PPE (i.e., respirator for BAPMA salt formulation only). Based on the Agency's current practices, a quantitative non-cancer occupational post-application inhalation exposure assessment was not performed for dicamba at this time. If new policies or procedures are put into place, the Agency may revisit the need for a quantitative occupational post-application inhalation exposure assessment for dicamba.

**Human Studies:** This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide to determine their exposure. Appendix C provides additional information on the review of human research used to complete the risk assessment. There is no

regulatory barrier to continued reliance on these studies, and all applicable requirements of EPA's Rule for the Protection of Human Subjects of Research (40 CFR Part 26) have been satisfied.

## **2.0 HED Conclusions**

There are no human health risk estimates of concern identified for the proposed uses of dicamba DGA salt or dicamba BAPMA salt on dicamba-tolerant cotton and soybean.

### **2.1 Data Deficiencies**

There are no residue chemistry, toxicology, or exposure data deficiencies identified.

### **2.2 Tolerance Considerations**

#### **2.2.1 Enforcement Analytical Method**

Adequate methods are available for the enforcement of the newly proposed cotton seed and cotton gin byproducts as well as soybean seed, forage and hay tolerances. The existing analytical method AM-0691B-0297-4 is the latest revision of the Agency validated method AM-0691B-0297-2, which was submitted to the Food and Drug Administration (FDA) for inclusion into PAM volume II.

An independent laboratory validation of the liquid chromatography/mass spectrometer/mass spectrometer (LC/MS/MS) method, BASF Method D0902, used for analyzing the field trial samples in the bridging studies has also been provided for assessment. BASF Analytical Method D0902 meets these conditions depicting the suitability of an enforcement methodology. Pending editorial revisions recommended by the independent validation laboratory, HED determines the BASF method to be adequate for the tolerance enforcement of crops.

Dicamba is completely recovered through the FDA multi-residue method (MRM) testing protocols using Section 402 E2 of Protocol B but is partially recovered using Section 402 E1 of Protocol B (Appendix II of PAM Volume I). The multi-residue testing data submitted by BASF Corporation for dicamba and its 5-OH dicamba and DCSA metabolites are scientifically acceptable and adequate for regulatory purposes (A. Kamal, D375578, 2011-06-11).

Analytical standards for dicamba and its metabolites of concern are currently available in the EPA National Pesticide Standards Repository (email communication, C. Vigo to M. Jackson, BEAD, 2025-01-08). The current stock of standards is set to expire on 2029-03-01 (for DCSA), 2032-04-01 (for 5-OH dicamba) and 2032-11-16 (for dicamba).

#### **2.2.2 Recommended Tolerances**

The residues of dicamba in plants, which are currently regulated for tolerance expression in three separate subparts of 40 CFR §180.227, have been reviewed and should be harmonized and consolidated under 40 CFR §180.227 (a)(1) to read as follows:

“Tolerances are established for residues of the herbicide dicamba (3,6-dichloro-2-methoxybenzoic acid), including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only the sum of the residues of dicamba (3,6-dichloro-2-methoxybenzoic acid), and its metabolites 3,6-dichloro-5-hydroxy-2-methoxybenzoic acid, and 3,6-dichloro-2-hydroxybenzoic acid, calculated as the stoichiometric equivalent of dicamba, in or on the following commodities:”

The HED-recommended tolerances for dicamba in/on plants are summarized in Table 2.2.2. In addition to the tolerance recommendations for the current action, recommended tolerance changes for harmonization with Codex are also included for asparagus, barley grain, and sugarcane per the registrants’ request and previous HED recommendations (P. Savoia *et al.*, D461765, 2021-04-21).

<b>Commodity/ Correct Commodity Definition</b>	<b>Established Tolerance (ppm)</b>	<b>Recommended Tolerance (ppm)</b>	<b>Comments</b>
<b>Cotton, undelinted seed</b>	3.0	3	Crop tolerances consolidated under a single tolerance expression (P. Savoia, D450731, 2019-03-05). Corrected value to be consistent with OECD Rounding Class Practice.
<b>Soybean, seed</b>	10.0	10	
<b>Asparagus</b>	4.0	5	Crop tolerances consolidated under a single tolerance expression (P. Savoia, D450731, 2019-03-05). Corrected value to be consistent with OECD Rounding Class Practice. Harmonization with Codex (P. Savoia, D461765, 2021-04-21).
<b>Barley, grain</b>	6.0	7	Corrected value to be consistent with OECD Rounding Class Practice. Harmonization with Codex (P. Savoia, D461765, 2021-04-21).
<b>Sugarcane, cane</b>	0.3	1	Harmonization with Codex (P. Savoia, D461765, 2021-04-21).

### 2.2.3 Revisions to Petitioned-For Tolerances

No tolerance petition was submitted (nor required) to support the current registration request.

### 2.2.4 International Harmonization

There are maximum residue limits (MRLs) set by Canada and Codex on a number of established crop uses registered in the U.S. Mexico adopts U.S. tolerances and/or Codex MRLs for its export purposes. The Canadian MRLs established for dicamba are all harmonized with U.S. tolerance levels. At present, the tolerance expression for dicamba is not harmonized with Codex or Canada following the U.S. registration for use on genetically modified dicamba-tolerant crops starting in 2016. Because Codex only regulates on the parent compound and the U.S. includes metabolites, lowering tolerances for harmonization is unavoidable. However, the U.S. tolerances for asparagus, barley grain and sugarcane cane are lower than the Codex MRLs established on these crops. For the purposes of harmonization,

the tolerances can be raised for asparagus to 5 ppm, barley grain to 7 ppm, and sugarcane cane to 1 ppm. All U.S. tolerances are therefore harmonized with international MRLs to the greatest extent possible.

A summary of the international residue limits established for dicamba and its metabolites is presented in Table D.1 of Appendix D.

## **2.3 Label Recommendations**

### **2.3.1 Recommendations from Residue Reviews**

None.

### **2.3.2 Recommendations from Occupational Exposure Assessment**

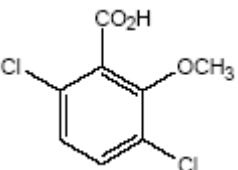
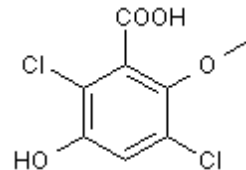
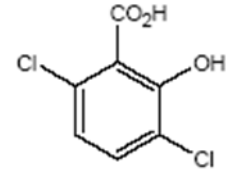
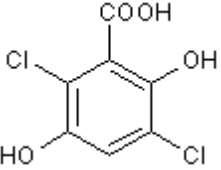
There are no specific label recommendations being made.

*Note on mixing/loading liquid formulation scenarios:* A 2019 study by the Agricultural Handler Exposure Task Force (AHETF), a consortium of pesticide manufacturing companies, measured dermal and inhalation exposure for workers who loaded liquid pesticides using closed loading systems such as gravity feed, container breach, and suction/extraction systems. As a result of the review and acceptance of that data, labels for liquid pesticide products for which suction/extraction systems are applicable should instruct users to rinse extraction probes within the pesticide container prior to removal of the probes. These instructions will ensure that users of suction/extraction systems do not remove and handle chemical extraction probes still coated with the concentrated liquid formulation.

## **3.0 Introduction**

### **3.1 Chemical Identity**

Dicamba is an auxin agonist, that induces abnormal and uncontrollable growth to disrupt normal plant functions at high concentrations. For dicamba-tolerant varieties, the DMO gene is introduced into dicamba-tolerant seeds to encode the enzyme dicamba *O*-demethylase to convert dicamba into the non-herbicide metabolite DCSA, thus causing the plant to tolerate the herbicidal effect of dicamba. Dicamba-tolerant varieties demonstrate further hydroxylation of DCSA to form the DCGA metabolite. HED considers available study data for the dicamba acid, salt forms [IPA, DGA, and BAPMA], and metabolites [DCSA, DCGA, and 5-OH dicamba] when assessing human health risks from exposures to dicamba. Table 3.1 shows the chemical names and structures of dicamba and its residues of concern.

Table 3.1. Test Compound Nomenclature: Dicamba and Its Residues of Concern.	
Compound	Chemical Structure 
Common name	Dicamba
IUPAC name	3,6-Dichloro- <i>o</i> -anisic acid
CAS name	Benzoic acid, 3,6-dichloro-2-methoxy-
CAS #	1918-00-9, 105-83-9, 104040-79-1
End-use product/EP	KHNP0090 Herbicide (264-REUR), Engenia Herbicide (7969-LNT), and Tavium Plus Vapor Grip Technology (100-RTLG)
Compound	
Common name	5-Hydroxy-dicamba
IUPAC name	2,5-dichloro-3-hydroxy-6-methoxybenzoic acid
CAS name	Benzoic acid, 2,5-dichloro-3-hydroxy-6-methoxy-
CAS registry number	7600-50-2
Compound	
Common name	DCSA; 3,6-dichlorosalicylic acid
IUPAC name	3,6-dichloro-2-hydroxybenzoic acid
CAS name	Benzoic acid, 3,6-dichloro-2-hydroxy-
CAS registry number	3401-80-7
Compound	
Common name	DCGA; 3,6-dichlorogentisic acid
IUPAC name	2,5-dichloro-3,6-dihydroxybenzoic acid
CAS name	Benzoic acid, 2,5-dichloro-3,6-dihydroxy-
CAS registry number	18688-01-2

### 3.2 Physical/Chemical Characteristics

Technical dicamba is a light cream/tan colored solid composed of granules, lumps, flakes. Dicamba has a vapor pressure of  $3.4 \times 10^{-5}$  mm Hg at 25 °C and is known to volatilize in the field. Dicamba is not

expected to bioaccumulate in aquatic organisms because it is an anion (pH 2.5-3.0) at environmental pH values. Dicamba is not significantly broken down by water or light. Aerobic soil metabolism is the main degradative process for dicamba. A single observed half-life for dicamba was 6 days with the formation of the intermediate degradate 3,6-dichloro-2-hydroxybenzoic acid (aka 3,6-dichlorosalicylic acid or DCSA). DCSA was found to degrade roughly at the same rate as dicamba. Dicamba was found to be very soluble (6100 ppm) and very mobile ( $K_{oc}=13.4$ ) in the laboratory. Results from two acceptable field dissipation studies conducted with the dimethylamine salt of dicamba indicated it dissipated with a half-life of 4.4 to 19.8 days. DCSA was the major degradate in both studies with both DCSA and dicamba being found in soil segments deeper than 10 cm. If any dicamba did reach anaerobic groundwater, it would be somewhat persistent due to its observed anaerobic half-life of 141 days. Given these factors dicamba and the DCSA metabolite may remain evident in water to reach water supplies for human consumption. See Appendix B for a table of physio-chemical properties of dicamba.

### 3.3 Pesticide Use Pattern

KHNP0090 Herbicide [264-REUR] and Tavium® Plus VaporGrip® Technology [100-RTLG] are restricted use pesticide products formulated as a liquid concentrate and capsule suspension, containing 42.8% and 17.7% of the ai dicamba DGA salt, respectively. Engenia Herbicide [7969-LNT] is also a restricted use pesticide product and is formulated as a liquid concentrate containing 60.8% of the ai dicamba BAPMA salt.

For dicamba-tolerant cotton and soybean, broadcast, banded, or spot treatment applications are permitted via ground equipment only at a single use maximum application rate of 0.5 lb ae/A. These applications are permitted during preplant, at-plant, preemergence, and/or postemergence, where specified. Aerial and chemigation applications of these products are not permitted. For broadcast applications, a minimum of 15 gallons of spray solution per acre is recommended. No more than two applications are permitted per growing season for a maximum annual application rate of 1.0 lb ae/A. A minimum retreatment interval of 7 days is specified on the proposed KHNP0090 HERBICIDE [264-REUR] and Engenia Herbicide [7969-LNT] product labels.

All proposed product labels require workers to wear baseline attire (i.e., long-sleeve shirt, long pants and shoes plus socks) along with PPE including chemical resistant gloves when handling these products. A NIOSH-approved dust/mist filtering respirator with any R, P, or HE filter is also required for all handlers of the BAPMA salt formulated product. An REI of 24 hours is listed on all labels.

The use profiles summary for the proposed end-use products are summarized in Tables 3.3.1-3.3.3.

**Table 3.3.1. Summary of Directions for Use of Proposed Dicamba DGA Salt End-Use Product 264-REUR.**

Applic. Timing, Type, and Equip. <sup>1</sup>	Formulation [File Symbol]	Applic. Rate (lb ae/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ae/A)	Use Directions and Limitations (PHI, RTI, REI, PPE) <sup>2</sup>			
Preplant, At-Plant, Preemergence, and Postemergence. Broadcast, Band, or Spot Treatments Ground Equipment	Liquid Concentrate KHNP0090 HERBICIDE 2.9 lb ae/gallon [264-REUR]	Dicamba-tolerant Cotton and Soybean <sup>3,4</sup>			0.5	2	1.0	<ul style="list-style-type: none"> <li>▪ Restricted Use Pesticide: PPE listed on the label.</li> <li>▪ REI is 24 hours.</li> <li>▪ Minimum RTI is 7 days.</li> <li>▪ PHI for cotton and soybean is 7 days.</li> <li>▪ A minimum of 15 gal of spray solution/A.</li> <li>▪ Aerial/chemigation applications are prohibited.</li> <li>▪ Post-application grazing/feeding of livestock is permitted for cotton and soybean.</li> </ul>

1. Optional use of a Hooded/Shielded Broadcast sprayer is on the proposed label as a potential drift reduction technology.

2. PHI = pre-harvest interval. REI = re-entry interval. RTI = re-treatment interval. PPE = personal protective equipment. Label requires all handlers to wear baseline attire defined as single layer clothing consisting of long-sleeved shirts, long pants, shoes plus socks, and chemical resistant gloves.

3. For dicamba-tolerant cotton, do not exceed any combination of two preplant, at-planting, preemergence, or postemergence applications.

4. For dicamba-tolerant soybean, a maximum of two preplant, at-planting, or preemergence applications may be made. Postemergence applications are not directly specified on the label, however, the label states that this product may be applied before, during, or immediately after planting, and through emergence.

**Table 3.3.2. Summary of Directions for Use of Proposed Dicamba DGA Salt End-Use Product 100-RTLG.**

Applic. Timing, Type, and Equip. <sup>1</sup>	Formulation [File Symbol]	Applic. Rate (lb ae/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ae/A)	Use Directions and Limitations (PHI, RTI, REI, PPE) <sup>2</sup>			
Preplant, At-Plant, Preemergence, and Postemergence. Broadcast, Band, or Spot Treatments Ground Equipment	Capsule Suspension Tavium® Plus VaporGrip® Technology 1.12 lb ae/gallon [100-RTLG]	Dicamba-tolerant Cotton and Soybean <sup>3,4</sup>			0.5	2	1.0	<ul style="list-style-type: none"> <li>▪ Restricted Use Pesticide: PPE listed on the label.</li> <li>▪ REI is 24 hours.</li> <li>▪ Minimum RTI is not specified.</li> <li>▪ PHI for cotton is 100 days.</li> <li>▪ PHI for soybean is 75 days.</li> <li>▪ A minimum of 15 gal of spray solution/A.</li> <li>▪ Aerial/chemigation applications are prohibited.</li> <li>▪ Do not use in nurseries, turf, or landscapes.</li> <li>▪ Post-application grazing/feeding of livestock restrictions are specified on the label.</li> </ul>

1. Optional use of a Hooded/Shielded Broadcast sprayer is on the proposed label as a potential drift reduction technology.

2. PHI = pre-harvest interval. REI = re-entry interval. RTI = re-treatment interval. PPE = personal protective equipment. Label requires all handlers to wear baseline attire defined as single layer clothing consisting of long-sleeved shirts, long pants, shoes plus socks, and chemical resistant gloves.

3. For dicamba-tolerant cotton, do not make more than one preplant or at-planting or preemergence application, and/or one postemergence (In-crop) application on medium-or fine-textured soils. Do not apply to non-dicamba-tolerant cotton.

4. For dicamba-tolerant soybean, do not make more than one preplant or at-planting or preemergence application, and/or one postemergence (In-crop) application. Do not apply to non-dicamba-tolerant soybeans.

**Table 3.3.3. Summary of Directions for Use of Proposed Dicamba BAPMA Salt End-Use Product 7969-LNT.**

Applic. Timing, Type, and Equip. <sup>1</sup>	Formulation [File Symbol]	Applic. Rate (lb ae/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ae/A)	Use Directions and Limitations (PHI, RTI, REI, PPE) <sup>2</sup>			
Preplant, At-Plant, Preemergence, and Postemergence. Broadcast, Band Applications Ground Equipment	Liquid Concentrate Engenia Herbicide 5.0 lb ae/gallon [7969-LNT]	Dicamba-tolerant Cotton and Soybean <sup>3,4</sup>			0.5	2	1.0	<ul style="list-style-type: none"> <li>▪ Restricted Use Pesticide: PPE listed on the label.</li> <li>▪ REI is 24 hours.</li> <li>▪ Minimum RTI is not specified.</li> <li>▪ PHI for cotton and soybean forage is 7 days.</li> <li>▪ PHI for soybean hay is 14 days.</li> <li>▪ A minimum of 15 gal of spray solution/A.</li> <li>▪ Aerial/chemigation applications are prohibited.</li> <li>▪ Do not use in nurseries, turf, or landscapes.</li> <li>▪ Cotton gin byproducts may be fed to livestock.</li> </ul>

1. Optional use of a Hooded/Shielded Broadcast sprayer is on the proposed label as a potential drift reduction technology.

2. PHI = pre-harvest interval. REI = re-entry interval. RTI = re-treatment interval. PPE = personal protective equipment. Label requires all handlers to wear baseline attire defined as single layer clothing consisting of long-sleeved shirts, long pants, shoes plus socks, and waterproof gloves. This product also requires all handlers to wear a NIOSH-approved dust/mist filtering respirator with any R, P, or HE filter.

3. For dicamba-tolerant cotton, applications may only occur through July 30.
4. For dicamba-tolerant soybean, applications may only occur through June 12 or V2 growth stage, whichever occurs first.

*Note:* No new rotational crop data have since been submitted in support of these requests; therefore, the plant back restrictions noted in the 2005 RED<sup>4</sup> are appropriately specified on the proposed product label for treating these dicamba-tolerant crops. Specifically, a 120-day plant back interval (PBI) is followed when dicamba is applied at a maximum seasonal rate of 0.75 lb ae/A or less. At seasonal application rates of 0.75-1.0 lb ae/A, only crops with established tolerances can be rotated for planting. The proposed end-use product labels are consistent with these recommendations.

The proposed use directions for the BAPMA salt formulation of dicamba are adequate to allow evaluation with respect to the previously submitted bridging study data. These residue data examined the broad use pattern of dicamba using post-emergence broadcast treatments made at the maximum application rate following the specified minimum pre-harvest interval (PHI). Prior residue data submitted for dicamba-tolerant cotton showed that later post-emergence treatments give much higher residues than those made at earlier growth stages. Following the pattern of late season use demonstrated by these field trial data, HED previously concluded that no more than two (2) post-emergence applications may be made after the first open boll stage when treating dicamba-tolerant cotton. The proposed dicamba BAPMA salt product label is consistent with these recommendations.

### **3.4 Anticipated Exposure Pathways**

Dicamba is currently registered for use on agricultural and non-agricultural use sites, including turf. Humans may be exposed to dicamba DGA salt and dicamba BAPMA salt residues in food and drinking water, since the proposed end-use products may be applied directly to growing crops and may result in reaching surface and ground water sources of drinking water. There are no residential uses and/or residential use sites proposed as part of these requests, so residential handler and/or post-application exposures are not likely. However, there is the potential for dermal and inhalation exposures from the residential application of registered dicamba products by adults. In addition, there is the potential for residential post-application exposures for both adults (dermal only) and children (dermal and incidental oral) from currently registered uses on turf. Non-occupational exposures to dicamba DGA salt and dicamba BAPMA salt via spray drift is anticipated. In an occupational setting, applicators may be exposed while handling the pesticide prior to application, as well as during application. There is a potential for post-application exposure for workers re-entering treated fields.

Risk assessments have been previously prepared for the existing uses of dicamba. This risk assessment considers all of the aforementioned exposure pathways based on the proposed new uses of dicamba, including the counter ions of its various salt forms such as the BAPMA salt, but also considers the existing uses as well, particularly for the dietary exposure assessment. There are several compounds that have been considered, including dicamba acid, the dicamba metabolites (DCSA, 5-OH dicamba, and DCGA), and the dicamba BAPMA counter ion. Separate assessments of dicamba acid, the dicamba metabolites (DCSA, 5-OH dicamba, and DCGA), and the BAPMA counter ion were not needed because the selected endpoints are protective of all forms.

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<sup>4</sup> Reregistration Eligibility Decision for Dicamba and Associated Salts. 2006-06-06

### 3.5 Population Considerations

As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the U.S. Department of Agriculture's National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age and ethnic group. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post-application are evaluated. Spray drift can also potentially result in post-application exposure, and it is also being considered whenever appropriate. Further considerations are also currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to other types of possible bystander exposures and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

### 4.0 Hazard Characterization and Dose-Response Assessment

Dicamba is a selective benzoic acid herbicide currently registered in various acid and salt formulations. The toxicology database for dicamba contains studies on dicamba acid, dicamba salt forms [isopropylamine (IPA) and diglycolamine (DGA), and N, N-Bis-(3-aminopropyl) methylamine (BAPMA)], and dicamba metabolites [DCSA, DCGA, and 5-hydrocydicamba (5-OH dicamba)]. Based on available toxicity studies and structural similarities, the various forms of dicamba are considered to be of comparable toxicity and are assessed concurrently.

#### 4.1 Toxicology Studies Available for Analysis

The toxicology database on dicamba is extensive and complete with respect to 870 guideline requirements for characterizing the hazard of dicamba, with routes of administration that are consistent with potential exposure scenarios. No new toxicological studies have been submitted since the last human health risk assessment conducted in support of registration review (P. Savoia *et al.*, D461765, 2021-04-21). The toxicology studies for dicamba acid, its salts [IPA, DGA, and BAPMA], and plant metabolites [DCSA, and DCGA] are summarized in Appendix A. A comparison of the toxicity endpoints between the acid, salt and metabolite form is also available in Table A.3.10. The data from the following studies were used to evaluate the hazard potential of dicamba, including the dicamba DGA salt and dicamba BAPMA salt formulations:

##### Dicamba Acid, IPA and DGA Salts:

- Sub-chronic Oral Study: 90-day oral toxicity (rat)
- Dermal Studies: 28-day dermal toxicity (rat), 21-day dermal toxicity (rabbit)
- Developmental Studies: rat and rabbit developmental toxicity studies
- Reproduction Study: 2-generation reproduction study (rat)

- Chronic Studies: combined oral chronic toxicity/carcinogenicity (rat), carcinogenicity (mouse), chronic oral toxicity (dog)
- Neurotoxicity Studies: acute and subchronic neurotoxicity (rat)
- Inhalation Study: 28-day inhalation study (rat)
- Immunotoxicity Study: Immunotoxicity (rat)
- Mutagenicity Battery
- Metabolism

#### DCSA Metabolite:

- Subchronic Studies: 90-day oral toxicity (rat), 90-day oral toxicity (dog)
- Developmental Studies: rat and rabbit developmental toxicity studies
- Reproduction Study: 2-generation reproduction study (rat)
- Chronic Study: combined oral chronic toxicity/carcinogenicity (rat)
- Mutagenicity Battery
- Metabolism

#### DCGA Metabolite:

- Sub-chronic Study: 28-day oral toxicity (rat)
- Mutagenicity Battery

#### Dicamba BAPMA Salt

- Inhalation Study: 28-day inhalation study (rat)
- 90-Day Oral Study in Rats
- Developmental Study (rat)
- Mutagenicity Battery

#### BAPMA Cation Base

- OECD 422 Reproduction/Developmental Study

## **4.2 Absorption, Distribution, Metabolism, & Elimination (ADME)**

The metabolism study in rats showed that following oral gavage administration at 400 mg/kg, dicamba is rapidly absorbed within a few hours and rapidly excreted. The phase I plasma half-life is less than 4 hours at doses of 400 mg/kg or lower and essentially all of the radio-labelled dicamba is eliminated in 48 hours. Over 95% of the administered dose is excreted in the urine. The compound is not metabolized nor accumulated by the tissues in adult, non-pregnant rats. However, approximately 13% of dicamba in the urine is conjugated as the glucuronide. In plants, dicamba is converted to the DCSA and DCGA metabolites, which have dietary exposures.

The gavage plasma pharmacokinetic studies in rats showed that absorption of radiolabeled dicamba was rapid, with peak plasma concentrations found within 2 hours of treatment. Absorption was not saturated, even at the highest dose (800 mg/kg), as indicated by increasing plasma concentrations with doses. However, the increase in plasma concentration was non-linear/disproportionate from one dose to the next dose and serum half-life increased with dose, which is consistent with saturation of excretion. Another plasma pharmacokinetic study suggests that dicamba is an inhibitor of renal anion

transport (i.e. urinary excretion) since co-dosing with an inhibitor of this process (i.e. probenecid) increased plasma levels of dicamba and decreased its clearance rate. No significant treatment-related differences between the genders were found. A DCSA study demonstrates that DCSA has a similar structure and metabolism as dicamba, with rapid absorption and rapid elimination. DCSA is poorly metabolized (except for some glucuronide conjugates) and predominantly excreted in the urine as the parent compound.

#### 4.2.1 Dermal Absorption

An acceptable guideline dermal absorption study is not available for dicamba. However, quantification of dermal risk is not required based on the lack of systemic toxicity at the limit dose (1000 mg/kg/day) following repeated application to rats and/or rabbits with the dicamba acid and the IPA and DGA salts. In addition, there was no concern for susceptibility based on the findings of the developmental and reproduction studies.

#### 4.3 Toxicological Effects

Reviewing the various toxicity studies on the different forms of dicamba acid, BAPMA salt, and DCSA plant metabolite, it appears that the mode of administration (i.e. gavage vs. dietary) had an impact on the type of toxicity observed for these compounds. For example, the repeat dietary administration demonstrated effects at higher doses than the acute gavage dosing. Following gavage administration, there were rapid onset of clinical signs at lower doses when compared to dietary administration as seen in the metabolism study.

The dicamba acid and dicamba BAPMA studies indicate that the nervous system is the major target following gavage exposure. These clinical signs include ataxia, decreased foot splay, decreased arousal and rears/minutes and decreased motor activity. For dicamba acid and the BAPMA salt, signs consistent with neurotoxicity were observed in several gavage studies in rats and rabbits without accompanying histopathology. For dicamba acid, when comparing the gavage acute neurotoxicity (ACN) study with the dietary sub-chronic neurotoxicity (SCN) study, the acute effect level was over 2.5X lower than the subchronic effect level for the same endpoints of rigidity and impaired gait and impaired righting reflex. The DCSA metabolite is less neurotoxic than dicamba acid. For DCSA, clinical signs were only evident at gavage doses of 1000 mg/kg or greater in the mouse micronucleus study (hypo-activity, squinted eyes, hunched posture) or the rat acute oral toxicity study at 2000 mg/kg (wobbly gait), while clinical signs for dicamba acid (hypo-activity, ataxia) were apparent at gavage doses of 250 mg/kg or greater in the mouse micronucleus assay. DCSA caused decreased body weight and increased creatinine levels (a measure of renal deficiency) in the rat 90-day dietary study at 659 mg/kg/day. DCSA produced decreased body weight, emesis, and an increase in clotting time in the dog sub-chronic 90-day oral study only at the highest doses tested (HDT, capsule, 150 mg/kg/day). Dicamba BAPMA caused increased clotting time and increased creatinine levels in the rat 90-day dietary study at the limit dose. However, in the gavage rat developmental study, dicamba BAPMA caused ataxia, unsteady gait and convulsions at 86 mg/kg/day. The creatinine effects, along with the pharmacokinetics/excretion data, suggests that the kidney is also a target organ and that adverse effects begin to occur at doses where kidney clearance starts to become non-linear. There was no evidence of immunotoxicity with the acid form.

Pre-natal developmental gavage toxicity studies in rats and rabbits, and two-generation reproduction studies in rats were available with the dicamba acid and the DCSA plant metabolite. The developmental studies in rats and rabbits showed no evidence (qualitative or quantitative) for increased susceptibility following *in utero* exposure of dicamba acid or the dicamba BAPMA salt. In the rat developmental studies for dicamba acid or dicamba BAPMA, there was no developmental toxicity up to the highest dose tested, but the BAPMA salt was approximately 4 times more toxic to the dams than dicamba acid based on the common effect of ataxia. A single incidence of abortion in the dicamba rabbit developmental toxicity study (1 in 20 does, 4 days after dosing ceased) occurred at a maternally toxic dose (manifested as ataxia and decreased motor activity). For the DCSA metabolite, there was no developmental toxicity up to the highest doses tested in the definitive studies in rats and rabbits. At higher doses in the DCSA developmental range-finding studies, there were decreased fetal weights in rats at the same dose that caused rales in the dams and dam deaths occurred at the highest dose tested in rabbits. In the OECD 422 reproduction/developmental screening study (870.3650) with the BAPMA base, decreased motor activity and water consumption were observed in dams at the mid dose while pronounced toxicity and deaths were observed in the dams at the highest dose tested (HDT). This OECD 422 study did not identify developmental toxicity. However, dicamba product exposure is not to the pure BAPMA base and the base composition in the dicamba BAPMA salt is only one-fourth that of the dicamba component in this salt form. Thus, the dicamba BAPMA salt rat developmental study PODs will be protective for the BAPMA base effects.

The BAPMA amine base does not require a separate assessment since the OECD 422 developmental/reproduction toxicity screening study on the pure compound had a LOAEL of 100 mg/kg/day based on decreased motor activity and water consumption with a NOAEL of 25 mg/kg/day. Thus, the dicamba BAPMA rat developmental study will be protective for its exposure and considering the BAPMA composition in this salt is 4 times less than the dicamba acid composition. Furthermore, the BAPMA cation is predicted to degrade much faster than the dicamba anion.

In contrast, following pre and/or post-natal exposures in the two-generation reproduction studies, the DCSA metabolite was more toxic to the offspring than the acid form. In the reproduction study with DCSA, offspring toxicity manifested as decreases in body weight at a dose (37 mg/kg/day) that is approximately 10-fold lower than the dose (362 mg/kg/day) that caused parental/systemic toxicity (decreased body weight) demonstrating increased susceptibility in the young. Furthermore, when the adverse effects observed in the offspring were compared for the two compounds (*i.e.* LOAEL comparison), the DCSA dose (37 mg/kg/day) at which decreased pup weight was observed was approximately 12-fold lower than the dicamba acid dose (450 mg/kg/day) that caused the same effect.

Conversely, in the reproduction study with dicamba acid there was no evidence (qualitative or quantitative) for increased susceptibility following *pre and/or* or postnatal exposure. Decreased pup body weights were observed in all generations and matings at the mid (136 mg/kg/day) (86 - 90% of control) and at the high (450 mg/kg/day) (74 - 94% of control) dose groups throughout lactation, relative to the concurrent controls. Based on detailed statistical analysis (multivariate) comparison with the MARTA historical control data (Middle-Atlantic Reproduction and Teratology Association, See Appendix A.6 for details), it was concluded that there was no adverse effect on pup body weights during the F1 generation lactation period or post-weaning phase at the low and mid dose groups. The offspring NOAEL was established at 136 mg/kg/day and the offspring LOAEL was 450 mg/kg/day based

on decreased pup weights in the F1 and F2B generations. At the 450 mg/kg/day dose, there were adverse decreases in the F1 pup body weights at PND 0 before the lactation phase.

In the dicamba acid, dicamba IPA and dicamba DGA salts sub-chronic dermal toxicity studies, there were no adverse effects observed up to the limit dose (1000 mg/kg/day). However, the dicamba BAPMA salt was demonstrated to be more toxic than dicamba acid via the inhalation route. The inhalation study for dicamba acid revealed hyperplasia in the lung with a clear NOEL, while the dicamba BAPMA salt produced hyperplasia and ulceration of the larynx at a dose approximately 35 times lower than dicamba acid effects and a NOEL was not established. The inhalation effects for both dicamba acid and the BAPMA salt were local and non-systemic.

Dicamba acid has a low acute toxicity via oral, dermal and inhalation routes (Acute Toxicity Categories III or IV). It is an eye irritant, but it is not a dermal irritant or skin sensitizer. The dicamba BAPMA base is Category II or III toxicity via oral, dermal or inhalation routes, but it is corrosive to the eyes and a dermal irritant and sensitizer. The dicamba BAPMA salt has a low acute toxicity via oral, dermal or inhalation route (Acute Toxicity Categories III or IV). The dicamba BAPMA salt is not a dermal irritant but is slightly irritating to the eye and is a skin sensitizer.

#### 4.4 Safety Factor for Infants and Children (FQPA Safety Factor)<sup>5</sup>

The FQPA SF may be reduced (i.e. 1X) for all exposure routes, except for inhalation for the BAPMA salt, for the following reasons:

1. The toxicity database for dicamba is complete and adequate for FQPA SF consideration.
2. For the dicamba acid, there is no evidence of increased susceptibility following *in utero* exposures to rats and rabbits and following pre and/or post-natal exposure to rats in a two-generation reproduction study. For the dicamba acid and BAPMA salt, no developmental toxicity was seen at the highest doses tested in the prenatal developmental studies with rats. Although quantitative offspring susceptibility was observed in the 2-generation reproduction study for the DCSA metabolite based on decreased pup weights, the degree of concern for the susceptibility is low because there is a well-established NOEL for offspring toxicity in that study and DCSA has rapid clearance. Additionally, the current points of departure are health protective and therefore address the concern for offspring toxicity observed in this reproduction study.
3. Consistent neurotoxic signs (e.g., ataxia, decreased motor activity, impaired righting reflex and gait) were observed in multiple studies in rats and rabbits. After considering the available toxicity data, EPA determined that there is no need for a developmental neurotoxicity study or additional UFs to account for neurotoxicity for the following reasons: (1) although clinical signs of neurotoxicity were seen in pregnant animals, no evidence of developmental anomalies of the fetal nervous system were observed in the prenatal developmental toxicity studies, in either rats or rabbits, at maternally toxic doses up to 300 or 400 mg/kg/day, respectively; (2) there was no evidence of behavioral or neurological effects on the offspring in the two-generation reproduction study in rats; (3) the ventricular dilation of the brain in the combined chronic

<sup>5</sup> HED's standard toxicological, exposure, and risk assessment approaches are consistent with the requirements of EPA's children's environmental health policy (<https://www.epa.gov/children/epas-policy-evaluating-risk-children>).

toxicity and carcinogenicity study in rats was only observed in females at the high dose after two years of exposure at doses of 127 mg/kg/day. The significance of this observation is questionable, since no similar histopathological finding was seen in two sub-chronic neurotoxicity study at the limit dose or other chronic studies.

4. There are no residual uncertainties identified in the exposure databases. The dietary food exposure assessments were performed based on tolerance-level residues for the acute dietary, average field trial data for the chronic dietary and available % crop-treated information. Conservative ground and surface water modeling estimates were used. Similarly, conservative residential SOPs were used to assess residential exposure. These assessments will not underestimate the exposure and risks posed by dicamba.

However, the 10X FQPA SF is retained for assessing inhalation risks for the dicamba BAPMA salt. The FQPA SF is retained in the form of a LOAEL to NOAEL factor ( $UF_L$ ) since the POD used was a LOAEL (See Table 4.5.3.1).

#### **4.4.1 Completeness of the Toxicology Database**

The toxicity database for dicamba is adequate in terms of endpoint selection and dose response information to characterize the potential for prenatal or postnatal risk to infants and children. The database contains acceptable prenatal developmental studies in both the rat and rabbit, two rat 2-generation reproduction studies, an immunotoxicity study in rats and both acute and subchronic neurotoxicity studies in rats.

#### **4.4.2 Evidence of Neurotoxicity**

There is evidence of neurotoxicity resulting from exposure to dicamba throughout the toxicology database (i.e. impaired gait, impaired righting reflex, ataxia, decreased motor activity, rigidity upon handling, etc). After consideration of the available toxicity data, the Agency determined that a DNT is not required, as described previously.

#### **4.4.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal**

No evidence of increased susceptibility was observed in the rat or rabbit prenatal developmental studies or the 2-generation reproduction toxicity studies following exposure to dicamba acid, dicamba BAPMA salt, or DCSA.

Increased quantitative susceptibility was observed in the 2-generation reproduction study for the DCSA metabolite based on decreased pup weights. However, the degree of concern is low as there is a well-established NOAEL for offspring toxicity in the study and DCSA has rapid clearance. Additionally, the current PODs are health protective and therefore address the concern for offspring toxicity observed in the reproduction studies.

#### **4.4.4 Residual Uncertainty in the Exposure Database**

There are no residual uncertainties identified in the exposure databases. The dietary food exposure assessments were performed based on tolerance-level residues for the acute dietary, average field trial

data for the chronic dietary and available % crop-treated information. Conservative ground and surface water modeling estimates were used. Similarly, conservative residential SOPs were used to assess residential exposure. These assessments will not under-estimate the exposure and risks posed by dicamba.

#### 4.5 Toxicity Endpoint and Point of Departure Selections

The toxicology database for dicamba is complete for assessing potential exposures to the proposed dicamba DGA salt and dicamba BAPMA salt formulations. No additional data are required, nor are additional updates required at this time. The dietary, incidental oral and dermal endpoint determinations for dicamba are protective for assessing anticipated exposures from dicamba acid, DGA salt and BAPMA salt end-use products. However, due to differences in the toxicological inhalation endpoints between the dicamba acid (which is protective of the DGA salt form) and BAPMA salt forms, separate inhalation PODs have been selected for these assessments. The endpoints, doses, and safety factors used for assessing human health risks from exposure to dicamba remain current and are summarized below in Table 4.5.3.1.

*Acute Dietary Exposure (General Population):* The rat developmental study for the dicamba BAPMA salt was selected to assess a single oral exposure of the general population, including infants and children, to dicamba acid or its BAPMA salt. The NOAEL is 29 mg/kg/day, and the LOAEL is 86 mg/kg/day based on clinical signs of neurotoxicity (ataxia, unsteady gait and convulsions) in the dams. This finding is considered appropriate for the acute duration of exposure since the signs occurred within 3 hours after dosing. This study was selected because it represents the most sensitive endpoint in the dicamba database for exposure to the parent dicamba acid or its BAPMA salt demonstrating an acute response with a well-defined NOAEL value. The selected POD will be protective of the effects of dicamba acid and the BAPMA salt via the oral route. A separate acute dietary assessment for females 13-49 was not performed since there was no developmental toxicity attributed to a single dose in the toxicology data base. The single incidence of abortion in the rabbit developmental study occurred late in gestation and therefore is likely not from a single exposure.

An uncertainty factor of 100X (10X to account for interspecies extrapolation, 10X for intraspecies variation, and 1X for FQPA SF) is applied to the NOAEL to obtain an acute RfD of 0.29 mg/kg/day. Since the FQPA SF is reduced, the acute Population Adjusted Dose (PAD) is equivalent to the acute RfD (0.29 mg/kg/day).

*Chronic Dietary Exposure (all populations):* The chronic dietary scenario for dicamba acid and all of its salt forms is based on decreased pup weights observed at 37 mg/kg/day (LOAEL) in a reproduction study on the DCSA plant metabolite; the NOAEL of 4 mg/kg/day is selected for deriving the chronic RfD. This POD is protective of all chronic effects seen following exposure to dicamba acid or dicamba BAPMA salt. An uncertainty factor of 100X (10X to account for interspecies extrapolation, 10X for intraspecies variation, and 1X for FQPA SF) is applied to the NOAEL to obtain a chronic RfD of 0.04 mg/kg/day. Since the FQPA SF was reduced, the chronic PAD is equivalent to cRfD (0.04 mg/kg/day).

*Short-Term Incidental Oral Exposure:* The toxicology studies on the plant metabolites are not appropriate for this scenario since these metabolites are generated inside the plants and unavailable

for incidental oral exposure. The developmental studies are not appropriate for incidental oral scenarios involving hand-to-mouth behavior. The dicamba BAPMA salt has no residential uses other than potential for spray drift. The most appropriate study was the multi-generation reproductive toxicity study in rats dosed with parent compound and was selected based on impaired pup growth at 450 mg/kg/day (LOAEL); the NOAEL of 136 mg/kg/day was selected as the POD for this scenario. The Level of Concern (LOC) is a Margin of Exposure (MOE) of 100 which includes the 10X factor accounts for interspecies extrapolation, a 10X factor accounts for intraspecies variation, and a 1X FQPA SF.

*Short- and Intermediate-Term Inhalation Exposures:* The dose and endpoint selected for dicamba acid and dicamba BAPMA risk assessment utilized the route-specific aerosol inhalation studies for each AI. For the dicamba acid inhalation risk assessment (short and intermediate term durations), the POD was based on the route-specific dicamba acid inhalation toxicity study in Wistar rats with a LOAEC of 0.050 mg/L based on local effects of hyperplasia in the lungs and lymph nodes (NOAEC = 0.005 mg/L, non-systemic, pulmonary RDDR = 0.590). The dose and endpoint selected for the dicamba BAPMA salt inhalation risk assessment for short and intermediate term durations were based on the dicamba BAPMA salt inhalation toxicity study in rats with a LOAEC of 0.0014 mg/L based on local effects of hyperplasia and ulceration of the larynx (no NOAEC, non-systemic, extra-thoracic RDDR = 0.190).

The standard interspecies extrapolation UF can be reduced from 10X to 3X for dicamba acid and BAPMA salt due to the calculation of human equivalent concentrations (HECs) accounting for pharmacokinetic (not pharmacodynamic) interspecies differences. Therefore, the LOC for dicamba acid inhalation exposures is for MOEs less than 30 (3X for interspecies extrapolation, 10X for intraspecies variation, and 1X for FQPA SF when applicable). For BAPMA salt, an additional 10X UFL is applied due to lack of a NOAEL; therefore, the LOC for BAPMA salt inhalation exposures is for MOEs less than 300. The inhalation HEC/HED results are listed in Table 4.5.3.2 and 4.5.3.3.

*Short- and Intermediate-term Dermal Exposures:* A dermal endpoint was not selected as there are no adverse systemic effects up to the limit dose (1000 mg/kg/day) in the dermal studies for dicamba acid, IPA salt and DGA salt. Additionally, the dicamba anion is the major component in the BAPMA salt and the BAPMA base component of the dicamba BAPMA salt is only 20% of the salt mass (and 28% on a molar basis), thus, the dicamba BAPMA salt is unlikely to have adverse dermal effects. In support, the acute dermal toxicity for the dicamba BAPMA salt is low (Category IV).

The detailed description of the toxicity studies considered for selecting toxicity endpoints and PODs for various exposure scenarios are presented in Appendix A.

#### **4.5.1 Recommendation for Combining Routes of Exposures for Risk Assessment**

When there are potential occupational and residential exposures to a pesticide, the risk assessment must address exposure from the three major routes (oral, dermal and inhalation) and determine whether the individual exposures from these routes can be combined. If two or more exposures have endpoints based on the same target organ or system, then they can be combined. Since there is no dermal hazard identified for dicamba, and the inhalation and incidental oral endpoints are selected based on different toxicological effects; the incidental oral, dermal and inhalation routes should not be combined.

#### 4.5.2 Cancer Classification and Risk Assessment Recommendation

In accordance with the EPA Final Guidelines for Carcinogen Risk Assessment (March 29, 2005), dicamba is classified as “*Not Likely to be Carcinogenic to Humans*”. This decision was based on the lack of findings in the cancer studies in rats and mice which were tested at adequate dose levels to assess the carcinogenicity of dicamba (J. Kidwell, TXR No. 0053647, 2005-08-16).

Mutagenicity studies generally did not demonstrate evidence of mutagenic potential for dicamba although some positive results were reported *in vitro*. Dicamba acid and the dicamba BAPMA salt both induced chromosomal aberrations in human lymphocytes *in vitro*, however, genotoxicity was negative *in vivo* in the mouse micronucleus assay, thus the concern for genotoxicity for dicamba or its salts is low. The BAPMA base was negative for genotoxicity in bacteria, but positive for genotoxicity based on *in vitro* mammalian cell culture. Additionally, the DCSA metabolite also had a lack of findings in a chronic/carcinogenicity study in rats.

#### 4.5.3 Summary of Points of Departure and Toxicity Endpoints Used in Human Risk Assessment

<b>Exposure/ Scenario</b>	<b>POD</b>	<b>UF, FQPA SF/ RfD, PAD, LOC</b>	<b>Study and Toxicological Effects</b>
Acute Dietary (General population including infants and children)	NOAEL = 29 mg/kg/day (20 mg/kg/day as acid equivalent)	UF <sub>A</sub> =10X UF <sub>H</sub> =10X FQPA SF = 1X  aRfD = 0.29 mg/kg/day aPAD = 0.29 mg/kg/day	<b>Dicamba BAPMA Salt</b> <b>Rat Prenatal Developmental Study</b>  <b>Maternal</b> LOAEL = 86 mg/kg/day in dams, based on ataxia, unsteady gait and convulsions observed shortly after dosing (60 mg/kg/day as acid equivalent)  <b>Developmental</b> NOAEL > 288 mg/kg/day (200 mg/kg/day as acid equivalent)
Acute Dietary (Females 13-49 years of age)	N/A	N/A	No developmental toxicity attributed to acute exposure in the toxicology database. The abortions in the rabbit developmental study occurred at gestation day 22.
Chronic Dietary (All populations)	Offspring NOAEL= 4 mg/kg/day	UF <sub>A</sub> =10X UF <sub>H</sub> =10X FQPA SF = 1X  cRfD = 0.04 mg/kg/day cPAD = 0.04 mg/kg/day	<b>DCSA Metabolite</b> <b>Rat Reproductive Toxicity Study</b>  Offspring LOAEL = 37 mg/kg/day based on decreased pup weights in F1 generation on PND 14 and 21 (both sexes) and week 18 (females)
Short-Term (1 - 30 Days) Incidental Oral	Offspring NOAEL= 136 mg/kg/day	Residential LOC = 100  UF <sub>A</sub> =10X UF <sub>H</sub> =10X FQPA SF = 1X	<b>Dicamba Acid</b> <b>Rat Reproductive Toxicity Study</b>  Offspring LOAEL=450 mg/kg/day based on decreased pup weights.
Short- and Intermediate-term Dermal	No dermal assessment for dicamba acid or salts since the dermal toxicology studies for dicamba acid, IPA and DGA salts all had NOAELs of 1000 mg/kg/day.		

**Table 4.5.3.1. Toxicological Doses and Endpoints for Dicamba Acid and Dicamba BAPMA Salt for use in Human Health Risk Assessments**

Exposure/ Scenario	POD	UF, FQPA SF/ RfD, PAD, LOC	Study and Toxicological Effects
<u>Dicamba Acid</u> Short- and Intermediate-Term Inhalation	NOAEL=0.005/0.005 mg/L (M/F) See Table 4.5.3.2 for HEC/HED Calculations	Residential/ Occupational LOC = 30  UF <sub>A</sub> = 3X UF <sub>H</sub> = 10X FQPA SF = 1X	<b>Dicamba Acid</b> <b>Rat Aerosol Inhalation Study</b>  NOAEL=0.005/0.005 mg/L (M/F) LOAEL=0.050/0.050 mg/L (M/F), based on minimal multifocal bronchiole-alveolar hyperplasia in males; multiple microscopic findings in the lung and associated lymph nodes in females
<u>Dicamba BAPMA Salt</u> Short- and Intermediate-Term Inhalation	LOAEL = 0.0014 mg/L (0.001 mg/L as acid equivalent) See Table 4.5.3.3 for HEC/HED Calculations	Residential/Occupational LOC = 300  UF <sub>A</sub> = 3X UF <sub>H</sub> = 10X UF <sub>L</sub> = 10X	<b>Dicamba BAPMA Salt</b> <b>Rat Inhalation Study</b>  NOAEL=NA LOAEL=0.0014 mg/L (LDT), based on ulcers in epithelial tissues of the larynx and single/multifocal hyperplasia in the larynx (0.001 mg/L as acid equivalent)
Cancer (Oral, dermal, inhalation)	Dicamba is classified as "Not Likely to be Carcinogenic to Humans".		

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF<sub>A</sub> = extrapolation from animal to human (interspecies). UF<sub>H</sub> = potential variation in sensitivity among members of the human population (intraspecies). UF<sub>L</sub> = use of a LOAEL to extrapolate a NOAEL. UF<sub>S</sub> = use of a short-term study for long-term risk assessment. FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

**Table 4.5.3.2. Summary of HEC/HED values for Dicamba Acid\*.**

Population	Scenario	Toxicity Duration Adjustment <sup>A</sup>		HEC <sup>B</sup>		HED (mg/kg/day) <sup>H</sup>
		Daily	Weekly	mg/L	mg/m <sup>3</sup>	
Occupational	Handler	8	5	0.002 <sup>C</sup>	2.21	0.21 <sup>I</sup>
Residential	Handler	NA	NA	0.003 <sup>D</sup>	2.95	0.07 <sup>J</sup>
	Outdoor post-application	NA	NA	0.003 <sup>E</sup>	2.95	0.08 <sup>K</sup>
	Indoor post-application	NA	7	0.002 <sup>F</sup>	2.11	0.05 <sup>L</sup>
	Bystander	24	7	0.001 <sup>G</sup>	0.53	--

\*The inhalation values have been calculated based on the 2016 revised spreadsheets. The HED calculation has been revised to be based on the same breathing rate used to derive the HEC – resulting in a single HED as the toxicological point of departure. In terms of risk estimates, the effect of this error correction is not unidirectional – some previously-calculated risks will be higher, while some will be lower.

NA = not applicable (the expected duration of the exposure scenario is less than the duration in the available inhalation toxicity studies; downward adjustments are not permitted).

<sup>A</sup> Toxicity duration adjustment from 6 hours/day, 5 days/week in the route-specific inhalation study.

<sup>B</sup> HEC = human-equivalent concentration; HEC = rat POD x daily duration adjustment x weekly daily duration adjustment x RDDR.

<sup>C</sup> Occupational Handler HEC (portal of entry endpoint) = 0.005 mg/L \* (6 hrs/8 hrs) \* (5 days/5 days) \* 0.59 = 0.002 mg/L

<sup>D</sup> Residential Handler HEC (portal of entry endpoint) = 0.005 mg/L \* 0.59 = 0.003 mg/L

<sup>E</sup> Residential Outdoor Post Application HEC (portal of entry endpoint) = 0.005 mg/L \* 0.59 = 0.003 mg/L

<sup>F</sup> Residential Indoor Post Application HEC (portal of entry endpoint) = 0.005 mg/L \* (5 days/7 days) \* 0.59 = 0.002 mg/L

<sup>G</sup> Residential Bystander HEC (portal of entry endpoint) = 0.005 mg/L \* (6 hrs/24 hrs) \* (5 days/7 days) \* 0.59 = 0.001 mg/L

<sup>H</sup> HED = human-equivalent dose; HED = HEC (mg/L) x human specific conversion factor (11.8 L/hr-kg) x respiratory tract to oral absorption ratio (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).

<sup>I</sup> (0.0022 mg/L) x (11.8 L/hr/kg) x 1 x (8 hrs) = 0.21 mg/kg/day

<sup>J</sup> (0.003 mg/L) x 1 x (11.8 L/hr/kg) x (2 hrs) = 0.07 mg/kg/day

<sup>K</sup> (0.003 mg/L) x 1 x (11.8 L/hr/kg) x (2.3 hrs) = 0.08 mg/kg/day

<sup>L</sup> (0.002 mg/L) x 1 x (11.8 L/hr/kg) x (2 hrs) = 0.05 mg/kg/day

Population	Scenario	Toxicity Duration Adjustment <sup>A</sup>		HEC <sup>B</sup>		HED (mg/kg/day) <sup>H</sup>
		Daily	Weekly	mg/L	mg/m <sup>3</sup>	
Occupational	Handler	8	5	0.00 <sup>C</sup>	0.20	0.02 <sup>I</sup>
Residential	Handler	NA	NA	0.00 <sup>D</sup>	0.27	0.01 <sup>J</sup>
	Outdoor post-application	NA	NA	0.00 <sup>E</sup>	0.27	0.01 <sup>K</sup>
	Indoor post-application	NA	7	0.00 <sup>F</sup>	0.19	0.00 <sup>L</sup>
	Bystander	24	7	0.00 <sup>G</sup>	0.05	--

\*The inhalation values have been calculated based on the 2016 revised spreadsheets. The HED calculation has been revised to be based on the same breathing rate used to derive the HEC – resulting in a single HED as the toxicological point of departure. In terms of risk estimates, the effect of this error correction is not unidirectional – some previously-calculated risks will be higher, while some will be lower.

NA = not applicable (the expected duration of the exposure scenario is less than the duration in the available inhalation toxicity studies; downward adjustments are not permitted).

<sup>A</sup> Toxicity duration adjustment from 6 hours/day, 5 days/week in the route-specific inhalation study.

<sup>B</sup> HEC =human-equivalent concentration; HEC = rat POD x daily duration adjustment x weekly daily duration adjustment x RDDR.

<sup>C</sup> Occupational Handler HEC (portal of entry endpoint) = 0.0014 mg/L \* (6 hrs/8 hrs) \* (5 days/5 days) \* 0.19 = 0.0002 mg/L

<sup>D</sup> Residential Handler HEC (portal of entry endpoint) = 0.0014 mg/L \* 0.19 = 0.0003 mg/L

<sup>E</sup> Residential Outdoor Post Application HEC (portal of entry endpoint) = 0.0014 mg/L \* 0.19 = 0.0003 mg/L

<sup>F</sup> Residential Indoor Post Application HEC (portal of entry endpoint) = 0.0014 mg/L \* (5 days/7 days) \* 0.19 = 0.0001 mg/L

<sup>G</sup> Residential Bystander HEC (portal of entry endpoint) = 0.0014 mg/L \* (6 hrs/24 hrs) \* (5 days/7 days) \* 0.19 = 0.00005 mg/L

<sup>H</sup> HED =human-equivalent dose; HED = HEC (mg/L) x human specific conversion factor (11.8 L/hr-kg) x respiratory tract to oral absorption ratio (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).

<sup>I</sup> (0.0002 mg/L) x 1 x (11.8 L/hr/kg) x 1 x (8 hrs)= 0.02 mg/kg/day

<sup>J</sup> (0.0003 mg/L) x 1 x (11.8 L/hr/kg) x (2 hrs)= 0.01 mg/kg/day

<sup>K</sup> (0.0003 mg/L) x 1 x (11.8 L/hr/kg) x (2.3 hrs)= 0.01 mg/kg/day

<sup>L</sup> (0.0001 mg/L) x 1 x (11.8 L/hr/kg) x (2 hrs)= 0.002 mg/kg/day

## 5.0 Dietary Exposure and Risk Assessment

### 5.1 Metabolite/Degradate Residue Profile

#### 5.1.1 Summary of Plant and Animal Metabolism Studies

For non-dicamba-tolerant plants, the nature of the residue was previously determined to be understood (C. L. Olinger, D317699, 2005-12-20). Prior plant metabolism studies were reviewed in part with the 1983 residue chemistry chapter of the dicamba registration standard. The studies demonstrate that dicamba is rapidly absorbed and translocated by grasses, grapes, black valentine beans, wheat and bluegrass, as well as in soybeans. Dicamba is metabolized in plants mainly by demethylation and hydroxylation.

For dicamba-tolerant cotton, previously-submitted metabolism study data demonstrate that metabolism was found to occur at an appreciable rate with the first step in the process being demethylation of parent into the DCSA metabolite. Residue levels were considerably lower for the pre-emergence samples in comparison to those obtained following post-emergence treatment. Parent dicamba was identified in all the matrices tested which include both gin byproducts and in seed at lower levels. The metabolites DCSA glucoside, DCSA, and DCGA glucoside were found to be present in all matrices as well. The 5-OH dicamba metabolite was not identified in any matrix. For dicamba-tolerant cotton, DCSA glucoside was the major metabolite obtained with the highest levels being found in the gin byproducts samples. These data are summarized in (P. Savoia, D408384, 2016-03-29).

For dicamba-tolerant soybean, previously-submitted metabolism study data demonstrate that the dicamba metabolites were DCSA glucoside (60.32-74.48% of total radioactive residue (TRR)), which was the major component in dicamba-tolerant soybean, DCSA HMGglucoside (1.14-7.62% of TRR), DCGA glucoside (0.75-4.32%), DCGA malonylglucoside (0.73-5.46% of TRR), and DCSA (1.54-4.08% of TRR), in addition to two minor un-identified metabolites characterized as mixtures of unknown DCSA and DCGA conjugates, each constituting less than 2.0% of the TRR. The metabolite 5-OH dicamba, which is part of the current tolerance expression, has not been detected. These data are summarized in (A. Kamel, D384422, 2013-04-17).

The nature of dicamba residues in animals was previously determined based on acceptable metabolism studies conducted on ruminants and poultry (L. Cheng, D204482, 1996-03-07). The residues of concern in meat, milk, poultry and eggs consisted of dicamba and DCSA [40 CFR §180.227 (a)(2)].

The nature of the dicamba residue in rotational crops was previously reviewed. It has been concluded that limited and/or extensive field accumulation studies with dicamba were not necessary and rotational crop tolerances need not be established provided the registrants amended all dicamba labels to specify a 120-day plant-back interval (PBI) when dicamba is applied at a maximum seasonal rate of 0.75 lb ae/A or less. At application rates of 0.75-2.0 lb ae/A, only crops with established tolerances can be rotated for planting. A 0-day PBI is listed on the labels for dicamba-tolerant cotton and dicamba-tolerant soybean (when dicamba is applied at a single maximum rate of 0.5 lb ae/A).

### 5.1.2 Summary of Environmental Degradation

Dicamba is very soluble in water (6100 ppm) and very mobile ( $K_{oc} = 13.4$ ) in the laboratory. Because dicamba is not persistent under aerobic conditions, very little dicamba could be expected to leach to groundwater. If any dicamba did reach anaerobic ground water, it would be somewhat persistent (due to its anaerobic half-life of 141 days); any DCSA that reached ground water would be expected to persist. Results from two acceptable field dissipation studies conducted with dimethylamine salt of dicamba, indicated that dicamba dissipated with a half-life range of 4.4 to 19.8 days. The DCSA was the major degradate in both studies. Both, dicamba and its degradate (DCSA) were found in soil segments deeper than 10 cm.

Aerobic soil metabolism is the main degradative process for dicamba. A single observed half-life for dicamba was six days; with formation of the intermediate non-persistent degradate DCSA. DCSA degraded at roughly the same rate as dicamba; the final metabolites were carbon dioxide and microbial biomass. Dicamba is stable to abiotic hydrolysis at all pH's and photodegrades slowly in water and on soil. Dicamba is more persistent under anaerobic soil:water systems in the laboratory, with a half-life of 141 days. The major degradate under anaerobic conditions was DCSA, which was persistent, comprising > 60% of the applied dose after 365 days of anaerobic incubation. No other anaerobic degradates were present at > 10% during the incubation. There are no acceptable data for the aerobic aquatic metabolism of dicamba; supplemental information indicates that dicamba degrades more rapidly in aquatic systems when sediment is present (I. Abdel-Saheb, D317705, 2005-05-31).

Dicamba is not expected to bioaccumulate in aquatic organisms because it is an anion (pH of 2.5-3.0) at environmental pHs.

### 5.1.3 Comparison of Metabolic Pathways

The metabolism of dicamba is qualitatively similar in all plants. Dicamba is metabolized in plants mainly by demethylation and hydroxylation. The main metabolites are 5-OH dicamba and DCSA. The DCGA metabolite has been identified in dicamba-tolerant plants. DCGA is formed by the hydroxylation of DCSA. In dicamba tolerant plants, the relative amounts of the metabolites DCSA, 5-OH dicamba and DCGA vary significantly when compared to the corresponding dicamba non-tolerant plants.

Metabolism in ruminants was similar to poultry, the metabolism proceeds in a similar fashion to that seen in plants described above, however, an additional metabolite, 2-amino-3,6-dichlorophenol has been identified in low amounts only in hen liver. In rat, dicamba is rapidly absorbed and excreted. The compound is not metabolized or accumulated by the tissues.

### 5.1.4 Residues of Concern Summary and Rationale

The risk assessment team for dicamba-tolerant cotton and soybean met in consultation with the co-chairs of the HED Residues of Concern Knowledgebase Sub-committee (ROCKS) on 18-MAR-2013 to discuss determining the residues of concern (ROC) for tolerance and risk assessment. For cotton, the ROC for both tolerance expression and risk assessment were determined to be parent dicamba, DCSA, and 5-OH dicamba. For soybean, the ROC for tolerance setting were determined to be parent dicamba, DCSA, and 5-OH dicamba, but for soybean risk assessment, the ROC were parent dicamba, DCSA, DCGA and 5-OH dicamba (A. Kamel & P. Savoia, D410934, 2013-06-03). However, after review of the field corn residue data submitted to support the registration of dicamba on genetically modified dicamba-tolerant field corn in 2018 (PP#8F8659), the ROCKS was consulted for reassessment of the ROC in plants for both tolerance enforcement and risk assessment. For all plant crops, the ROCKS recommended that the ROC for tolerance enforcement be updated to exclude metabolite DCGA and that all crop tolerances, currently regulated in three separate subparts of the 40 CFR CFR §180.227, be harmonized and consolidated into a single tolerance expression under 40 CFR §180.227(a)(1) (P. Savoia, D450731, 2019-03-05). Given that the analytical enforcement method detects all proposed ROC, there is no need for differences between the ROC for tolerance expression and risk assessment. Therefore, the ROC in plants for both tolerance enforcement and risk assessment are parent dicamba, DCSA, and 5-OH dicamba (P. Savoia, D450731, 2019-03-05).

The rationale for this decision follows that residues present in both cotton and dicamba-tolerant cotton were comprised of dicamba, and its metabolites, 5-OH dicamba, DCSA, and DCGA. However, dicamba, 5-OH dicamba, and DCSA account for the majority of the residues in both tolerant and non-tolerant cotton and will provide sufficient residues with which to monitor for misuse for both tolerant and non-tolerant cotton; therefore, the ROC for tolerance setting purposes is dicamba, 5-OH dicamba, and DCSA. For the purpose of risk assessment, HED considered both the exposure and hazard profiles for dicamba, 5-OH dicamba, DCSA, and DCGA and is including dicamba, 5-OH dicamba, and DCSA as the ROC for tolerant and non-tolerant cotton. While DCGA may be of comparable toxicity, it was present in the cotton metabolism studies at less than 10% of the TRR, and is only detected in livestock feed items, not in human food items. Further, inclusion of this metabolite as a ROC in feed items would have no material impact on the livestock dietary burden since calculation of the reasonably balanced livestock diets are driven by other feed items with far higher residues. Therefore, HED is not including the DCGA

metabolite as a ROC for risk assessment. For dicamba-tolerant soybean, the total concentration of DCGA is 10-fold less on average in comparison to conventional (non dicamba-tolerant) crops. As a result, conventional crop data are used for dietary exposure assessments since they provide a more conservative estimation of residues in soybean commodities. Therefore, HED is not including metabolite DCGA as a ROC for risk assessment in soybean as these residues are considered negligible. Currently available metabolism and field trial studies for dicamba-tolerant soybean, demonstrate that residues present in both soybean and dicamba-tolerant soybean were comprised of dicamba, 5-OH dicamba, DCSA and DCGA (A. Kamel, D384422, 2013-04-17). HED evaluated both the exposure and hazard profiles for dicamba, 5-OH dicamba, DCSA and DCGA. Based on available toxicity studies and structural similarities, HED considers the parent and all three metabolites to be of comparable toxicity. Current data support the existing tolerance expression for dicamba on soybean which includes parent dicamba, the DCSA metabolite and the 5-OH dicamba metabolite found in non-resistant varieties as the residues monitored in the tolerance expression. Since dicamba, 5-OH dicamba, and DCSA account for the majority of residues in tolerant and/or non-tolerant soybean, this tolerance expression provides sufficient residues to monitor for misuse for both tolerant and non-tolerant soybean; therefore, the ROC for tolerance setting purposes and risk assessment are dicamba, 5-OH dicamba and DCSA. The residues of concern that are included for tolerance expression and risk assessment based on all the available data for dicamba are presented below in Table 5.1.4.

<b>Matrix</b>	<b>Tolerance Expression</b>	<b>Residues for Risk Assessment</b>
Plants <sup>1,2</sup>	Dicamba + 5-OH dicamba + DCSA (free and conjugated)	Dicamba + 5-OH dicamba + DCSA (free and conjugated)
Livestock <sup>1,2</sup>	Dicamba + DCSA (free and conjugated)	Dicamba + DCSA (free and conjugated)
Drinking Water	NA <sup>3</sup>	Dicamba + DCSA (free and conjugated)

<sup>1</sup> DCSA also referred to as 3,6-dichloro-2-hydroxybenzoic acid or as 3,6-dichlorosalicylic acid.

<sup>2</sup> OH-Dicamba also referred to as 5-hydroxydicamba.

<sup>3</sup> NA – Not Applicable.

## 5.2 Food Residue Profile

Permanent tolerances are currently established for residues of dicamba, including its metabolites and degradates, in/on agricultural commodities under 40 CFR §180.227(a)(1). For the proposed uses of dicamba DGA salt and dicamba BAPMA salt on dicamba-tolerant cotton and dicamba-tolerant soybean, adequate crop field trial data are available (W. Irwin, D378366, 2016-03-29) and have been reviewed by HED in support of these requests.

The residue chemistry database for dicamba is adequate to support the proposed new uses on dicamba-tolerant cotton and dicamba-tolerant soybean. The nature of the residue is adequately understood based on available metabolism studies for wheat, grape, asparagus, sugarcane, cotton, and soybean, as well as on dicamba-tolerant cotton, dicamba-tolerant corn, and dicamba-tolerant soybean. Data on the metabolism of dicamba in dicamba-tolerant cotton and dicamba-tolerant soybean demonstrate that dicamba is rapidly absorbed and translocated in the plants. Adequate storage stability data are available which demonstrate residues of dicamba are stable when stored frozen in dicamba-tolerant soybeans for up to 9.6 months, and dicamba-tolerant cotton for up to 6 months.

The available crop field trial data (P. Savoia *et al.*, D461765, 2021-04-21; P. Savoia, D408384, 2016-03-29; A. Kamel, D384422, 2013-04-17) and bridging data to demonstrate product equivalency between the dicamba formulations are adequate (P. Savoia, D429868 & D429964, 2016-03-29).<sup>6</sup> These data demonstrate that the average combined residues of dicamba are protective for potential residues resulting from the use of dicamba BAPMA salt formulations, which fall below established tolerance limits. Processing study data were provided and residues of dicamba were found not to concentrate in the processed commodities of dicamba-tolerant cotton, but slightly concentrated in soybean hull (1.4 ×), flour (1.2 ×) and meal (1.3 ×) fractions. Based on the maximum residues found in soybean seeds and processed fractions using a 50% exaggerated application rate, the existing tolerances for soybean commodities are adequate. Permanent tolerances are currently established for residues of dicamba, including its metabolites and degradates, in/on cotton and soybean commodities under 40 CFR §180.227(a)(3).

The nature of the residue is adequately understood in livestock based on previous metabolism studies made on ruminants and poultry. The highest levels of dicamba residues in beef accumulated in kidney and liver tissues. The occurrence of quantifiable residues of dicamba or DCSA in poultry eggs and meat as a result of treating crops with poultry feed items at the maximum use patterns are not anticipated. Permanent tolerances are currently established for residues of dicamba, including its metabolites and degradates, in/on livestock commodities under 40 CFR §180.227(a)(2).

These data remain current and have been incorporated for dietary risk assessment.

### 5.3 Water Residue Profile

The EDWCs used in the dietary risk assessment were provided by EFED in the following memorandum: “Drinking Water Memo for the Registration Review of Dicamba Acid, Salts, and Degradate 3,6-dichlorosalicylic acid (DCSA)” (C. Peck, D460422, 2021-03-04) and incorporated directly into this dietary assessment. This assessment remains current as no new fate data have been submitted and it was derived with the latest models used by EFED for estimating pesticide residues in drinking water (email communication, M. Corbin to M. Jackson, 2024-11-21). Water residues were incorporated in the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID) into the food categories “water, direct, all sources” and “water, indirect, all sources.”

For this determination, EFED conducted a Tier I Pesticide Root Zone Model for GroundWater (PRZM GW) drinking water assessment from groundwater sources for the proposed new use. Residues of concern for drinking water for risk assessment purposes were the parent and its DCSA metabolite. Table 5.3.1 and Table 5.3.2 provide the modeling estimates for drinking water summarized from surface water and ground water sources for dicamba and DCSA, respectively. For the purposes of this assessment, the highest (most conservative) PRZM-GW values were used for the acute (329 ppb parent + 0.041 ppb DCSA) and chronic (187 ppb parent + 0.041 ppb DCSA) assessments.

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<sup>6</sup> Dicamba is available in acid or salt forms. When the dicamba BAPMA salt product was first registered, bridging data were provided to demonstrate equivalency of residues resulting from the various forms of dicamba.

The drinking water models and their descriptions are available at the EPA internet site:  
<https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/models-pesticide-risk-assessment>

Model	Use/Scenario	Acute (µg/L)	Chronic (µg/L)	30-year average (µg/L)
SW (PRZM/EXAMS)	CAcotton_wirrgSTD.txt	7.72	6.62	1.07
	MScottonSTD.txt	<b>53.37</b>	<b>44.5</b>	<b>6.52</b>
	NCcottonSTD.txt	32.14	27.32	4.24
Groundwater		Peak	Post breakthrough average	30-year average
PRZM-GW (no pca applied)	GAcoastal	41.9	28.2	24.9
	DELMARVA	192	121	117
	FLCitrus	238	161	155
	FLPotato	56.8	19.2	18.1
	NCcoastal	65.3	32.6	29.3
	WIsands	<b>329</b>	<b>187</b>	<b>158</b>
SCIGROW	-----	0.0015	-----	-----

Note: the highest estimates are in bold.

Model	Use/Scenario	Acute (µg/L)	Chronic (µg/L)	30-year average (µg/L)
SW (PRZM/EXAMS)	MScottonSTD.txt	<b>2.97</b>	<b>2.59</b>	<b>0.63</b>
Groundwater		Peak	Post breakthrough average	30-year average
PRZM-GW (no pca applied)	GAcoastal*	4.47E-5	3.93E-5	2.38E-5
	DELMARVA	1.94E-4	1.65E-4	4.45E-5
	FLCitrus	<b>0.041</b>	<b>0.041</b>	<b>0.018</b>
	FLPotato*	5.71E-11	3.67E-11	3.114E-11
	NCcoastal	7.31E-5	3.64E-5	2.59E-5
	WIsands*	8.3E-4	7.66e-4	3.67E-4
SCIGROW	-----	0.0059	-----	-----

\*100 year simulation

Note: the highest estimates are in bold.

*Note:* While this assessment is for proposed registration of dicamba products containing the DGA salt, the drinking water assessment considered all registered uses of dicamba, including the other salt and acid forms. In regard to the dicamba BAPMA formulation, the BAPMA counter ion is known to have greater toxicity than the dicamba active ingredient. Because it is not possible to delineate exposure between the dicamba and BAPMA portion of the molecule when those end-use products are applied, drinking water estimates must be adequately protective. To ensure the dicamba drinking water estimates are protective, EFED examined drinking water exposures for dicamba versus the BAPMA counter ion (personal communication, W. Eckel to P. Savoia, 2015-07-15). EFED used the Mississippi (MS) cotton scenario, a benchmark high-runoff scenario, to compare exposures from applications of the BAPMA end-use product. This modeling found the 365-day average concentrations for dicamba-acid and BAPMA were comparable at 11 ppb and 11.8 ppb, respectively, for the Index Reservoir. The drinking water estimates provided are considered to be protective of all dicamba formulations since the lowest adverse effect doses were selected for assessment.

## 5.4 Dietary Risk Assessment

### 5.4.1 Description of Residue Data Used in Dietary Assessment

Acute and chronic aggregate dietary (food and drinking water) exposure and risk assessments were conducted using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID) Version 4.02. This software uses 2005-2010 food consumption data from the U.S. Department of Agriculture's (USDA's) National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA).

Acute and chronic aggregate dietary (food and drinking water) risk assessments were conducted to include all registered and proposed uses of dicamba. These assessments assume a 100 PCT and HED default processing factors, where applicable. EDWCs were modeled by EFED and were incorporated directly into these dietary assessments.<sup>7</sup> The unrefined acute dietary assessment was conducted using tolerance level residues. The refined chronic dietary assessment was conducted using average field trial residues for crops, and tolerance level residues for livestock commodities.

The use of anticipated residues, empirical processing factors, and additional PCT data would refine further HED's exposure and risk estimates for dicamba.

### 5.4.2 Percent Crop Treated Used in Dietary Assessment

Percent crop treated information was not used for this assessment. The acute and chronic exposure assessments assumed 100 PCT for all commodities.

### 5.4.3 Acute Dietary Risk Assessment

Acute dietary risk estimates are not of concern for the general U.S. population and all population subgroups assessed (<100% of the aPAD) at the 95<sup>th</sup> percentile; with the most highly exposed population subgroup being all infants (<1 year old) at 39% of the aPAD. The acute dietary risk estimates for population subgroups assessed are summarized in Table 5.4.5.

### 5.4.4 Chronic Dietary Risk Assessment

Chronic dietary risk estimates are not of concern for the general U.S. population and all population subgroups assessed (<100% of the cPAD)) at the 95<sup>th</sup> percentile; with the most highly exposed population subgroup being children ages 1-2 at 51% of the cPAD. The chronic dietary risk estimates for population subgroups assessed are summarized in Table 5.4.5.

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<sup>7</sup> D460422. Peck, C. 04-MAR-2021. Drinking Water Memo for the Registration Review of Dicamba Acid, Salts, and Degradate 3,6-dichlorosalicylic acid (DCSA).

### 5.4.5 Summary Table

Population Subgroup	Acute or Chronic Dietary (95 <sup>th</sup> Percentile)		Chronic Dietary	
	Dietary Exposure (mg/kg/day)	% aPAD	Dietary Exposure (mg/kg/day)	% cPAD
General U.S. Population	0.048850	17	0.007846	20
All Infants (<1 year old)	<b>0.111736</b>	<b>39*</b>	0.019226	48
Children 1-2 years old	0.084550	29	<b>0.020243</b>	<b>51*</b>
Children 3-5 years old	0.073872	25	0.014606	37
Children 6-12 years old	0.052448	18	0.009545	24
Youth 13-19 years old	0.037524	13	0.006244	16
Adults 20-49 years old	0.040372	14	0.006950	17
Adults 50-99 years old	0.034062	12	0.006453	16
Females 13-49 years old	0.035960	12	0.006462	16

\*The population subgroups with the highest risk estimates.

## 6.0 Residential (Non-Occupational) Exposure/Risk Characterization

There are no proposed residential uses at this time; however, there are existing residential uses that have been previously assessed using current data and assumptions. The registered residential uses include solid products and liquid products in concentrates, granules or ready-to-use sprays for use as spot and broadcast treatments on turf and were most recently assessed in (A. Gavelek & K. Lowe, D429870, 2016-03-29) and evaluated in (P. Savoia *et al.*, D461765, 2021-04-21) in support of registration review. No residential handler and/or post-application risks of concern were identified. Since the proposed end-use products are restricted for professional use only to agricultural use sites, the previous aggregate recommendations remain current and are summarized below.

### 6.1 Residential Risk Estimates for Use in Aggregate Assessment

Table 6.1 reflects the residential risk estimates that are recommended for use in the aggregate assessment for dicamba. Inhalation exposures are not included in the aggregate assessment since effects from the inhalation route are not systemic/cannot be aggregated. Post-application episodic granular ingestion following applications to lawns and turf are not included in the aggregate assessment as this exposure would not occur as a result of routine behavior and is considered an episodic event related to poisoning. There is no recommended residential exposure for use in the adult aggregate assessment since there is no hazard via the dermal route of exposure and inhalation exposures are not included, as described above. Therefore, the only residential exposures recommended for the dicamba aggregate assessment are the following:

- The recommended residential exposure for use in the children (1 to <2 years old) aggregate assessment reflects hand-to-mouth exposures from post-application turf scenario (i.e., post-application exposure to treated turf).

Table 6.1. Recommendations for the Residential Exposures for the Dicamba Aggregate Assessment.									
Lifestage	Exposure Scenario	Dose (mg/kg/day) <sup>1</sup>				MOE <sup>2</sup> [LOC=100]			
		Dermal	Inhalation	Oral	Total	Dermal	Inhalation	Oral	Total
Children 1 to < 2	Hand-to-Mouth Post-application Exposure – Treated Turf	N/A	N/A	0.02055	0.02055	N/A	N/A	6,600	<b>6,600</b>

1. Doses are provided for the highest doses for each applicable lifestage of all residential scenarios assessed. Total = dermal + inhalation + incidental oral (where applicable).
2. Margins of Exposure (MOEs) associated with the highest residential doses. Total =  $1 \div (1/\text{Dermal MOE}) + (1/\text{Inhalation MOE}) + (1/\text{Incidental Oral MOE})$ , where applicable. Level of Concern (LOC) for incidental oral exposure is 100.

## 7.0 Aggregate Exposure/Risk Characterization

In accordance with the FQPA, HED must consider and aggregate (add) pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure. Since residential exposure is expected, aggregate exposure consists of exposure from residential, food and drinking water sources.

Acute and chronic aggregate risks include only dietary exposure from food and drinking water sources. Since there are residential uses, short-term aggregate risks were assessed which include contributions from food, drinking water, and residential exposure. Intermediate-term aggregate risks were not considered as residential exposure is not expected to occur for more than 30 days. Dicamba is classified as *“Not Likely to be Carcinogenic to Humans”*, therefore a quantitative aggregate cancer risk assessment is not conducted at this time. No dermal hazard has been identified for dicamba, and the inhalation and incidental oral endpoints are selected based on different toxicological effects, therefore, the short-term aggregate risk assessment only includes applicable oral exposures (e.g., food, water and incidental oral).

For dicamba, the child lifestage with the highest dietary exposure (all infants <1 year old) does not match the child lifestage with the highest residential exposure (children 1 to <2 years old). The lifestages selected for each residential post-application scenario are based on an analysis provided as an Appendix in the 2012 Residential SOPs.<sup>8</sup> This analysis provides a quantitative and qualitative basis for why children 1 to <2 years old are the representative lifestage for most residential post-application scenarios involving young children, as well as reasons why a residential assessment is not conducted for infants. For children, therefore, the dicamba aggregate assessment only combines the residential exposure estimates for children 1 to <2 years old with the dietary exposure estimates for that same lifestage, children 1-2 years old.

<sup>8</sup> Available: <https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide>.

## 7.1 Acute Aggregate Risk

The acute aggregate risk estimates for dicamba includes food and drinking water only and are equivalent to the acute dietary risk estimates (Section 5.4.3), which are not of concern.

## 7.2 Short-Term Aggregate Risk

The short-term aggregate assessment is comprised of dietary (food and drinking water) exposure and residential activities (handler and post-application). Chronic (average) food and water exposure estimates were used in the assessment. The residential scenario that resulted in the highest exposures for children was the post-application exposure on turf.

A short-term aggregate assessment was not conducted for adults since there is no dermal hazard identified for dicamba and the inhalation and incidental oral endpoints are selected based on different toxicological effects. For children, the short-term aggregate [(food, water, and residential (incidental oral))] MOE is 3300, which is above the LOC of 100 and not of concern. The results of the short-term aggregate assessments for children are presented in Table 7.2.

Population	Short-Term Scenario						
	NOAEL mg/kg/day	LOC <sup>1</sup>	Max Allowable Exposure <sup>2</sup> mg/kg/day	Average Food and Water Exposure mg/kg/day	Residential Exposure mg/kg/day <sup>3</sup>	Total Exposure mg/kg/day <sup>4</sup>	Aggregate MOE (food, water, and residential) <sup>5</sup>
Child (1-2 years)	136	100	1.36	0.020243	0.02055	0.040724	3300

1 The aggregate level of concern (LOC) is 100 (10X for inter-species and 10X for intra-species).

2 Maximum Allowable Exposure (mg/kg/day) = no observed adverse effects level (NOAEL)/LOC.

3 Residential Exposure = [Oral exposure + Dermal exposure + Inhalation Exposure]. See Table 6.1.

4 Total Exposure = (Avg Food & Water Exposure + Residential Exposure)

5 Aggregate margin of exposure (MOE) = [NOAEL / (Avg Food & Water Exposure + Residential Exposure)]. Aggregate level of concern (LOC) is 100.

## 7.3 Intermediate-Term Aggregate Risk

Intermediate-term residential exposures are not anticipated from the registered uses; therefore, an intermediate-term aggregate risk assessment was not conducted.

## 7.4 Chronic Aggregate Risk

Since the residential uses of dicamba are not expected to occur over the long-term (or chronic) duration, chronic aggregate risk is comprised of dietary (food and drinking water) exposure only. The chronic dietary assessment in Section 5.4 represents chronic aggregate risk. Chronic aggregate risk is not of concern for any population.

## 7.5 Cancer Aggregate Risk

Dicamba is classified as “*Not Likely to be Carcinogenic to Humans*”, thus a quantitative aggregate cancer risk assessment is not applicable and not assessed. This conclusion was based on the lack of treatment related findings in carcinogenicity studies in rats and mice which were tested at adequate dose levels to assess the carcinogenicity of dicamba (J. Kidwell, TXR No. 0053647, 2005-08-16).

Additionally, the DCSA metabolite had a lack of treatment related findings in its rat carcinogenicity study.

## 8.0 Non-Occupational Spray Drift Exposure and Risk Estimates

HED conducts human health spray drift assessments to determine potential risk from indirect exposure to pesticides that may drift during or immediately after an application. Pesticide applications made in the form of a spray and applied aerially or via airblast or groundboom may result in pesticide drift and deposition in non-target areas adjacent to the application site.

On July 15th, 2024, the Agency updated its practice on spray drift<sup>9</sup> to include chemical-specific spray drift assessments for proposed uses through Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) registration actions (e.g., Section 3 new active ingredient and/or new use registrations, label amendments, Section 18 emergency exemptions, etc). Historically, chemical-specific spray drift assessments have only been routinely incorporated within human health draft risk assessments (DRAs) for registration review; as of July 15th, 2024, new active ingredients seeking initial US registration and any future new uses will be subject to the consideration of a chemical-specific spray drift assessment. Additionally, registration actions submitted to the Agency for active ingredients which have had a human health DRA completed during the registration review process will also be subject to consideration of spray drift within the risk assessment. Registration actions submitted for active ingredients without an initial completed spray drift assessment, whether within a DRA or at the time of initial US registration, will not be subject to the consideration of a chemical-specific spray drift assessment for the proposed uses. These active ingredients will be assessed for spray drift during the subsequent registration review process to ensure that all uses are considered concurrently prior to any new use evaluations. During registration review, the Agency will continue to evaluate each pesticide for the potential for spray drift in accordance with the most up-to-date science and policy. Dicamba has had a comprehensive spray drift assessment completed in (A. Gavelek & K. Lowe, D429870, 2016-03-29) and most recently evaluated in (P. Savoia *et al.*, D461765, 2021-04-21) conducted in support of registration review. Therefore, the proposed new uses of the dicamba DGA salt and dicamba BAPMA salt are being assessed for spray drift. Because the toxicological profile for dicamba is protective for the dicamba DGA salt formulation, the proposed agricultural uses for the dicamba DGA salt formulation are considered with all currently registered uses of dicamba, including turf. However, because there are no registered turf uses for the dicamba BAPMA salt formulation, the potential for spray drift from these proposed uses are evaluated separately from the proposed uses of the dicamba DGA salt formulations.

*Dicamba DGA Salt:* Dicamba has existing labels for registered uses on turf, thus it was considered whether the risk assessment for the turf uses may be considered protective of any type of exposure expected to result from spray drift. If the maximum application rate on crops adjusted by the amount of drift expected is less than or equal to existing turf application rates, the existing turf assessment is considered protective of spray drift exposure. Note that this assumes similar formulations are being applied to the agricultural crops and the residential turf (i.e., if a granular product is registered for use on residential turf, the scenarios assessed for that use may not be protective of liquid applications

<sup>9</sup> *Implementing Chemical Specific Human Health Spray Drift Analysis for Pesticide Registration Action.* Available online: <https://www.regulations.gov/document/EPA-HQ-OPP-2013-0676-0124>.

made to agricultural crops). The proposed maximum single application rate of dicamba DGA salt for dicamba tolerant cotton/soybean is 0.5 lb ae/A. The highest degree of spray drift noted for any application method immediately adjacent to a treated field (Tier 1 output from the aerial application using fine to medium spray quality) results in a deposition fraction of 0.26 of the application rate. A quantitative spray drift assessment for dicamba DGA salt is not required because the maximum application rate to a crop/target site multiplied by the adjustment factor for drift of 0.26 is less than the maximum direct spray residential turf application rate 1 lb ae/A.<sup>10</sup> The turf post-application MOEs have been previously assessed, are based on the revised SOPs for Residential Exposure Assessment (i.e., see above in Section 5.0), and are not of concern.

*Dicamba BAPMA Salt:* The most recent quantitative spray drift assessment for the dicamba BAPMA salt formulation was conducted in 2016 (A. Gavelek & K. Lowe, D429870, 2016-03-29) and evaluated in (P. Savoia *et al.*, D461765, 2021-04-21) in support of registration review. However, since that time, those end-use products have since been vacated<sup>11</sup> and HED has updated its practices for conducting spray drift assessments (as detailed above). As such, HED has conducted a quantitative assessment for the proposed new use of dicamba BAPMA salt on dicamba tolerant cotton and dicamba tolerant soybean. These results are summarized in Section 6.1.

### Methodology for Quantitative Spray Drift Assessments

Off-target movement of pesticides can occur via many types of pathways and is governed by a variety of factors. Sprays that are released and do not deposit in the application area end up off-target and can lead to exposures to those it may directly contact. They can also deposit on surfaces where contact with residues can eventually lead to indirect exposures (e.g., children playing on lawns where residues have deposited next to treated fields). The potential risk estimates from these residues can be calculated using drift modeling onto 50 feet wide lawns coupled with methods employed for residential risk assessments for turf products.

The approach to be used for quantitatively incorporating spray drift into risk assessment is based on a premise of compliant applications which, by definition, should not result in direct exposures to individuals because of existing label language and other regulatory requirements intended to prevent them.<sup>12</sup> Direct exposures would include inhalation of the spray plume or being sprayed directly. Rather, the exposures addressed here are thought to occur indirectly through contact with impacted areas, such as residential lawns, when compliant applications are conducted. Given this premise, indirect exposures for children (1 to <2 years old) and adults who have contact with turf where residues are assumed to have deposited via spray drift are the focus of this analysis and is analogous to how exposures to turf products are considered in risk assessment.

To evaluate the drift potential and associated risks, an approach based on drift modeling coupled with techniques used to evaluate residential uses of pesticides was utilized. Essentially, a residential turf assessment based on exposure to deposited residues has been completed to address drift from the agricultural applications of dicamba BAPMA salt. In the spray drift scenario, the deposited residue value was determined based on the amount of spray drift that may occur at varying distances from the

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<sup>10</sup>  $0.5 \text{ lb ae/A} \times 0.26 \leq 1 \text{ lb ae/A}$

<sup>11</sup> See <https://www.epa.gov/pesticides/epa-provides-update-over-top-uses-dicamba>.

<sup>12</sup> This approach is consistent with the requirements of the EPA's Worker Protection Standard.

edge of the treated field using the AgDrift (v2.1.1) model and the *Residential Exposure Assessment Standard Operating Procedures Addenda 1: Consideration of Spray Drift Policy*. Once the deposited residue values were determined, the remainder of the spray drift assessment was based on the algorithms and input values specified in the revised (2012) *Standard Operating Procedures for Residential Risk Assessment (SOPs)*.

A screening approach was developed based on the use of the AgDrift model in situations where specific label guidance that defines application parameters is not available.<sup>13</sup> AgDrift is appropriate for use only when applications are made by aircraft, airblast orchard sprayers, and groundboom sprayers. When AgDrift was developed, a series of screening values (i.e., the Tier 1 option) were incorporated into the model and represent each equipment type and use under varied conditions. The screening options specifically recommended in this methodology were selected because they are plausible and represent a reasonable upper bound level of drift for common application methods in agriculture. In all cases, each scenario is to be evaluated unless it is not plausible based on the anticipated use pattern (e.g., herbicides are not typically applied to tree canopies) or specific label prohibitions (e.g., aerial applications are not allowed). Section 6.1 provides the screening level drift related risk estimates.

### 8.1 Combined Risk Estimates from Lawn Deposition Adjacent to Applications

The spray drift risk estimates are based on an estimated deposited residue concentration as a result of the screening level agricultural application scenarios. Dicamba BAPMA salt is proposed for use on dicamba tolerant cotton and dicamba tolerant soybean and can be applied via groundboom equipment. The recommended drift scenario screening level options are listed below:

- Groundboom applications are based on the AgDrift option for high boom height and using very fine to fine spray type using the 90<sup>th</sup> percentile results.

Adult dermal and children (1 to <2 years old) dermal exposures were not assessed since there were no adverse effects observed in the route specific dermal toxicity study up to and including the limit dose. Therefore, only incidental oral exposures for children (1 to <2 years old) have been quantitatively assessed and there are no additional routes to combine. Exposures were considered for 50 feet wide lawns where the nearest side of the property was directly adjoining the treated field (at field edge) and at varied distances up to 300 feet downwind of a treated field.

Results are presented in Tables 8.1.1 and indicate that there are no risks of concern at the field edge. The algorithms used in the spray drift assessment are presented in Appendix B of the supporting occupational and residential exposure assessment (D. Carter, 029801\_TG00619469\_ORE, 2025-07-10).

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<sup>13</sup> Available online: [Models for Pesticide Risk Assessment | US EPA](#).

Table 8.1.1. Children's Risk Estimates (MOEs) Related to Indirect Exposure to Spray Drift for Dicamba BAPMA Salt.				
Crop/Rate Group	Spray Type/ Nozzle Config	App Rate (lb ae/A)	Estimated TTR ( $\mu\text{g}/\text{cm}^2$ ) <sup>1</sup>	Incidental Oral MOE <sup>2</sup>
				At Field Edge
<b>Dicamba Tolerant Cotton/Soybean</b>				
Groundboom	High Boom Very fine to Fine	0.5 lb ae/A	0.056	96,000

1. Turf transferable residue (TTR) ( $\mu\text{g}/\text{cm}^2$ ) = Application Rate  $\times$  F  $\times$  (1-D)<sup>t</sup>  $\times$  4.54E8  $\mu\text{g}/\text{lb}$   $\times$  2.47E-8 acre/ $\text{cm}^2$ , where F = fraction of ai as transferable residue following application (0.01), D = fraction of residue that dissipates daily (0.1).
2. Margins of exposure (MOEs) at field edge = Incidental Oral POD (136 mg/kg/day)  $\div$  Dose (incidental oral) (0.001417 mg/kg/day), where the incidental oral doses are calculated using the algorithms provided in the Turf Residential SOPs. The incidental oral level of concern (LOC) is 100.

## 9.0 Non-Occupational Bystander Post-Application Inhalation Exposure and Risk Estimates

The potential for non-occupational exposure to vapor phase dicamba residues emitted from treated fields for application rates up to 2.0 lb ae/A were evaluated previously in (A. Gavelek & K. Lowe, D429870, 2016-03-29) and most recently in (P. Savoia *et al.*, D461765, 2021-04-21). The volatilization modeling was completed using PERFUM and chemical/formulation-specific flux data. HED concluded that while volatilization of dicamba from treated crops (at rates up to 2.0 lb ae/A) does occur and could result in bystander exposure, airborne concentrations, even at the edge of the treated fields, were not of concern. HED notes that the volatilization assessment SOP's, methodologies, and data assumptions remain current. Since the proposed agricultural uses of dicamba DGA salt and dicamba BAPMA salt are at application rates lower (0.5 lb ae/A) than those previously assessed (2.0 lb ae/A), these assessments are considered protective for the proposed uses. Therefore, there are no non-occupational bystander inhalation risks of concern anticipated from these proposed uses.

HEDs previously completed volatilization modeling and non-occupational bystander post-application inhalation exposure and risk assessments are summarized below.

A submitted flux study was reviewed by EFED<sup>14</sup>, which estimated the flux of dicamba vapors after spray application of the DGA salt formulation. This study was determined to be acceptable for use in the human health risk assessment. The dicamba DGA salt formulation was used alone without any tank adjuvants, and the test surface was zoysia grass. The trial was performed in August 2012 near Columbia, IL, and experienced minimum and maximum temperatures of 21.1°C and 26.2°C, respectively. The estimated 6-hour average flux was 0.0004  $\mu\text{g}/\text{m}^2/\text{sec}$ , representing 0.008% of the application rate.

Exposure modeling for a single day was completed using PERFUM. There are a variety of factors that potentially affect the emission rates of dicamba and subsequent offsite transport including: field condition (bare soil, growing or mature crop canopy), field parameters (soil type, moisture, etc.), formulation type, meteorological conditions, and application scenario (rate, method). The flux estimates from the study (0.0004  $\mu\text{g}/\text{m}^2/\text{s}$ ), a single 40A field, and the Bradenton, FL meteorological data (which would provide worst case meteorological conditions) were used with PERFUM to estimate risk based on the dicamba field volatility study. The results indicate that volatilization of dicamba from treated crops does occur and could result in bystander exposure; however, PERFUM modeling

<sup>14</sup> D411382. W. Eckel. MRID 49022501. Sall, E.; Smith, H.; Findley, D.; *et al.* (2013) Measurement of the Volatile Flux of Dicamba under Field Conditions using the Theoretical Profile Shape Method. Project Number: RPN/2012/0662, MSL0024798.

indicates that airborne concentrations, even at the edge of the treated fields, are negligible, and risk estimates are not of concern.

While the flux data are specific to the DGA salt of dicamba, it is considered protective for the other forms of dicamba (e.g., the sodium salt, the potassium salt, and the BAPMA salt), with the exception of the DMA salt and the dicamba acid formulations, for the following reasons:

- Based on modeling data using Estimation Programs Interface Suite (EPI Suite), the volatility of the sodium salt, the potassium salt, and the BAPMA salt is lower than that of the DGA salt.
- Based on registrant submitted information, the vapor pressure of the DGA salt is less than that of the DMA salt. In addition, the DGA salt formulation showed a 7-fold decrease in volatility as compared to the DMA formulation under identical conditions.<sup>15</sup>
- A BASF patent<sup>16</sup> provides a relative ranking of the volatility of the various forms of dicamba, with the DMA, DGA, and BAPMA salt being 17.8%, 5.4% and 0.5% of the volatility of the dicamba acid (100%), respectively.

Based on the relative ranking of volatility, it appears that the DGA salt is approximately 20x and 4x less volatile than the dicamba acid and the DMA salt, respectively. In order to address this uncertainty, HED modeled the volatilization of the DGA salt assuming 10x (0.004  $\mu\text{g}/\text{m}^2/\text{sec}$ ) and 100x (0.04  $\mu\text{g}/\text{m}^2/\text{sec}$ ) the estimated flux rate from the available flux study. When assuming 10x or 100x the flux rate, air concentrations were still found to be negligible at the edge of the treated fields, and not of concern.

Additional updates to the volatilization assessment are not required at this time since the most recent risk assessment reflects current HED practices and policies.

## 10.0 Cumulative Exposure/Risk Characterization

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to dicamba and any other substances and dicamba does not appear to produce a toxic metabolite produced by other substances. For the purposes of this action, therefore, EPA has not assumed that dicamba has a common mechanism of toxicity with other substances. In 2016, EPA's Office of Pesticide Programs released a guidance document entitled, *Pesticide Cumulative Risk Assessment: Framework for Screening Analysis* [<https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/pesticide-cumulative-risk-assessment-framework>]. This document provides guidance on how to screen groups of pesticides for cumulative evaluation using a two-step approach beginning with the evaluation of available toxicological information and if necessary, followed by a risk-based screening approach. This framework supplements the existing guidance documents for establishing common mechanism groups (CMGs)<sup>17</sup> and conducting cumulative risk assessments (CRA).<sup>18</sup> During Registration Review, the Agency will utilize this framework to determine if the available toxicological data for dicamba suggests a candidate CMG may be established with other pesticides. If a CMG is established, a screening-level

<sup>15</sup> BASF Reg Doc 1975/5161, 1994/5202, 1982/5169, 1986/5195, 1984/5093.

<sup>16</sup> Low volatile amine salts of anionic pesticides. USPTO Application: #20150210723. <http://images3.freshpatents.com/pdf/US20150210723A1.pdf>

<sup>17</sup> Guidance For Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity (USEPA, 1999).

<sup>18</sup> Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity (USEPA, 2002).

toxicology and exposure analysis may be conducted to provide an initial screen for multiple pesticide exposure.

## 11.0 Occupational Exposure/Risk Characterization

### 11.1 Short-/Intermediate-Term Occupational Handler Exposure and Risk Estimates

HED uses the term handlers to describe those individuals who are involved in the pesticide application process. HED believes that there are distinct job functions or tasks related to applications and exposures can vary depending on the specifics of each task. Based on the anticipated use patterns and current labeling, types of equipment and techniques that can potentially be used, occupational handler exposure is expected from the proposed uses. The assumptions and exposure factors incorporated for assessing these use scenarios are detailed in Section 8.1 of the associated occupational and residential exposure risk assessment (D. Carter, 029801\_TG00619469\_ORE, 2025-07-10).

Occupational handler exposure and risk estimates for the proposed agricultural uses are summarized in Tables 11.1.1 and 11.1.2.

#### Summary of Occupational Handler Non-Cancer Exposure and Risk Estimates

*Dicamba DGA Salt:* There are no occupational handler inhalation risks of concern assuming baseline attire (e.g., single layer of clothing, and no respirator); MOEs are 490 (mixer/loaders) and 770 (applicators), which are above the LOC of 30.

Table 11.1.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Dicamba DGA Salt.						
Exposure Scenario	Crop or Target <sup>1</sup>	Inhalation Unit Exposure <sup>2</sup> (µg/lb ai) [PPE]	Maximum Application Rate <sup>3</sup>	Area Treated <sup>4</sup>	Inhalation	
					Dose <sup>5</sup> (mg/kg/day)	MOE <sup>6</sup> [LOC=30]
<b>Mixer/Loader</b>						
Liquid, Groundboom, Broadcast	Field crop, high-acreage	0.219 [No-R]	0.5 lb ae/acre	200 acres	0.00027	770
<b>Applicator</b>						
Spray (all starting formulations), Groundboom, Broadcast	Field crop, high-acreage	0.219 [No-R]	0.5 lb ae/acre	200 acres	0.00043	490

1 Crop/Target: High acreage field crops include cotton and soybean.

2 Unit Exposures: Based on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" ([Occupational Pesticide Handler Unit Exposure Surrogate Reference Table 2021 \(epa.gov\)](#)); Level of PPE: No-R = no respirator.

3 Maximum Application Rate: Based on proposed labels (see Tables 4.1-4.2).

4 Area Treated or Amount Handled: Exposure Science Advisory Council Policy #9.2.

5 Inhalation Dose = Inhalation Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre) × Area Treated or Amount Handled Daily (A/day) ÷ BW (80 kg).

6 Inhalation margin of exposure (MOE) = Inhalation POD (0.21 mg/kg/day) ÷ Inhalation Dose (mg/kg/day). Level of Concern (LOC) = 30.

*Dicamba BAPMA Salt:* There are no inhalation risks of concern for occupational handlers assuming baseline attire (e.g., single layer of clothing) and label-required PPE (i.e., respirator); MOEs are 470 (mixer/loaders) and 730 (applicators), which are above the LOC of 300.

Table 11.1.2. Occupational Handler Non-Cancer Exposure and Risk Estimates for Dicamba BAPMA Salt.						
Exposure Scenario	Crop or Target <sup>1</sup>	Inhalation Unit Exposure <sup>2</sup> (µg/lb ai) [PPE]	Maximum Application Rate <sup>3</sup>	Area Treated <sup>4</sup>	Inhalation	
					Dose <sup>5</sup> (mg/kg/day)	MOE <sup>6</sup> [LOC=300]
<b>Mixer/Loader</b>						
Liquid, Groundboom, Broadcast	Field crop, high-acreage	0.0219 [PF10R]	0.5 lb ae/acre	200 acres	0.000027	730
<b>Applicator</b>						
Spray (all starting formulations), Groundboom, Broadcast	Field crop, high-acreage	0.034 [PF10R]	0.5 lb ae/acre	200 acres	0.000043	470

1 Crop/Target: High acreage field crops include cotton and soybean.

2 Unit Exposures: Based on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" ([Occupational Pesticide Handler Unit Exposure Surrogate Reference Table 2021 \(epa.gov\)](#)); Level of PPE: PF10 = respirator assumed to reduce inhalation exposure by 90%.

3 Maximum Application Rate: Based on proposed labels (see Table 4.3).

4 Area Treated or Amount Handled: Exposure Science Advisory Council Policy #9.2.

5 Inhalation Dose = Inhalation Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre) × Area Treated or Amount Handled Daily (A/day) ÷ BW (80 kg).

6 Inhalation margin of exposure (MOE) = Inhalation POD (0.02 mg/kg/day) ÷ Inhalation Dose (mg/kg/day). Level of Concern (LOC) = 300.

*Note on mixing/loading liquid formulation scenarios:* A 2019 study by the AHETF measured dermal and inhalation exposure for workers who loaded liquid pesticides using closed systems such as gravity feed, container breach, and suction/extraction systems. After analyzing the exposure monitoring data, the AHETF observed that exposures were higher than expected and subsequently identified that, when using suction/extraction systems, removing and handling chemical extraction probes without rinsing them prior to removal from the pesticide container had the potential to result in high exposures via direct exposure to the liquid concentrate. The AHETF therefore submitted to the Agency a dataset that excludes monitoring of those workers who handled unrinsed chemical extraction probes and recommended that the Agency take additional regulatory actions to ensure workers do not remove and handle chemical extraction probes still coated with the concentrated liquid formulation.

The Agency agreed with the AHETF proposal, recognizing that handling of unrinsed chemical extraction probes is inconsistent with the exposure reduction principles of closed systems. Closed loading systems are an engineering control designed to prevent direct contact between users and the pesticide formulation, thereby reducing exposures. According to EPA's Worker Protection Standard (WPS), a closed system must remove the pesticide from its original container and transfer the pesticide product through connecting hoses, pipes and couplings that are sufficiently tight to prevent exposure of handlers to the pesticide product, except for the negligible escape associated with normal operation of the system [40 CFR § 170.607(d)(2)(i)]. However, in addition to considerations regarding closed systems, given the high exposure potential from this activity, the Agency is requiring revisions to applicable product label instructions to restrict handling un-rinsed extraction probes and conducting stakeholder outreach and revising worker training modules to ensure that users of suction/extraction systems rinse the chemical extraction probes within the pesticide container prior to their removal so that they are not exposed to the concentrated liquid formulation.

## 11.2 Short-/Intermediate-Term Post-Application Exposure and Risk Estimates

HED uses the term post-application to describe exposures that occur when individuals are present in an environment that has been previously treated with a pesticide (also referred to as re-entry exposure). Such exposures may occur when workers enter previously treated areas to perform job functions, including activities related to crop production, such as scouting for pests or harvesting. Post-

application exposure levels vary over time and depend on such things as the type of activity, the nature of the crop or target that was treated, the type of pesticide application, and the chemical's degradation properties. In addition, the timing of pesticide applications, relative to harvest activities, can greatly reduce the potential for post-application exposure.

### 11.2.1 Dermal Post-Application Exposure and Risk Estimates

There is no potential hazard *via* the dermal route for dicamba; therefore, a quantitative occupational post-application dermal risk assessment was not completed.

*Restricted Entry Interval:* The REI specified on the proposed label is based on the acute toxicity of dicamba. Dicamba is classified as Toxicity Category III via the dermal route, Toxicity Category IV for skin irritation potential, and Toxicity Category I-II for eye irritation. It is not a skin sensitizer. As there is no hazard via the dermal route of exposure, there are no post-application risks of concern on day 0 (12 hours following application). Under 40 CFR 156.208 (c) (2) (iii), ai's classified as Acute II for acute dermal, eye irritation or primary skin irritation are assigned a 24-hour REI. Therefore, the [156 subpart K] Worker Protection Statement interim REI of 24 hours is adequate to protect agricultural workers from post-application exposures to dicamba.

### 11.2.2 Inhalation Post-Application Risk

There are multiple potential sources of post-application inhalation exposure to individuals performing post-application activities in previously treated fields. These potential sources include volatilization of pesticides and resuspension of dusts and/or particulates that contain pesticides. The Agency sought expert advice and input on issues related to volatilization of pesticides from FIFRA Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010<sup>19</sup>. The Agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (*Human Health Bystander Screening Level Analysis: Volatilization of Conventional Pesticides*<sup>20</sup>). During Registration Review, the Agency will utilize this analysis to determine if data (i.e., flux studies, route-specific inhalation toxicological studies) or further analysis is required for dicamba.

Although a quantitative occupational post-application inhalation exposure assessment was not performed, an inhalation exposure assessment was performed for occupational/commercial handlers. Handler exposure resulting from application of pesticides outdoors is likely to result in higher exposure than post-application exposure, and all of the occupational handler scenarios resulted in inhalation risk estimates that were not of concern at baseline (i.e., all inhalation MOEs without a respirator  $\geq$  the LOC). Therefore, it is expected that these handler inhalation exposure estimates would be protective of most occupational post-application inhalation exposure scenarios.

<sup>19</sup> Available online: [A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding Field Volatilization of Conventional Pesticides | US EPA ARCHIVE DOCUMENT](#)

<sup>20</sup> Available online: [Regulations.gov](#)

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## Appendix A. Toxicology Profile and Executive Summaries

### A.1 Dicamba Active Ingredients in Case No. 0065

Active ingredient name	PC code
Dicamba	029801
Dicamba, dimethylamine salt (DMA)	029802
Dicamba, diethanolamine salt	029803
Dicamba, sodium salt	029806
Dicamba, diglycoamine salt (DGA)	128931
Dicamba, potassium salt	129043
Dicamba, isopropylamine salt	128944
BAPMA salt of Dicamba	100094

### A.2 Toxicology Data Requirements

The requirements (40 CFR 158.340) for food use for dicamba are in Table 1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Guideline Number and Toxicity Study	Required	Satisfied
870.1100 Acute Oral Toxicity .....	yes	yes
870.1200 Acute Dermal Toxicity .....	yes	yes
870.1300 Acute Inhalation Toxicity .....	yes	yes
870.2400 Primary Eye Irritation .....	yes	yes
870.2500 Primary Dermal Irritation .....	yes	yes
870.2600 Dermal Sensitization .....	yes	yes
870.3100 90-Day Oral Toxicity (Rodent) .....	yes	yes
870.3150 90-Day Oral Toxicity (Non-Rodent) .....	yes+	yes
870.3200 21/28-Day Dermal Toxicity .....	yes	yes
870.3250 90-Day Dermal Toxicity .....	CR	--
870.3465 90/28-Day Inhalation .....	yes	yes
870.3700a Prenatal Developmental Toxicity (Rodent) .....	yes	yes
870.3700b Prenatal Developmental Toxicity (Non-rodent) .....	yes	yes
870.3800 Reproduction and Fertility Effects .....	yes	yes
870.4100a Chronic Toxicity (Rodent) .....	yes	yes
870.4100b Chronic Toxicity (Non-rodent) .....	no	yes
870.4200a Carcinogenicity (Rat) .....	yes	yes
870.4200b Carcinogenicity (Mouse) .....	yes	yes
870.4300 Combined Chronic/Carcinogenicity .....	yes	yes
870.5100 Mutagenicity: Bacterial Reverse Mutation Test .....	yes	yes
870.5300 Mutagenicity: Mammalian Cell Gene Mutation Test .....	yes	yes
870.5375 Mutagenicity: Structural Chromosomal Aberrations .....	yes	yes
870.5395 Mutagenicity: Micronucleus Assay .....	yes	yes
870.5500 Mutagenicity: Unscheduled DNA Synthesis .....	yes	yes
870.6200a Acute Neurotoxicity Screening Battery (Rat) .....	yes	yes
870.6200b 90-Day Neurotoxicity. Screening Battery (Rat) .....	yes	yes
870.6300 Developmental Neurotoxicity .....	CR	
870.7485 Metabolism and Pharmacokinetics .....	yes	yes
870.7600 Dermal Penetration .....	CR	-
870.7800 Immunotoxicity .....	yes	yes

+ Requirements are satisfied by chronic oral toxicity studies. CR: Conditionally Required

### A.3 Toxicity Profiles

The study NOAELs and LOAELs may not reflect current HED policies, but the updates would not impact endpoint selection or PODs, which are protective of all effects observed in the database.

Guideline No.	Study Type	MRID(s)	Results	Toxicity Category
870.1100	Acute oral toxicity / rat	49712705 (97.8% a.i.)	LD <sub>50</sub> = > 2000 mg/kg (F)	III
870.1200	Acute dermal toxicity / rat	49712706 (97.8% a.i.)	LD <sub>50</sub> = > 2000 mg/kg (M & F)	III
870.1300	Acute inhalation toxicity / rat	49712707 (97.8% a.i.)	LC <sub>50</sub> = > 5.14 mg/L (M & F)	IV
		49552703 (98.62% a.i.)	LC <sub>50</sub> = > 2.71 mg/L (M & F)	IV
870.2400	Primary eye irritation / rabbit	49712708 (97.8% a.i.)	Severely irritating	I
		49551104 (98.62% a.i.)	Severely irritating (reversible corneal effects)	II
870.2500	Primary dermal irritation / rabbit	49712709 (97.8% a.i.)	Non-irritating	IV
870.2600	Dermal sensitization / guinea pig	47504702 (86.3% a.i.)	Non-Sensitizer (Maximization test)	--
		49527512 (97.4% a.i.)	Not a dermal sensitizer (Buehler Method)	--
	Dermal sensitization / mouse	49712710 (97.8% a.i.)	Not a dermal sensitizer (LLNA)	--
		50831317 (99.18% a.i.)	Dermal sensitizer (LLNA)	--

Guideline No.	Study Type	MRID(s)	Results	Toxicity Category
870.1100	Acute oral toxicity / rat	48599303	LD <sub>50</sub> >2,000 mg/kg (F)	III
870.1200	Acute dermal toxicity / rat	48599304	LD <sub>50</sub> > 5000 mg/kg (M & F)	IV
870.1300	Acute inhalation toxicity / rat	48599305	LC <sub>50</sub> = >0.557 mg/L (M & F)	III
870.2400	Primary eye irritation / rabbit	48599306	Slightly Irritating	IV
870.2500	Primary dermal irritation / rabbit	48599307	Non-Irritating	IV
870.2600	Dermal sensitization / mice	48599308	Positive (LLNA)	N/A

Guideline No.	Study Type	Source	Results	Toxicity Category
BASF Test	Acute oral toxicity / rat	MSDS Sheet	LD <sub>50</sub> = 691 mg/kg	III
BASF Test	Acute dermal toxicity / rabbit	MSDS Sheet	LD <sub>50</sub> = 200 mg/kg	II
BASF Test	Acute inhalation toxicity / rat	MSDS Sheet	LC <sub>50</sub> = 0.07 mg/L	II
OECD 404	Primary eye irritation / rabbit	MSDS Sheet	Corrosive	I
QSAR	Primary dermal irritation	MSDS Sheet	Irritant	II
OCED 429	Dermal sensitization / Mouse	MSDS Sheet	Sensitizer	--

Table A.3.3. Acute Toxicity of BAPMA Base.				
Table A.3.4 Acute Toxicity Profile – Dicamba, Dimethylamine salt				
Guideline No.	Study Type	MRID(s)	Results	Toxicity Category
870.1100	Acute Oral Toxicity (rat)	45646602	LD <sub>50</sub> > 5000 mg/kg (M & F)	IV
870.1200	Acute Dermal Toxicity (rat)	45646602	LD <sub>50</sub> > 5000 mg/kg (M & F)	IV
870.1300	Acute Inhalation Toxicity (rat)	45646602	LC <sub>50</sub> > 3.27 mg/L (M & F)	IV
870.2400	Primary Eye Irritation (rabbit)	45646602	Mild irritant	IV
870.2500	Primary Skin Irritation (rabbit)	45646602	Non-irritating	IV
870.2600	Dermal Sensitization (guinea pig)	45646602	Not a dermal sensitizer (Maximization Method)	N/A

Table A.3.5 Acute Toxicity Profile – Dicamba, diglycolamine salt				
Guideline No.	Study Type	MRID(s)	Results	Toxicity Category
870.1100	Acute Oral Toxicity (rat)	00078444	LD <sub>50</sub> = 2740 (2010 – 3740) mg/kg (M)	III
870.1200	Acute Dermal Toxicity (rat)	47759401	LD <sub>50</sub> > 2000 mg/kg (M & F)	III
870.1300	Acute Inhalation Toxicity (rat)	47504703	LC <sub>50</sub> > 1.18 mg/L (M & F)	III
870.2400	Primary Eye Irritation (rabbit)	43599101	Self-validated	I
870.2500	Primary Skin Irritation (rabbit)	47759402	Minimally irritating	IV
870.2600	Dermal Sensitization (guinea pig)	47504702	Non-sensitizer (Maximization test)	N/A

Table A.3.6 Acute Toxicity Profile – Dicamba, sodium salt				
Guideline No.	Study Type	MRID(s)	Results	Toxicity Category
870.1100	Acute Oral Toxicity (rat)	00025372	LD <sub>50</sub> = 1879 (1305 – 2704) mg/kg (M) LD <sub>50</sub> = 1581 (1150 – 2174) mg/kg (F) LD <sub>50</sub> = 1707 (1345 – 2166) mg/kg (C)	III
870.1200	Acute Dermal Toxicity (rabbit)	00025372	LD <sub>50</sub> > 2000 mg/kg (M & F)	III
870.1300	Acute Inhalation Toxicity (rat)	00143011	LC <sub>50</sub> > 5.2 mg/L (M & F)	IV
870.2400	Primary Eye Irritation (rabbit)	43599101	Moderately irritating	II
870.2500	Primary Skin Irritation (rabbit)	00025372	Slightly irritating	IV
870.2600	Dermal Sensitization (guinea pig)	47504701	Non-sensitizer (Buehler Method)	N/A

Table A.3.7 Acute Toxicity Profile – Dicamba, potassium salt (97%)				
Guideline No.	Study Type	MRID(s)	Results	Toxicity Category
870.1100	Acute Oral Toxicity (rat)	45774601	LD <sub>50</sub> > 2500 mg/kg and < 3200 mg/kg (M & F)	III
	Acute Oral Toxicity (mouse)	45774601	LD <sub>50</sub> > 3200 mg/kg and < 4000 mg/kg (M & F)	III
870.1200	Acute Dermal Toxicity (rat)	45774601	LD <sub>50</sub> > 2000 mg/kg (M & F)	III
870.1300	Acute Inhalation Toxicity (rat)	45774601	LC <sub>50</sub> > 3.72 mg/L (M & F)	IV
870.2400	Primary Eye Irritation (rabbit)	46603103	Corneal opacity (clearing within 7 days) and conjunctival irritation (clearing within 4 days)	III
870.2500	Primary Skin Irritation (rabbit)	46603102	Slightly irritating	IV
870.2600	Dermal Sensitization (	---	Study required	N/A

\*Note: Studies without TXR numbers listed do not have DER available for review

Table A.3.8. Sub-chronic, Chronic and Other Toxicity Profile for Dicamba Acid		
Guideline No./ Study Type/	MRID No. (Year), TXR No. Doses/Classification	Results
870.3100 90- Day Oral Toxicity (Rat)	44623101 (1997) TXR 0052528 (0, 500, 3000, 6000, 12000 ppm) M:0,40.1,238.7,479.4,1000 mg/kg/day F:0,43.2,266.4,535.6,1065.3 mg/kg/day Acceptable/Guideline	NOAEL= 479.4/535.6 mg/kg/day(M/F). LOAEL= 1000/1065.3 mg/kg/day (M/F) based on clinical signs, increased liver weight and increased hepatocyte hypertrophy and hepatocellular pigmentation.
870.3200 21-Day Dermal Toxicity (Rabbit)	40547901 (1986) TXR 0007968 0, 40, 200 and 1000 mg/kg/day as a 42.0% Dicamba formulation (Lot No. 52410301) Supplementary	<b>Systemic:</b> NOAEL > 1000 mg/kg/day LOAEL= Not established <b>Dermal:</b> NOAEL = 40 mg/kg/day LOAEL = 200 mg/kg/day (fissuring, acanthosis and hyperkeratosis). At 1000 mg/kg/day - desquamation, moderate erythema, edema and atonia, fissuring, acanthosis and hyperkeratosis. Classified minimum.
870.3200 28-Day Dermal Toxicity (Rat)	45814501 (2002) TXR 0052528 0, 30, 300, 1000 mg/kg/day (M/F) Acceptable/Guideline	NOAEL= 1000 mg/kg/day (HDT) LOAEL= not determined.
870.3465 28-Day Inhalation Toxicity (Rat)	49461101 (2014) 0, 0.001, 0.005, 0.050 mg/L Acceptable/Guideline	NOAEC=0.005/0.005 mg/L (M/F) LOAEC=0.050/0.050 mg/L (M/F), based on minimal multifocal bronchiole-alveolar hyperplasia in males; multiple microscopic findings in the lung and associated lymph nodes in females
870.3700a Prenatal Developmental (Rat)	00084024 (1981) TXR 0011702 0,64,160,400 mg/kg/day (GD 6-19) Acceptable/Guideline	<b>Maternal:</b> NOAEL= 160 mg/kg/day. LOAEL= 400 mg/kg/day based on increased mortality, clinical signs (ataxia, stiffening of body when touched, decreased motor activity) and decreased food consumption. <b>Developmental:</b> NOAEL= 400 mg/kg/day (HDT) LOAEL not established.
870.3700b Prenatal Developmental (New Zealand White Rabbit)	42429401 (1992) TXR 0010617 0, 30, 150, 300 mg/kg/day (GD 6-18) Range-finding study: 0, 62.5, 125, 250, 500 mg/kg/day (GD 6-18) Acceptable/Guideline	<b>Maternal:</b> NOAEL= 62.5 mg/kg/day LOAEL= 150 mg/kg/day based on increased abortion, clinical signs (decreased motor activity, ataxia) <b>Developmental:</b> NOAEL= 62.5 mg/kg/day, LOAEL= 150 mg/kg/day based on increased abortion at gestation day 22 (1 in 20 does), after dosing ceased on day 18

Table A.3.8. Sub-chronic, Chronic and Other Toxicity Profile for Dicamba Acid		
Guideline No./ Study Type/	MRID No. (Year), TXR No. Doses/Classification	Results
870.3800 Reproduction and Fertility Effects (Rat)	43137101 (1993) TXR 0011391 (0,500,1500,5000 ppm) M: 0,40,122,419 mg/kg/day F: 0,45, 136, 450 mg/kg/day Acceptable/Guideline	<b>Parental/Systemic:</b> NOAEL= 122/136 mg/kg/day (M/F) LOAEL= 419/450 mg/kg/day (M/F) based on clinical signs (slow righting reflex)  <b>Reproductive:</b> NOAEL=122 mg/kg/day LOAEL= 419 mg/kg/day based on delayed sexual maturation in F1 males  <b>Offspring:</b> NOAEL=136 mg/kg/day LOAEL= 450 mg/kg/day based on decreased pup weights in the F1 generation at PND0/PND21 and F2B generation at PND21, relative to the MARTA historical control database. Classified minimum
870.4200a Combined Chronic Toxicity/ Carcinogenicity (Rat)	00146150 (1985) TXR 0005516 (0,50,250,2500 ppm) M: 0,2,11,107 mg/kg/day F: 0,3,13,127 mg/kg/day Acceptable/Guideline	NOAEL= 107/127 mg/kg/day (M/F)  LOAEL was not established. Brain ventricular dilation in females at the highest dose, but not observed in other studies.  Not carcinogenic- The study is considered adequate for evaluating the carcinogenic potential.
870.4100b Chronic toxicity (Dog)	40321102 (1986) TXR 0006393 (0,100,500,2500 ppm) 0,2,11,52 mg/kg/day Acceptable/Guideline	NOAEL=52 mg/kg/day (HDT)  LOAEL= Not Achieved
870.4200b Carcinogenicity (Mouse)	40872401 (1988) TXR 0012041 (0,50,150,1000,3000 ppm) M: 0,5.5,17.2,108,358 mg/kg/day F: 0,5.8,18.8,121,354 mg/kg/day Acceptable/Guideline	NOAEL=358/354 mg/kg/day (M/F)  LOAEL = Not Established.  Not carcinogenic- the study is considered adequate for evaluating the carcinogenic potential.
870.5100 Bacterial Reverse Mutation	00143001 (1979) TXR 0004286 Acceptable/Guideline	Negative- Not mutagenic.
870.5100 Bacterial Reverse Mutation	47899525 (2006) TXR 0055497 Acceptable/Guideline	Negative- Not mutagenic.
870.5300 Gene Mutation Assay in CHO Cells	47899526 (2007) TXR 0055497 Acceptable/Guideline	Negative- Not mutagenic.

Table A.3.8. Sub-chronic, Chronic and Other Toxicity Profile for Dicamba Acid		
Guideline No./ Study Type/	MRID No. (Year), TXR No. Doses/Classification	Results
870.5375 Chromosomal aberration assay in human lymphocytes	47899527 (2010) TXR 0055497 Acceptable/Guideline	Positive, however the S9-activated portion of the assay should have been repeated
870.5375 <i>In vitro</i> Chromosome Aberration (CHO)	40321101 (1986) TXR 0009718 0, 2330, 1170, 590, and 300 µg/mL Acceptable/Guideline	Negative- Chromosome aberrations were not induced in a cultured CHO cells at concentrations tested either with or without S-9 activation.
870.5395 Erythrocyte Micronucleus Assay (Mice)	47899528 (2006) TXR 0055497 0, 250, 500, and 1000 mg/kg by gavage (corn oil) Acceptable/Guideline	Negative, was neither clastogenic nor aneugenic in mouse bone marrow. At doses of 250 mg/kg or more, slight hypo-activity and ataxia were observed
870.5550 Unscheduled DNA Synthesis (UDS)	00143001 (1979) TXR 0004286 Acceptable/Guideline	Negative- No evidence of UDS at levels 0.1 to 3000 µg/mL
In Vivo Comet Test (Rat)	51129101 (2019) TXR 0058082 0, 37.5, 75, or 150 mg/kg/day Acceptable/Non-Guideline	DNA damage reported in duodenum of male rats at 37.5 and 75 mg/kg/day. DNA damage was observed in the presence of "hedgehog" cells suggestive evidence of cell death (cytotoxicity) No evidence of genotoxicity or hedgehog cells were seen in the liver
Histopathological Study (Follow-Up to Comet Assay)	51129102 (2020) TXR 0058082 0, 37.5, or 75 mg/kg/day Acceptable/Non-Guideline	No evidence of treatment-related cytotoxicity, necrosis, or apoptosis
Mechanistic Follow-Up Study in Rats (Follow-Up to Comet Assay)	51129103 (2020) TXR 0058082 0 or 75 mg/kg/day Acceptable/Non-Guideline	Inconclusive regarding the mechanism of DNA damage
Duodenum Kinetics in Rats (Follow-Up to Comet Assay)	51129104 (2020) TXR 0058082 75 mg/kg/day Acceptable/Non-Guideline	Dicamba was rapidly absorbed when administered by oral gavage and similar concentrations were observed in the duodenum and liver, although DNA damage was only observed in the duodenum in the comet assay
OECD 488 Transgenic Mice (Muta™ Mouse) Gene Mutation Assay	51129105 (2020) TXR 0058082 0, 1200, 3000, or 7000 ppm (equivalent to 0, 176.4, 431.1, and 924.9 mg/kg/day) Acceptable/Non-Guideline	Did not result in the induction of gene mutations in the duodenum of the transgenic mice

<b>Table A.3.8. Sub-chronic, Chronic and Other Toxicity Profile for Dicamba Acid</b>		
<b>Guideline No./ Study Type/</b>	<b>MRID No. (Year), TXR No. Doses/Classification</b>	<b>Results</b>
870.6200 Acute Neurotoxicity (Rat)	42774104 (1993) TXR 0010653 0,300,600,1200 mg/kg Acceptable/Guideline	NOAEL= Not Established LOAEL= 300 mg/kg based on severe neurological signs (impaired respiration, rigidity upon handling, prodding, or dropping, impaired gait and righting reflex in both sexes.
870.6200 Sub-chronic Neurotoxicity (Rat)	43245210 (1994) TXR 0011493 0,3000,6000,12000 ppm M:0,197.1,401.4,767.9 mg/kg/day F: 0,253.4,472.0,1028.9 mg/kg/day Acceptable/Guideline	NOAEL= 401.4/472.0 mg/kg/day (M/F). LOAEL= 767.9/1028.9 mg/kg/day (M/F) based on rigidity body tone, slightly impaired righting reflex and gait.
870.3100 and 870.6200 Combined Sub- chronic Toxicity/ Sub-chronic Neurotoxicity Study (Rat)	48358001 (2011) TXR 0055497 0, 500, 3000, 6000, 12000 ppm M: 0, 34, 197, 397, 803 mg/kg/day F: 0, 39, 230, 458, 938 mg/kg/day CrI:CD® [SD] rats Acceptable/Guideline	NOAEL = 397/458 mg/kg/day (M/F) LOAEL = 803/938 mg/kg/day (M/F) based on behavioral signs (uncoordinated righting, decreased hindlimb foot splay, unkempt appearance, gasping, rales in males and impaired equilibrium, rigid muscle tone in females)
870.7485 Metabolism and Pharmacokinetics	44609801 (1998) TXR 0050578 Acceptable/Non-guideline 46022302 (2003) TXR 0052156 Acceptable/Non-guideline 46022303 (2003) TXR 0052156 Acceptable/Non-guideline 00028261(1967) TXR 0004036 Acceptable/guideline	Rapidly absorbed and rapidly excreted in urine and feces. Dicamba is not metabolized or bioaccumulation. Approximately 13% of dicamba in the urine is conjugated as the glucuronide.
870.7800 Immunotoxicity (Rat)	48081601 (2010) TXR 0050539 0, 500, 1500, or 4000 ppm (0, 37, 108, or 307 mg/kg/day) Acceptable/Guideline	Negative for immunotoxicity The NOAEL for immunotoxicity and systemic toxicity is 307 mg/kg/day. LOAEL is undetermined

<b>Table A.3.9. Sub-chronic, Chronic and Other Toxicity Profile for Dicamba Metabolites and BAPMA Salt.</b>		
<b>Study Type Chemical</b>	<b>MRID (year)</b>	<b>Results</b>
870.1100 DCSA Acute Oral Toxicity	47899504 (2007) TXR 0055497 Acceptable/Guideline	LD <sub>50</sub> = 2641 mg/kg Wobbly gait at 2000 mg/kg
870.1100 DCGA Acute Oral Toxicity	47899505 (2009) TXR 0055497 Acceptable/Guideline	LD <sub>50</sub> = 1460 mg/kg
870.3050 DCGA Subchronic Toxicity (Rat, 28 days)	47899506 (2009) TXR 0055497 0, 500, 3000, 6000, 12000 ppm M: 0, 40, 240, 474, 956 mg/kg/day F: 0, 45, 265, 519, 1063 mg/kg/day for females. Acceptable/Guideline	Included FOB and motor activity. NOAEL = 474 mg/kg/day LOAEL = 956 mg/kg/day based upon decreased BW in males
870.3100 DCSA Subchronic Toxicity (Rat, 90 days)	47899507 (2009) TXR 0055497 0, 500, 3000, 6000, 12000 ppm M: 0, 32, 195, 362, 659 mg/kg/day F: 0, 37, 222, 436, 719 mg/kg/day CrI:CD <sup>0</sup> [SD] rats Acceptable/Guideline	Included FOB and MA. NOAEL = 362 mg/kg/day LOAEL = 659 mg/kg/day based on decreased body weight, increased motor activity, decreased hematological parameters (i.e. RBC count), and increased serum liver enzymes
870.3100 Dicamba BAPMA 90-Day Toxicity Study (Rat)	49441801 (2014) M: 0, 257, 513, 1027 mg/kg/day F: 0, 294, 589, 1178 mg/kg/day Acceptable/Guideline	NOAEL = 513/589 mg/kg/day (M/F) (357/409 as Acid form) LOAEL = 1027/1178 mg/kg/day (M/F) (714/819 as Acid Form), based on altered hematology, kidney effects, increased clotting time and clinical chemistry parameters
870.3150 DCSA Subchronic Toxicity (Dog, 90 days)	48358002 (2011) TXR 0055497 0, 15, 50 and 150 mg/kg/day 90- day capsule study. Acceptable/Guideline	NOAEL = 50 mg/kg/day LOAEL = 150 mg/kg/day based on mortality, decreased body weight, clinical signs (abnormal excreta and emesis), and increased clotting time.
870.3200 Dicamba DGA 21-Day Dermal Study (Rabbits)	43554206 (1994) TXR 0011636 Diglycolamine salt (DGA, 59%) of dicamba at 0, 100, 500 or 1000 mg/kg, 6 hours/day Acceptable/Guideline	NOAEL = 1000 mg/kg/day (Limit-Dose) for dermal irritation and systemic toxicity. LOAEL = Not established for either end-point.
870.3200 Dicamba IPA 21-Day Dermal Study (Rabbits)	43554207 (1994) TXR 0011636 Isopropylamine salt (IPA, 41%) of dicamba at 0, 100, 500 or 1000 mg/kg, 6 hours/day, 5 days/week Acceptable/Guideline	NOAEL = 1000 mg/kg/day (Limit-Dose) for dermal irritation and systemic toxicity. LOAEL = not established for either end-point.

<b>Table A.3.9. Sub-chronic, Chronic and Other Toxicity Profile for Dicamba Metabolites and BAPMA Salt.</b>		
<b>Study Type Chemical</b>	<b>MRID (year)</b>	<b>Results</b>
870.3465 Dicamba BAPMA 28-Day Inhalation Toxicity Study-Rats	49441803 (2014) 0, 0.0014, 0.0070, 0.0352 mg/L (0.001, 0.005, 0.025 as acid equivalent) Acceptable/Guideline	NOAEC = Not Established LOAEC = 0.0014 mg/L (LDT), based on ulcers in epithelial tissues of the larynx and single/multi-focal hyperplasia in the larynx (0.001 as acid equivalent)
870.3650 BAPMA Base OECD 422 Developmental- Reproduction Screening Test	N/A	NOAEL: 25 mg/kg/day LOAEL: 100 mg/kg/day based on decreased motor activity and decreased water consumption. At 500 mg/kg/day excessive toxicity and dam deaths
870.3700a DCSA Prenatal Developmental (Rat)	47899519 (2007), 47899518 (Range-Finding Study) TXR 0055497 0, 10, 30, 100 mg/kg/day (GD 6- 19) CrI:CD(SD) rats	<b>Maternal</b> NOAEL: 100 mg/kg/day, highest dose tested LOAEL: not attained <b>Developmental</b> NOAEL: 100 mg/kg/day, highest dose tested LOAEL: not attained Classified acceptable/guideline when considered with range-finding study. <u>Range-finding study:</u> 0, 50, 200, 500 or 1000 mg/kg/day: 8 females/dose 200 mg/kg/day: clinical signs (rales, red/clear material on body), decreased fetal weight 500 mg/kg/day: mortality, early resorptions in all survivors
870.3700a DCGA Prenatal Developmental Range-Finding Study (Rat)	47899520 (2009) TXR 0055497 0, 50, 200, 500, 1000 mg/kg/day Acceptable/Guideline	<b>Maternal:</b> NOAEL: 50 mg/kg/day LOAEL: 200 mg/kg/day based on signs of rales, clear material on body At 500 mg/kg/day: BW 4.0-6.6% lower GD 13-20 At 1000 mg/kg/day: Mortality. BW 4.4-12.1% lower GD 12-20 <b>Developmental:</b> No effects on uterine growth, survival, external malformations or variations. Fetuses received external exam only, no skeletal examination.
870.3700a Dicamba BAPMA Prenatal Developmental Toxicity Study (Rat)	49441802 (2014) 0, 29, 86, 288 mg/kg/day Acceptable/Guideline	<b>Maternal:</b> NOAEL = 29 mg/kg/day in dams (20 as Acid equivalent) LOAEL = 86 mg/kg/day in dams, based on ataxia, unsteady gait and convulsions (60 as Acid equivalent) <b>Developmental</b> NOAEL > 288 mg/kg/day (200 as acid equivalent)

<b>Table A.3.9. Sub-chronic, Chronic and Other Toxicity Profile for Dicamba Metabolites and BAPMA Salt.</b>		
<b>Study Type Chemical</b>	<b>MRID (year)</b>	<b>Results</b>
870.3700b  DCSA Prenatal Developmental (New Zealand White Rabbit)	47899522 (2009) TXR 0055497  0, 10, 25, 65 mg/kg/day (GD 6- 28)  Classified acceptable/guideline when considered with range- finding study  47899521 (2010) Range-finding study  0, 10, 30, 100, 300 mg/kg/day (6 females/dose)	<b>Maternal</b> NOAEL: 65 mg/kg/day (HDT) LOAEL = Not Established  <b>Developmental</b> NOAEL: 65 mg/kg/day (HDT) LOAEL = Not Established Classified acceptable/guideline when considered with range-finding study.  <u>Range-finding study:</u> 300 mg/kg/day was lethal dose
870.3800  DCSA Reproduction and Fertility Effects (Rat)	47899517 (2009) TXR 0055497  0, 50, 500, 5000 ppm M: 0, 4, 37, 362 mg/kg/day (F <sub>0</sub> generation) F: 0, 4, 43, 414 mg/kg/day (F <sub>0</sub> generation)  Crl:CD(SD) rats  Acceptable/Guideline	<b>Parental</b> NOAEL = 37 mg/kg/day LOAEL = 362 mg/kg/day based upon decreased body weight  <b>Reproduction</b> NOAEL = 362 mg/kg/day (HDT) LOAEL = Not Established  <b>Offspring</b> NOAEL = 4 mg/kg/day LOAEL = 37 mg/kg/day based upon decreased pup body weight in F <sub>1</sub> pups on postnatal days 14 and 21 during lactation and week 18 in females. At 5000 ppm, high incidence of pup mortality
870.4200a  DCSA Combined Chronic Toxicity/ Carcinogenicity (Rat)	47899516 (2009), 48358003 (2011) TXR 0055497  (0, 10, 100, 300, 1000, 3000 ppm) M: 0.5, 5.0, 14.6, 48.8, and 150.1 mg/kg/day F: 0.6, 6.1, 18.4, 60.9, and 181.5 mg/kg/day  Crl:CD®[SD] rats  Acceptable/Guideline	NOAEL = 150 mg/kg/day (HDT); Not carcinogenic. LOAEL = Not established
870.5100  DCSA Bacterial Reverse Mutation Test	47899509 (2006) TXR 0055497  Acceptable/Guideline	Negative- Not Mutagenic
870.5100  DCGA Bacterial Reverse Mutation Test	47899514 (2009) TXR 0055497  Acceptable/Guideline	Negative- Not Mutagenic

<b>Table A.3.9. Sub-chronic, Chronic and Other Toxicity Profile for Dicamba Metabolites and BAPMA Salt.</b>		
<b>Study Type Chemical</b>	<b>MRID (year)</b>	<b>Results</b>
870.5100 Dicamba BAPMA Bacterial Reverse Mutation Test	48718001 (2011) TXR 0056537 Acceptable/Guideline	Negative- Not Mutagenic
870.5100 Dicamba DMA Bacterial Reverse Mutation Test	43310301 (1994) TXR 0012000 Acceptable/Guideline	Negative- Not Mutagenic
870.5100 Dicamba IPA Bacterial Reverse Mutation Test	43310303 (1994) TXR 0012000 Acceptable/Guideline	Negative- Not Mutagenic
870. 5300 DCSA Mammalian Cell Gene Mutation (CHO)	47899512 (2006) TXR 0055497 Acceptable/Guideline	Negative- Not Mutagenic
870.5300 Dicamba BAPMA Mammalian Cell Gene Mutation (CHO)	48718002 (2012) TXR 0056537 Acceptable/Guideline	Negative- Not Mutagenic
870.5300 Dicamba DMA <i>In vitro</i> Mammalian Cell Gene Mutation- Mouse Lymphoma (L5178Y) Cells	43310304 (1994) TXR 0012000 Acceptable/Guideline	Negative- Not Mutagenic
870.5300 Dicamba IPA <i>In vitro</i> Mammalian Cell Gene Mutation- Mouse Lymphoma (L5178Y) Cells	43310306 (1994) TXR 0012000 Acceptable/Guideline	Negative- Not Mutagenic
870.5375 DCSA Chromosome aberration assay in human lymphocytes	47899510 (2006) TXR 0055497 Unacceptable/Non-Guideline	No conclusions can be reached; the data are inconclusive.
870.5375 Dicamba BAPMA Chromosomal aberration assay in human lymphocytes	48718003 (2012) TXR 0056537 Acceptable/Guideline	Positive, clastogenic +/- S9 fraction
870.5385 DCSA Chromosome aberration assay in rat bone marrow	47899513 (2006) TXR 0055497 Acceptable/Guideline	Negative- Not Mutagenic

Study Type Chemical	MRID (year)	Results
870.5385 DCGA Chromosome aberration assay in rat bone marrow	47899515 (2009) TXR 0055497 Acceptable/Guideline	Negative- Not Mutagenic
870.5395 DCSA Erythrocyte micronucleus assay in mice	47899511 (2006) TXR 0055497 0, 250, 500, and 1000 mg/kg by gavage (corn oil) Range-finding study: 0, 500, 1000, and 2000 mg/kg Acceptable/Guideline	Negative, did not induce a clastogenic or aneugenic response in mouse bone marrow cells of male mice. At doses above 1000 mg/kg, hypo-activity, squinted eyes, hunched posture clinical signs
870.5395 Dicamba BAPMA Bone marrow micronucleus assay in mice	48718004 (2012) TXR 0056537 0, 500, 1000 and 2000 mg/kg by gavage (water) Acceptable/Guideline	Negative, is neither clastogenic nor aneugenic up to the limit dose in vivo in mice. At doses of 500 mg/kg or more, hunched posture and reduced general condition were observed
870.5395 Dicamba IPA Bone Marrow Micronucleus Assay in mice	43354334 (1994) TXR 0012293 0, 500, 1000, 2000 mg/kg (IP) Acceptable/Guideline	Non-Mutagenic- no significant increase in frequency of MPCEs in bone marrow after treatment
870.5395 Dicamba DMA Bone Marrow Micronucleus Assay in mice	43354332 (1994) TXR 0012293 0, 450, 900, 1800 mg/kg (IP) Acceptable/Guideline	Non-Mutagenic- no significant increase in frequency of MPCEs in bone marrow after treatment
870.7485 DCSA Metabolism (single dose)	47899502 (2006) TXR 0055497 100 mg/kg Acceptable/Guideline	Extensively absorbed and excreted rapidly in urine with little metabolism.
870.7485 DCSA Metabolism (repeated doses)	47899503 (2006) TXR 0055497 42, 125, 250, 375, or 500 mg/kg/day Acceptable/Guideline	Well absorbed and rapidly excreted in urine with minimal metabolism.

Study	Dicamba Acid NOAEL/LOAEL	Dicamba BAPMA Salt NOAEL/LOAEL	DCSA Metabolite NOAEL/LOAEL
90-Day Oral Toxicity (Rat)	NOAEL= 479.4/535.6 mg/kg/day (M/F) LOAEL= 1000/1065.3 mg/kg/day (M/F), based on clinical signs, decreased BWG, increased liver weight,	NOAEL = 513/589 mg/kg/day (M/F) (357/409 as Acid form) LOAEL = 1027/1178 mg/kg/day (M/F) (714/819 as Acid Form), based on	NOAEL = 362 mg/kg/day LOAEL = 659 mg/kg/day, based on decreased BW, increased motor activity, decreased hematological parameters, increased liver enzymes

<b>Table A.3.10. Dicamba BAPMA Salt Toxicity: Comparison to Dicamba Acid and DCSA Metabolite.</b>			
<b>Study</b>	<b>Dicamba Acid NOAEL/LOAEL</b>	<b>Dicamba BAPMA Salt NOAEL/LOAEL</b>	<b>DCSA Metabolite NOAEL/LOAEL</b>
	increased hepatocyte hypertrophy and hepatocellular pigmentation.	altered hematology and clinical chemistry parameters	
Prenatal Developmental Toxicity (Rat)	<p><b>Maternal</b> NOAEL = 160 mg/kg/day LOAEL = 400 mg/kg/day in dams, based on mortality, ataxia, decreased motor activity</p> <p><b>Developmental</b> NOAEL &gt; 400 mg/kg/day</p>	<p><b>Maternal</b> NOAEL = 29 mg/kg/day in dams (20 as Acid form) LOAEL = 86 mg/kg/day in dams, based on ataxia, unsteady gait and convulsions (60 as Acid Form)</p> <p><b>Developmental</b> NOAEL &gt; 288 mg/kg/day (200 as acid equivalent)</p>	<p><b>Maternal</b> NOAEL &gt; 100 (HDT) in dams</p> <p><b>Developmental</b> NOAEL &gt; 100 (HDT)</p> <p><u>Range Finding Study:</u> At 200 mg/kg/day there was decreased fetal weight and mortality/early resorptions at 500 mg/kg/day</p>
Reproduction and Fertility Effects (Rat)	<p><b>Parental/Systemic:</b> NOAEL= 122/136 mg/kg/day (M/F) LOAEL= 419/450 mg/kg/day (M/F) based on clinical signs (slow righting reflex).</p> <p><b>Reproductive:</b> NOAEL=122 mg/kg/day LOAEL= 419 mg/kg/day based on delayed sexual maturation in F1 males.</p> <p><b>Offspring:</b> NOAEL=136 mg/kg/day LOAEL= 450 mg/kg/day based on impaired pup growth (decreased pup weights) in the F1 and F2B generations during lactation period.</p>	<p><b>BAPMA Base Cation</b> OECD 422 Reproduction Study</p> <p>NOAEL = 25 mg/kg/day LOAEL = 100 mg/kg/day based on decreased motor activity and water consumption.</p> <p>At 500 mg/kg/day dam deaths</p>	<p><b>Parental</b> NOAEL = 37 mg/kg/day LOAEL = 362 mg/kg/day based upon decreased body weight.</p> <p><b>Reproductive</b> NOAEL = 362 mg/kg/day (HDT) LOAEL = Not Established</p> <p><b>Offspring</b> NOAEL = 4 mg/kg/day LOAEL = 37 mg/kg/day based upon decreased pup body weight in F<sub>1</sub> pups on postnatal days 14 and 21. At 5000 ppm, high incidence of pup mortality</p>
28-Day Inhalation Toxicity Study	<p>NOAEL=0.005/0.005 mg/L (M/F)</p> <p>LOAEL=0.050/0.050 mg/L (M/F), based on minimal multifocal bronchiole-alveolar hyperplasia in males; multiple microscopic findings in the lung and associated lymph nodes in females</p>	<p>NOAEL=Not Established</p> <p>LOAEL = 0.0014 mg/L (LDT), based on ulcers in epithelial tissues of the larynx and single/multi-focal hyperplasia in the larynx</p>	N/A

## A.4 Hazard Identification and Endpoint Selection

### A.4.1 Acute Reference Dose (aRfD) - Females age 13-49

Study Selected: An acute endpoint for women of childbearing age was not selected because there were no developmental effects attributed to an acute exposure. There was no developmental toxicity in the developmental rabbit study with DCSA, in the developmental rat study with dicamba, or in the main developmental rat study with DCSA. In the range finding rat study with DCSA, early resorptions occurred, but this effect was only at a dose that was lethal to dams. In the developmental rabbit study with dicamba, there was one abortion out of 20 does (gestation day 22), but this was after last day of dosing at a dose where the majority of does were showing signs of neurotoxicity. Therefore, the endpoint of neurotoxicity selected for the general population will be protective of potential offspring effects.

### A.4.2 Acute Reference Dose (aRfD) - General Population: Dicamba and Dicamba BAPMA

Study Selected: Prenatal Developmental Toxicity in Rats– Dicamba BAPMA

MRID No.: 49441802

Executive Summary: See Appendix A.5.9 (870.3700a)

Dose and Endpoint for Risk Assessment: The NOAEL in this study was 29 mg/kg/day based on neurological signs such as ataxia, unsteady gait and convulsions (LOAEL = 86 mg/kg/day).

Comments about Study/Endpoint/Uncertainty Factors: These effects are considered a single-dose effect since the signs occurred within 3 hours after dosing. This study was selected because it represents the most sensitive endpoint in the dicamba database for exposure to the parent dicamba acid or its BAPMA salt demonstrating an acute response with a well-defined NOAEL value. The selected POD will be protective of the effects of dicamba acid and the BAPMA salt via the oral route. The decreased body weights observed in the dicamba acid or DCSA reproduction studies were considered to be the result of multiple doses and not an acute effect, thus those studies were not appropriate for this scenario. The ACN study was considered for this scenario with a LOAEL of 300 mg/kg, however the study did not have a NOAEL value and with a 10X UF<sub>L</sub> applied to this LOAEL would result in a similar POD of 30 mg/kg. An uncertainty factor of 100X (10X to account for interspecies extrapolation, 10X for intraspecies variation, and 1X for FQPA SF) is applied to the NOAEL to obtain an aPAD of 0.29 mg/kg/day.

### A.4.3 Chronic Reference Dose (cRfD): Dicamba and Dicamba BAPMA

Study Selected: Reproductive toxicity study in rats – DCSA Metabolite

MRID No.: 47899517

Executive Summary: See Appendix A.5.9 (870.3800)

Dose and Endpoint for Risk Assessment: NOAEL = 4 mg/kg/day based on decreased pup weights in F1 generation on PND 14 and 21 (both sexes) and week 18 (females) at a LOAEL of 37 mg/kg/day.

Comments about Study/Endpoint/Uncertainty Factors: This POD is protective of all chronic effects following exposure to dicamba acid or dicamba BAPMA salt. An uncertainty factor of 100X (10X to account for interspecies extrapolation, 10X for intraspecies variation, and 1X for FQPA SF) is applied to the NOAEL to obtain a cPAD of 0.04 mg/kg/day.

#### **A.4.4 Incidental Oral Exposure: Dicamba and Dicamba BAPMA**

Study Selected: Reproductive Toxicity Study in Rats- Dicamba Acid

MRID No.: 43137101

Executive Summary: See Appendix A.5.3 (870.3800)

Dose and Endpoint for Risk Assessment: The NOAEL in this study was 136 mg/kg/day based on decreased F1 and F2B pup weights (Offspring LOAEL = 450 mg/kg/day)

Comments about Study/Endpoint/Uncertainty Factors: The toxicology studies on the plant metabolites are not appropriate for this scenario since these metabolites are generated inside the plants and are unavailable for incidental oral exposure. The developmental studies are not appropriate for incidental oral scenarios involving hand-to-mouth behavior. The dicamba BAPMA salt has no residential uses other than potential for spray drift. The dicamba acid sub-chronic oral study in adult rats had a NOAEL of 479.4 mg/kg/day and a LOAEL of 1000 mg/kg/day and didn't provide the most sensitive POD for the incidental oral scenario life stage. Consequently, the most appropriate study was the multi-generation reproductive toxicity study in rats dosed with parent compound was selected based on impaired pup growth at 450 mg/kg/day (LOAEL); the NOAEL of 136 mg/kg/day was selected as the POD for this scenario. This POD will be protective of neurotoxicity in the other studies which occurred at higher doses. It is appropriate to use the reproduction study with dicamba, and not DCSA, because the population of concern, children, will be exposed mainly to dicamba through hand-to-mouth behaviors, and not to DCSA, which is not a mammalian metabolite. The DCSA metabolite is primarily present in dicamba-tolerant plants and not expected to be a concern for incidental oral scenarios. The LOC is a MOE of 100 which includes the 10X to account for interspecies extrapolation, 10X for intraspecies variation, and an FQPA factor of 1X).

#### **A.4.5 Dermal Exposure (Short- and Intermediate-Term)**

A dermal endpoint was not selected as there are no adverse systemic effects up to the limit dose (1000 mg/kg/day) in the dermal studies for dicamba acid, IPA salt and DGA salt. Additionally, the dicamba anion is the major component in the BAPMA salt and the BAPMA base component of the dicamba BAPMA salt is only 20% of the salt mass (and 28% on a molar basis), thus, the dicamba BAPMA salt is unlikely to have adverse dermal effects. In support, the acute dermal toxicity for the dicamba BAPMA salt is low (Category IV).

#### A.4.6 Inhalation Exposure (Short- and Intermediate-Term)

##### Dicamba

Study Selected: 28- Day Inhalation Toxicity Study in Rats- Dicamba Acid

MRID No.: 49461101

Executive Summary: See Appendix A.5.1 (870.3465)

Dose and Endpoint for Risk Assessment: The NOAEC in this study was 0.005 mg/L based on minimal multifocal bronchiole-alveolar hyperplasia in males with multiple microscopic findings in the lung and associated lymph nodes in females (LOAEC = 0.05 mg/L).

Comments about Study/Endpoint/Uncertainty Factors: The endpoint was selected from the route specific inhalation study. The endpoint is based on local respiratory effects observed which is protective of neurotoxicity in the other studies seen at much higher doses.

##### Dicamba BAPMA Salt

Study Selected: 28- Day Inhalation Toxicity Study in Rats- Dicamba BAPMA

MRID No.: 49441803

Executive Summary: See Appendix A.5.9 (870.3465)

Dose and Endpoint for Risk Assessment: The LOAEC in this study was 0.0014 mg/L based on local effects of ulcers and hyperplasia of the larynx (no NOAEC established).

Comments about Study/Endpoint/Uncertainty Factors: The endpoint was selected from the route specific inhalation study. The endpoint is based on local respiratory effects observed which is protective of neurotoxicity in the other studies seen at much higher doses.

The standard interspecies extrapolation UF can be reduced from 10X to 3X for dicamba acid and BAPMA salt due to the calculation of human equivalent concentrations (HECs) accounting for pharmacokinetic (not pharmacodynamic) interspecies differences. Therefore, the LOC for dicamba acid inhalation exposures is for MOEs less than 30 (3X for interspecies extrapolation, 10X for intraspecies variation, and 1X for FQPA SF when applicable). For BAPMA salt, an additional 10X UF<sub>L</sub> is applied due to lack of a study NOAEL. Therefore, the LOC for BAPMA salt inhalation exposures is for MOEs less than 300.

#### A.4.7 Carcinogenicity (All Routes)

Dicamba is classified as “*Not Likely to be Carcinogenic to Humans*” based on an absence of treatment-related tumors in mice and rats. Additionally, the mutagenicity studies generally did not demonstrate evidence of mutagenic potential for dicamba.

## A.5 Executive Summaries for Dicamba, Dicamba Metabolites and Dicamba Salts

### A.5.1 Sub-chronic Toxicity

#### 870.3100 90-Day Oral Toxicity - Rat

In a 13-week sub-chronic toxicity study (MRID 44623101), dicamba technical (89.4% a.i.) was administered to Hanlbm:WIST (Wistar) rats (10 or 20 rats/sex/dose) by feeding at dose levels of 0, 500, 3000, 6000, or 12,000 ppm (equivalent to 0/0, 40.1/43.2, 238.7/266.4, 479.4/535.6, or 1000.0/1065.3 mg/kg/day [M/F]) for 13 weeks. Following 13 weeks of treatment, 10 rats/sex/dose were sacrificed. Rats (10/sex) in the control and 12,000 ppm groups were maintained for a 4-week recovery period to determine the reversibility of effects.

No treatment-related deaths were observed in any treatment group. The liver was the target organ, as evidenced by microscopic liver changes associated with clinical serum chemistry changes and increased relative (to body) liver weights (-20-23%) in both sexes at the high dose. The livers of the 12,000 ppm females exhibited slight centrilobular hepatocyte hypertrophy (4/10) and an increased incidence of minimal to moderate hepatocellular pigmentation (5/10). Both sexes exhibited increased alkaline phosphatase (-62-76%), serum alanine aminotransferase (-59-66%), and serum aspartate aminotransferase (-29%) activities compared to the controls. Females exhibited an increase in mean gamma glutamyl transferase activity (-136%) while males showed a decrease activity (~50%) compared to the controls.

Other effects observed in the 12,000 ppm rats were transient hypothermia (weeks 1-4), reduced activity, slower movements, decreased food consumption, and less efficient food utilization than the controls throughout the treatment period. Lower mean final body weights (~18-20%), body weight gains (~28-40%) and adipose tissue content were observed compared to the controls. Decreases in protein (~10-15%) and globulin (~16-26%) levels were observed in both sexes. In females, decreased mean hemoglobin concentration (~4%) and red blood cell counts (~4%), and decreased mean corpuscular hemoglobin concentration (~3%) were observed. Significant ( $p < 0.05$  or  $p < 0.01$ ) increases of white blood cell count (-13%) and lymphocyte count (-33%) were observed in 12000 ppm females compared to the controls. Males had a lower mean platelet count (~7%) and shorter partial thromboplastin time (~11%) compared to the controls. Urinalysis showed that males excreted more triple phosphate crystals in the 12000 ppm group, whereas females excreted more uric acid crystals in the 12000 and 6000 ppm groups at week 12. Following a 4-week recovery period, all observed effects were recovered.

**The LOAEL for this study is 12,000 ppm (1000 mg/kg/day), based on clinical signs, reduced body weight gains, hematological and clinical serum chemistry changes in both sexes, centrolobular hepatocyte hypertrophy and hepatocellular pigmentation in females, and increased relative (to body) liver weights for both sexes. The NOAEL is 6000 ppm (479 mg/kg/day).**

#### 870.3100 90-Day Oral Toxicity - Mouse

N/A

**870.3150 90-Day Oral Toxicity - Dog**

N/A- See chronic dog study

**870.3200 21/28-Day Dermal Toxicity – Rat**

In a 28-day dermal toxicity study (MRID 45814501), Dicamba (91.0% a.i., batch #B2826511) was applied to the shaved skin of 10 male and 10 female Alpk:AP fSD rats /sex/dose at dose levels of 0, 30, 300 or 1000 mg/kg bw/day, 6 hours/day for 5 days/week during a 28-day period.

Clinical observations, body weights and food consumption were measured throughout the study. Urine samples were taken for clinical pathology during week 4 of the study. A functional observational battery of all animals consisting of: detailed clinical observations, including quantitative assessments of landing foot splay, sensory perception and muscle weakness, and assessment of motor activity was performed on day 22. At the end of the scheduled period, the animals were killed and subjected to a post mortem examination. Blood samples were taken for clinical pathology, selected organs and specified tissues were taken for subsequent histopathological examination.

There were no changes indicative of systemic toxicity in either sex. There were no compound related effects in mortality, clinical signs, body weight, food consumption, hematology, clinical chemistry, organ weights, or gross and histologic pathology. Histopathological changes indicative of irritation were seen in skin from the application site in both sexes given 1000 or 300 mg/kg/day and in some males given 30 mg/kg/day. **A LOAEL for systemic toxicity was not established. The NOAEL is 1000 mg/kg/day the highest dose tested.**

This 28-day dermal toxicity study in the rat is **acceptable/ guideline** and satisfies the guideline requirement for a 28-day dermal toxicity study (OPPTS 870.3200; OECD 410) in the rat.

**21/28-Day Dermal Toxicity – Rabbit (870.3200)**

In a 21-day dermal study (MRID 40547901), New Zealand white rabbits (5/sex/group) received 15 repeated dermal applications of Dicamba in deionized water at dose levels of 0, 40, 200, or 1000 mg/kg/day, 6 hours/day, 5 days/week over a three-week period. No systemic toxicity was observed at any dose level. Dose-related dermal irritation was observed at the application sites. Desquamation was seen predominantly in the 1000 mg/kg/day group while moderate erythema, moderate edema and atonia were observed exclusively in the 1000 mg/kg/day group. A dose-related incidence of fissuring was noted in the 200 and 1000 mg/kg/day groups. The severity of acanthosis and the incidence of hyperkeratosis was increased at these sites in rabbits at 200 and 1000 mg/kg. **For systemic toxicity, the NOAEL was 1000 mg/kg/day (HDT); a systemic LOAEL was not established.**

This 28-day dermal toxicity study in the rat is **acceptable/ guideline** and satisfies the guideline requirement for a 21-day dermal toxicity study (OPPTS 870.3200; OECD 410) in the rabbit.

### **870.3465 90-Day Inhalation – Rat**

In a nose-only inhalation toxicity study (MRID 49461101), four groups of Crl:WI(Han) rats (10/sex/group; ~7 weeks of age) were administered BAS 183 H [93.9% (Batch No. 0002B01BA-251)] as a dust aerosol at exposure concentrations of 0, 0.001, 0.005, or 0.050 mg/L for 28 days.

There were no mortalities or clinical signs observed at any exposure concentration. No substance-related adverse findings were observed on food consumption, hematology, clinical chemistry, or during ophthalmological examinations. Body weight was not adversely affected.

At 0.05 mg/L, lung weight was statistically increased in both sexes, and the following lung histological lesions were increased in incidence (# affected/10 in treated vs controls) in both sexes: (i) minimal to slight alveolar histiocytosis (10 vs 4 in males; 10 vs 1 in females); (ii) minimal macrophage aggregates (6 vs 0 in males; 8 vs 0 in females); (iii) minimal to slight bronchial hypertrophy/hyperplasia (10 vs 0 in males and females); and (iv) minimal to slight bronchiole-alveolar hyperplasia (8 vs 0 in males [only minimal]; 9 vs 0 in females). Additionally, one female had a few macrophage aggregates in the bronchus-associated lymphoid tissue. No adverse, treatment-related finding was noted at 0.001 or 0.005 mg/L.

**The LOAEL in male Wistar rats was 0.050 mg/L based on minimal multifocal bronchiole-alveolar hyperplasia in the lung, and 0.050 mg/L in females based on multiple microscopic findings in the lung and associated lymph nodes. The NOAEL was 0.005 mg/L in males and 0.005 mg/L in females.**

This inhalation toxicity study is classified as **Acceptable (Guideline)** and satisfies the guideline requirement for 4-week inhalation toxicity study in rats (OCSP 870.3465).

#### **A.5.2 Prenatal Developmental Toxicity**

##### **870.3700a Prenatal Developmental Toxicity Study - Rat**

In a developmental toxicity study (MRID No. 00084024), pregnant (CD Charles River) rats (25/dose group) received gavage administration of dicamba (85.3%) in corn oil at dose levels of 0, 64, 160, or 400 mg/kg/day during gestation days 6 through 19. Maternal toxicity limited to the high dose (400 mg/kg/day) was characterized by mortality in three gravid and one non-gravid dams that exhibited neurotoxic signs prior to death; clinical signs of nervous system toxicity that included ataxia, salivation, stiffening of the body when held, and decreased motor activity; statistically significant ( $p < 0.05$ ) decreases in body weight gain during the dosing period; and concomitant decreases in food consumption. Dicamba had no effect on any of the cesarean parameters.

**For maternal toxicity, the NOAEL was 160 mg/kg/day and the LOAEL was 400 mg/kg/day based on mortality, clinical signs, body weight changes and decreases in food consumption.** No Treatment-related fetal gross external, skeletal or visceral anomalies (malformations or variations) were seen at any dose level.

**For developmental toxicity, the NOAEL was >400 mg/kg/day; a LOAEL was not established.**

This study is classified **acceptable/guideline** (OPPTS 870.3700a) and satisfies the requirements for a developmental toxicity study in the rat.

#### **870.3700b Prenatal Developmental Toxicity Study - Rabbit**

In a developmental toxicity study (MRID No. 42429401), inseminated New Zealand White rabbit (19-20/dose) were given oral capsules containing dicamba (90.5%) at dose levels of 0, 30, 150, or 300 mg/kg/day from days 6 through 18 of gestation. No maternal or developmental toxicity was observed at 30 mg/kg/day. At 150 mg/kg/day, maternal toxicity was characterized by abortion (5%) at day 22 and clinical signs such as ataxia, rales, decreased motor activity. At 300 mg/kg/day maternal toxicity was manifested by abortions (20%), clinical signs, decreased body weight and body weight gain and food consumption. Developmental toxicity at 300 mg/kg/day was manifested by irregular ossification of the nasal bones of the skull. At 150 mg/kg/day, increased incidence of abortion was observed and was considered developmental toxicity. In a range-finding study, NZW rabbits were dosed at 0, 62.5, 125, 250, or 500 mg/kg/day from days 6 through 18 of gestation. No maternal or developmental toxicity was observed at 62.5 mg/kg/day. Treatment-related maternal toxicity was manifested by mortality, increased resorptions and reduction in the litter size at 500 mg/kg/day. Clinical signs occurred at 125, 250, and 500 mg/kg/day. Cesarean sections revealed no treatment-related differences between treated and control groups, and no external malformation or variations were seen in any of the fetuses of the treated does.

**The NOAEL for maternal toxicity was 62.5 mg/kg/day and the LOAEL was 150 mg/kg/day based on increased incidences of abortion and clinical signs (i.e., decreased motor activity, ataxia). For developmental toxicity, the NOAEL was 62.5 mg/kg/day and the LOAEL was 150 mg/kg/day based on increased incidence of abortion.**

This study is classified **acceptable/guideline** (OPPTS 870.3700b; OECD 414) and satisfies the requirements for a developmental toxicity study in the rabbit.

#### **A.5.3 Reproductive Toxicity**

##### **870.3800 Reproduction and Fertility Effects - Rat**

In a two-generation reproduction study (MRID 43137101), Sprague-Dawley rats (32 or 28/group) received dicamba technical (86.5%) in the diet at dose levels of 0, 500, 1500, or 5000 ppm (0, 40, 122, or 419 mg/kg/day for males and 0, 45, 136 or 450 mg/kg/day for females, respectively) for two generations. Systemic toxicity was observed at 5000 ppm, manifested as clinical signs in dams from both generations during lactation (tense/stiff body tone and slow righting reflex) and significantly increased relative liver to body weights (112% of control) in both generations and sexes, adults as well as weanlings. The increase (107%) in relative kidney weights observed at 1500 and/or 5000 ppm were not considered to be toxicologically significant due to lack of corroborative gross or histopathological lesions in the kidneys. Sexual maturation among male pups in the F1 generation was significantly delayed at 5000 ppm. Similar effects were not seen in females.

Significantly decreased pup body weights were observed in all generations and matings at 1500 ppm (86 - 90% of control) and at 5000 ppm (74 - 94% of control) throughout lactation, relative to the concurrent controls. There was no adverse effect on pup body weights during the F1 generation lactation period or post-weaning phase at the low and mid doses. However, the PND21 pup body weights for the 1500 ppm group (i.e. 136 mg/kg/day) were within the MARTA (Middle Atlantic Reproduction and Teratology Association, 1993) database historical control range and above the historical control mean value. The study concurrent control groups were also within the historical control range (37.3-65.1 grams). However, both the 2A and 2B generation concurrent control groups PND 21 pup body weights were over 2 standard deviations above the historical control mean value (i.e. 64.95, 61.76 versus 49.33 grams, respectively), thus the MARTA historical control results were utilized for toxicology decisions. As compared to the MARTA historical control database, there were only adverse decreases in pup body weight with statistical significance at 5000 ppm for the F1 generation at both PND 0 (-7.3%) and PND 21 (-7.9%) and the F2B generation at PND 21 (-12.4%).

The F1 animals chosen to produce the F2A and F2B generation offspring were not selected randomly, but rather the male and female animals with the median body weights in each litter were chosen, adding some bias to the F2 phase of the study.

**For parental systemic toxicity, the NOAEL was 122 and 136 mg/kg/day for males and females, respectively, and the LOAEL was 419 and 450 mg/kg/day in males and females based on clinical signs of neurotoxicity. For reproductive toxicity, the NOAEL was 122 mg/kg/day and the LOAEL was 419 mg/kg/day based on delayed sexual maturation in F<sub>1</sub> males. For offspring toxicity, the NOAEL was 136 mg/kg/day and the LOAEL was 450 mg/kg/day based on decreased pup body weight during the F1 and F2B generations during lactation.**

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.3800; OECD 416) for a two-generation reproduction study in the rat.

#### **A.5.4 Chronic Toxicity**

##### **870.4100a (870.4300) Chronic Toxicity – Rat**

See 870.4200a

##### **870.4100b Chronic Toxicity - Dog**

In a chronic oral toxicity study (MRID 40321102), dicamba (86.8, a.i., lot # 52625110) was administered to beagle dogs (4/sex/group) in diet at dose levels of 0, 100, 500, or 2500 ppm (0, 2, 11, or 52 mg/kg/day, respectively) for one year.

The investigated parameters in this study, which included behavior, mortality, body weight, food consumption, hematology, serum chemistry, urinalysis as well as macroscopic and histologic examination of tissues, did not reveal any apparent adverse effect from the test compound. **Therefore, the NOAEL for dicamba was 2500 ppm in the diet (about 52 mg/kg/day), the highest dosage**

**administered in this test. A study LOAEL was not observed. The absence of any adverse effects among treated animals indicated that the MTD was not attained.**

This one-year dog study is classified **Acceptable/Guideline** and satisfies the guideline requirement for a chronic toxicity study in dogs.

#### **A.5.5 Carcinogenicity**

##### **870.4200a Carcinogenicity Study - Rat**

In a combined chronic toxicity/carcinogenicity study (MRID 00146150), groups of 60 male and 60 female CD rats were fed diets containing dicamba (86.8% a.i.; Lot no. 52625110) at 0, 50, 250 or 2500 ppm for 115 (males) or 117 (females) weeks. These doses correspond to 0, 2, 11 or 107 mg/kg bw/day for males and 0, 3, 13 or 127 mg/kg bw/day for females. Treatment had no adverse effect on survival, body weight, body weight gain, food consumption, hematology, clinical chemistry, urinalysis, organ weights or gross pathology. Histopathology revealed increases in malignant lymphomas in males (0/60, 0/60, 4/60 and 4/60 at 0, 50, 250 and 2500 ppm, respectively) and thyroid parafollicular cell carcinomas in males (1/60, 0/60, 2/60 and 5/60 at 0, 50, 250 and 2500 ppm, respectively). The Cochran-Armitage trend test showed a statistically significant ( $p \leq 0.05$ ) tendency for the proportion of animals with tumors to increase steadily with increase in dose. Pairwise comparison (Fisher's Exact test) showed no statistical significance. Therefore, these tumors were not considered to be toxicologically significant.

Under the conditions of this study, dicamba was not carcinogenic in male or female rats at the doses tested. The lack of systemic toxicity indicate that the animals may have tolerated higher doses (i.e., an MTD was not achieved). However, the doses employed in this study were approved by the Agency (Memo: S. April to R. Taylor, RD, dated 09/26/86).

The administration of dicamba to rats up to 2500 ppm (107 mg/kg/day for males, 127 mg/kg/day for females) in the diet revealed increases in malignant lymphomas in males (0/60, 0/60, 4/60 and 4/60 at 0, 50, 250 and 2500 ppm, respectively) and thyroid parafollicular cell carcinomas in males (1/60, 0/60, 2/60 and 5/60 at 0, 50, 250 and 2500 ppm, respectively). The Cochran-Armitage trend test showed a statistically significant ( $p \leq 0.05$ ) tendency for the proportion of animals with tumors to increase steadily with increase in dose. Pairwise comparison (Fisher's Exact test) showed no statistical significance. Therefore, these tumors were not considered to be toxicologically significant.

The Dose Adequacy Review Team (DART) reviewed the dosages of the study and concluded that the dose levels in the chronic toxicity/carcinogenicity study in rats could have been higher based on kinetics data which indicated that saturation of excretion occurred at a dose ranging from >200 to 400 mg/kg/day. However, retesting at a dose greater than 300 mg/kg/day, for example, would not be recommended based on the saturation data, which showed evidence of saturation of excretion at >200 mg/kg/day. Retesting at a dose of 300 mg/kg/day would not be expected to alter the conclusion that there was no carcinogenic effect. Since the doses in the rat carcinogenicity study (107/127 mg/kg/day) were within a factor of around two-fold of the saturation point (>200-400 mg/kg/day), the doses were considered to be adequate for assessment of carcinogenicity. Therefore, the DART concluded that a new chronic toxicity/carcinogenicity study in the rat was not required (TXR No. 0053647).

### **870.4200b Carcinogenicity (feeding) - Mouse**

In a carcinogenicity study (MRID 40872401), groups of 52 male and 52 female CD-1 mice were fed diets containing dicamba (86.8% a.i.; Lot no. 52625110) at 0, 50, 150, 1000 or 3000 ppm for 89 (males) or 104 (females) weeks. These doses correspond to 0, 5.5, 17.2, 108 or 358 mg/kg bw/day for males and 0, 5.8, 18.8, 121 or 354 mg/kg bw/day for females. Mortality was significantly increased in males at 150 ppm and at 3000 ppm; the cause of mortality was amyloidosis. The incidence of this lesion was higher than any other single factor among males that died in all groups especially the high dose. Except for a significant decrease at 150 ppm, survival among treated females was comparable to that of the controls. Body weight gain was higher in treated males than control males while there was a 17% decrease in body weight gain in females at 3000 ppm. No treatment-related effects were seen in food consumption, hematology, organ weights or gross pathology. Histopathology revealed a statistically significant ( $p < 0.05$ ) increase in lymphosarcomas in females at 150 ppm only (8/52, 15%) compared to controls (2/52, 4%). The increase was not considered to be treatment-related due to lack of a dose-response and the incidences were within the historical control range (6-33%). Additionally, the incidence in the concurrent control (4%) was below the historical range.

Under the conditions of this study, dicamba was not carcinogenic in male or female mice at the doses tested. The lack of systemic toxicity indicate that the animals may have tolerated higher doses (i.e. and MTD was not achieved). However, the doses employed in this study were approved by the Agency (Memo: S. April to R. Taylor, RD, dated 11/15/84).

The administration of dicamba to mice up to 3000 ppm (358 mg/kg/day for males, 354 mg/kg/day for females) in the diet revealed a statistically significant ( $p < 0.05$ ) increase in lymphosarcomas in females at 150 ppm only (8/52, 15%) compared to controls (2/52, 4%). The increase was not considered to be treatment-related due to lack of a dose-response and the incidences were within the historical control range (6-33%). Additionally, the incidence in the concurrent control (4%) was below the historical range.

The DART revisited the 1995 decision by the RfD/Peer Review Committee that the mouse carcinogenicity study was not tested at a high enough doses to evaluate carcinogenicity in the mouse. The DART concluded that 3000 ppm is an adequate dose in the mouse cancer study and decided that a new mouse carcinogenicity study was not needed (TXR No. 0053647).

## A.5.6 Mutagenicity

### Gene Mutation

Guideline No./Study Type/MRID/Classification	Doses/Results
870.5100, Bacterial Reverse Mutation Test: <i>S. typhimurium</i> (TA1535, TA1537, TA1538, TA98, and TA100) MRID 00143001 Acceptable/Guideline	Results: Not Mutagenic
870.5100, Bacterial Reverse Mutation Test: <i>S. typhimurium</i> (TA1535, TA1537, TA98, and TA100) and <i>E. Coli</i> (WP2uvrA) MRID 47899525 Acceptable/Guideline	Preliminary Cytotoxicity Assay: 6.67, 10, 33.3, 66.7, 100, 333, 667, 1000, 3330 or 5000 µg/plate (±S9) Mutation Assay: 0, 33.3, 100, 333, 1000, 2500 or 5000 µg/plate (±S9) Vehicle Control/Solvent: DMSO Positive Controls: +S9: 2-Aminoanthracene, Benzo[a]pyrene; -S9: 2-Nitrofluorene, ICR-191, Sodium azide, 4-nitroquinoline-N-oxide Results: Not Mutagenic
870.5300, <i>In vitro</i> Mammalian Cell Gene Mutation Assay in CHO Cells MRID 47899526 Acceptable/Guideline	Preliminary Cytotoxicity Assay: 0, 4.7, 9.4, 18.8, 37.5, 75, 150, 300, 600, 1200, or 2400 µg/mL (±S9) Mutation Assay: 0, 1200, 1400, 1600, 1800, 2000, 2400 µg/mL (±S9) Vehicle Control/Solvent: DMSO Positive Control: +S9: 3-Methyl-cholanthrene; -S9: 5-Bromo-2' deoxyuridine Results: Not Mutagenic

### Cytogenetics

Guideline No./Study Type/MRID/Classification	Doses/Results
870.5375, <i>In Vitro</i> Mammalian Chromosome Aberration Test in Human Lymphocytes MRID 47899527 Acceptable/Guideline	Initial Trial: 0, 16.3, 23.3, 33.2, 47.5, 67.8, 96.8, 138, 198, 282, 403, 576, 823, 1180, 1680, 2400 µg/mL (±S9) Confirmatory Trial: +S9: 0, 450, 900, 1200, 1600, 2000, 2400; -S9: 0, 113, 225, 338, 450, 675, 900, 1200, 1600, 2000, 2400 Vehicle Control: DMSO Positive Control: +S9: Cyclophosphamide; -S9: Mitomycin C Results: Positive, however the S9 activated portion of the assay should have been repeated
870.5375, <i>In vitro</i> Mammalian Chromosomal Aberration Assay in CHO Cells MRID 40321101 Acceptable/Guideline	Preliminary Cytotoxicity Assay 1: 0.1, 0.3, 1, 3, 10, 30, 100, 300, 1000 µg/mL (±S9) Preliminary Cytotoxicity Assay 2: 740, 1100, 1460, 1830, 2180, 2560 µg/mL (±S9) Mutation Assay: 300, 590, 1170, 2330 µg/mL (±S9) Vehicle Control: DMSO Positive Control: +S9: Cyclophosphamide; S9: Triethylenemelamine Results: Not Mutagenic

**Other Genotoxicity**

<b>Guideline No./Study Type/MRID/Classification</b>	<b>Doses/Results</b>
870.5550, Unscheduled DNA Synthesis MRID 00143001 Acceptable/Guideline	0, 0.1, 1.0, 10, 100, 1000, 2000, 3000 µg/mL (±S9) Vehicle Control: DMSO 0.5% Positive Control: 4-nitroquinoline-N-oxide Results: Negative - did not induce UDS with or without metabolic activation
870.5395, Mammalian (mouse) Erythrocyte Micronucleus Assay MRID 47899528 Acceptable/Guideline	0, 250, 500, 1000 mg/kg Vehicle Control: Corn Oil (10 mL/kg) Positive Control: Cyclophosphamide (80 mg/kg) Results: Negative for clastogenic or aneugenic effects
In Vivo Comet Test (Rat) MRID 51129101 Acceptable/Non-Guideline	Comet Test: 0, 37.5, 75, 150 mg/kg Vehicle Control: Methylcellulose Positive Control: Ethyl methane-sulfonate (200 mg/kg) Results: DNA damage/hedgehog cells (cytotoxicity) in duodenum, no evidence in the liver
Histopathological Study (Follow-Up to Comet Assay) MRID 51129102 Acceptable/Non-Guideline	0, 37.5, 75 mg/kg Vehicle Control: Methylcellulose Results: Negative for cytotoxicity, necrosis, or apoptosis
Mechanistic Follow-Up Study in Rats (Follow- Up to Comet Assay) MRID 51129103 Acceptable/Non-Guideline	75 mg/kg Vehicle Control: Methylcellulose Positive Control: Ethyl methane-sulfonate (200 mg/kg) Results: Inconclusive regarding the mechanism of DNA damage
Duodenum Kinetics in Rats (Follow-Up to Comet Assay) MRID 51129104 Acceptable/Non-Guideline	75 mg/kg Vehicle Control: Methylcellulose Results: Rapidly absorbed, similar concentrations in duodenum and liver
OECD 488 Transgenic Mice (Muta™ Mouse) Gene Mutation Assay MRID 51129105 Acceptable/Non-Guideline	0, 176.4, 431.1, 924.9 mg/kg Positive Control: <i>N</i> -ethyl- <i>N</i> -nitrosourea (100 mg/kg) Results: Negative for mutagenicity in duodenum of transgenic mice

**A.5.7 Neurotoxicity****870.6100 Delayed Neurotoxicity Study - Hen**

N/A

**870.6200 Acute Neurotoxicity Screening Battery**

In an acute neurotoxicity study (MRID 42774104) groups of Crl:CD BR rats (10/sex/dose) received a single oral (gavage) administration of dicamba (86.9%) in corn oil at doses of 0, 300, 600, or 1200 mg/kg. Vehicle controls received corn oil only. Positive controls received acrylamide at 50 mg/kg/day by intraperitoneal injection on seven consecutive days. At 300 mg/kg, transiently impaired respiration; rigidity upon handling, prodding or dropping; freezing of movement when touched; decreased arousal and fewer rears/minute compared to controls; impairment of gait and righting reflex were observed in both sexes. In addition, males showed decreased forelimb grip strength. With the exception of the

decrease in forelimb grip strength, which persisted until day seven, these effects were observed only on the day of dosing. In addition, at 600 mg/kg, both sexes showed decreases in locomotor activity and males showed significant decreases in tail flick reflex and a raised posture when placed in an open field. These effects were also observed only on the day of dosing. At the highest dose level tested (1200 mg/kg), both males and females showed an impaired startle response to an auditory stimulus. The effect was significant in males on day seven and in females on the day of dosing. In addition, males showed decreases in body weight (5 - 9%), body weight gain (24%) and food consumption (13% between days 0 and 7).

**The LOAEL was 300 mg/kg based on the several neurologic signs listed above; a NOAEL was not established.**

The submitted study is classified as **acceptable/guideline** and satisfies the Guideline requirements (870.6200a) for an acute neurotoxicity study in rats.

#### **870.6200 Sub-chronic Neurotoxicity Screening Battery**

In a subchronic neurotoxicity study (MRID No. 43245210), Sprague-Dawley rats (10/sex/dose) were fed diets containing dicamba (86.9%) at 0, 3000, 6000, or 12000 ppm (0, 197.1, 401.4, 767.9 mg/kg/day for males and 0, 253.4, 472.0 or 1028.9 mg/kg/day for females, respectively) for 13 weeks. Neurobehavioral evaluations, consisting of FOB, locomotor activity, and auditory startle response, were conducted at pre-study and during Weeks 4, 8 and 13. No toxicologically significant differences were noted in either the mean body weights or food consumption of the treated animals. Neurobehavioral evaluations at the 4-, 8-, and 13-week evaluations revealed abnormal FOB observations consisting of rigid body tone, slightly impaired righting reflex and impaired gait. At Week 13 the incidences of these findings were decreased. Rigid body tone was also noted during evaluation of the righting reflex and landing foot splay.

**The NOAEL was 401 mg/kg/day and the LOAEL was 768 mg/kg/day based on rigid body tone, slightly impaired righting reflex and impaired gait.** The study is classified as **acceptable/guideline** and satisfies the guideline requirements (870.6200b) for a subchronic neurotoxicity study in the rat.

In a 90-day oral toxicity/neurotoxicity study in Sprague-Dawley (CrI:CD® [SD] rats (MRID 48358001), groups of 16 rats/sex were dosed with MON 11900 in daily diets with either 0, 500, 3000, 6000, or 12000 ppm test material, which corresponded to 0, 34, 197, 397, 803 mg/kg/day in males and 0, 39, 230, 458, 938 mg/kg/day in females. There were 6 animals /sex dose in subset A and B and 4/sex/dose in subset C. Subsets A and B were used for the functional observational battery (FOB) and subsets B and C were used for clinical and pathology determinations.

There were small body weight changes only in males. At the end of the study, 12000 ppm males weighed 5% less than controls with a cumulative weight gain of 9% less than controls; neither value was statistically significant.

Other than one death in a control male; all animals survived to sacrifice. Clinical observations in 12000 ppm males included unkempt appearance (2/16 males, vs 0/16 controls) and gasping/rales (1/16

males, 4 occurrences, vs 0/16 controls). Uncoordinated righting ability was noted in 3/12 males in the 12000 ppm group. There was also lower hindlimb footsplay in 12000 ppm males during week 7. Females in the 12000 ppm group had rigid muscle tone (6/16 females) and one of these showed an impaired equilibrium on 2 different times. Motor activity was unaffected by treatment.

**The NOAEL for MON 11900 is 397 mg/kg/day and the LOAEL is 803 mg/kg/day based on FOB and clinical observations (rigid muscle tone, impaired equilibrium, uncoordinated righting ability, and decreased lower hindlimb foot splay).**

This study is classified as acceptable/guideline and satisfies the guideline requirements for a 90-day rat toxicity study and neurotoxicity study (OECD 408 and EPA OPPTS 870.3100/870.6200).

#### **870.6300 Developmental Neurotoxicity Study**

N/A

#### **A.5.8 Metabolism**

##### **870.7485 Metabolism - Rat**

In a plasma kinetics study, (MRID 44609801), [phenyl-U-<sup>14</sup>C]- dicamba ( [<sup>14</sup>C]-dicamba; 86.0% a.i. radiochemical purity), was administered as a dietary admix to 4 male and 4 female Wistar and Sprague-Dawley at 900, 1500, 3000, 4500, and 12000 ppm (Wistar rats) and 900, 1500, 3000, 6000 and 9000 ppm (Sprague-Dawley rats) for fourteen days, followed by a radioactive dose of 90, 150, 300, 450 mg/kg bw (Wistar rats) and 75, 125, 250, 500 and 800 mg/kg bw by a single gavage dose (in 10 ml/kg body weight 0.5% Tylose CB 30.000 in aqua bidest). Plasma levels were measured at various time intervals following radioactive dose.

A preliminary study in Wistar rats suggests excessive toxicity following repeated gavage doses. Therefore, the main study in both strains of rats was conducted as a dietary ad mix followed by a gavage dose of radiolabeled dicamba. In both strains of rats, the plasma levels reached a maximum level after 0.5-1 hour following the gavage dose and declined thereafter. The AUC<sub>0-∞</sub> values were calculated from the plasma concentrations versus time curves at the respective dose levels indicated linear relationship with increase in dose up to a certain dose levels in both strains of rats indicating saturation of excretion. Initial plasma half-life was increased with increasing dose, but terminal half-life remains more or less constant in both strains of rats indicating saturation of excretion. Plasma half-life was increased with increasing dose giving no indication of saturation of oral absorption.

In Wistar rats, the increase in plasma AUC was linear with dose up to a level of 150 mg/kg bw in males and 300 mg/kg bw in females. Above these dose levels, plasma AUC-values increased more than dose. Sprague-Dawley rats showed similar results, with the increase in AUC being linear with dose up to a level of 125 and 250 mg/kg bw in males and females, respectively. Above these dose levels, plasma AUC-values increased more than dose. Considering that oral absorption was not saturated and that initial plasma levels went up with dose, the disproportionate increase in plasma AUC is clearly due to saturation of renal excretion of dicamba resulting in a longer plasma half-life. This is supported by half-life data in both species which showed an increase in plasma half-life with dose. This plasma kinetics study in the rats is classified **Acceptable/Non-guideline (§85-1)**.

In a plasma pharmacokinetic study (MRID 46022302), five groups of 4 male and 4 female Wistar rats received diets containing the equivalent of 50, 100, 200, 400, or 800 mg/kg dicamba/day for 90 days (Lot No. 52103810, 87.2% a.i.) . On study days 29, 63, and 91, dietary supplementation of dicamba was stopped and rats in each group received an equivalent gavage dose of  $^{14}\text{C}$ -dicamba (Lot No. 787-0102, >99% a.i., universally labeled in the phenyl group). Blood samples were drawn 0.5, 1, 2, 4, 6, 8, 12, 24, and 48 hours after treatment and the plasma radioactivity determined.

Absorption of the radiolabeled test material was rapid, with peak plasma concentrations found within 2 hours of treatment. Absorption was not saturated, even at the highest dose, as indicated by increasing plasma concentrations with dose. However, the increase in plasma concentration was disproportionate from dose as shown by the <sup>3</sup> 2-fold increase in AUC from one dose group to the next at doses >100 mg/kg. Elimination of radiolabel from the plasma was tri-phasic, with the terminal-phase consistent between doses. However, the initial elimination phase increased with dose, particularly in the 400 and 800 mg/kg dose groups and is consistent with excretion saturation. No significant treatment-related differences between the sexes or time of radiolabel administration were found. This plasma pharmacokinetic study in the rat is classified **Acceptable/Non-guideline** and satisfies its intent.

In a pharmacokinetic study (MRID 46022303), two groups of 3 male Wistar rats were given a single 200 mg/kg gavage dose of  $^{14}\text{C}$ -dicamba (Lot No. 787-0102, >99% a.i., universally labeled in the phenyl group). One group of rats was pretreated with a 150 mg/kg IP dose of probenecid, a known competitive inhibitor of renal anion transport, 30 minutes prior to dicamba dosing. Blood samples were drawn 0.5, 1, 2, 4, 6, 8, 12, 24, and 48 hours after gavage treatment and the plasma radioactivity determined. The time to peak plasma concentration in rats treated with  $^{14}\text{C}$ -dicamba occurred within 0.5 hours while peak plasma concentration was reached at 1.0 hour in the probenecid/dicamba rats. However, pretreatment with probenecid increased plasma AUC by a factor of 1.54. Although the terminal phase of elimination remained relatively the same, the initial and intermediate elimination phases were increased by a factor of two. These data suggest that both dicamba and probenecid, act as inhibitors of renal anion transport.

This pharmacokinetic study in the rat (MRID 46022303) is classified **Acceptable/Non-guideline** and satisfies its intent.

#### **870.7600 Dermal Absorption - Rat**

N/A

#### **A.5.9 Immunotoxicity**

##### **870.7800 Immunotoxicity**

In an immunotoxicity study (MRID 48081601), BAS 183 H (Dicamba technical) (92.9% a.i., Lot No. COD 001266) was administered to 8 male Crl:WI (Han) Wistar rats/dose in the diet at dose levels of 0, 500, 1500, or 4000 ppm (equivalent to 0, 37, 108, or 307 mg/kg/day) for 28 days. The male rat has been determined as the appropriate species/sex for this study. Cyclophosphamide monohydrate in water was administered daily by gavage to the positive control group (8 male rats) at a rate of 4.5 mg/kg/day. On Day 23, animals were immunized with an intraperitoneal injection of 0.5 mL sheep red blood cells

(SRBCs) in 0.9% saline ( $4 \times 10^8$  SRBCs)/mL). On Day 29, all animals were sacrificed, and T-cell dependent antibody responses (TDAR) were evaluated with an enzyme-linked immunosorbent assay (ELISA).

There were no treatment-related effects on clinical signs, mean body weight, mean body weight gain, or mean food and water consumption. In the positive control group, mean body weights were lower than the control value from Day 3 through Day 28, the differences reaching statistical significance ( $p \leq 0.05$ ) when measured on Days 24 and 28. Body weight gain in the positive control group also was consistently lower than the control group throughout the study, and was statistically significant over most of the measured intervals ( $p \leq 0.05$ ) within the study, and over the entire study (i.e., Day 0-28,  $p \leq 0.01$ ). Additionally, food consumption in the positive control group was lower than the control throughout the study; these data were not statistically analyzed. The decreases in weight, weight gain, and food consumption in the positive control group were considered to be treatment (cyclophosphamide)-related. No unscheduled mortalities occurred in any study group. The NOAEL for systemic toxicity related to treatment with BAS H 183 (dicamba techn.) is 4000 ppm (307 mg/kg/day), the highest dose tested. A LOAEL was not established.

There were no treatment-related changes in anti-SRBC IgM titers as measured by ELISA assay. The mean absolute and relative thymus weights did not differ significantly from the control in any test substance treatment group. In the positive control group, mean anti-SRBC IgM titers were markedly lower than the control, and absolute and relative spleen and thymus weights were significantly reduced when compared with the control ( $p \leq 0.01$ ).

The Natural Killer (NK) cell activity was not evaluated. Evaluation of toxicity database of dicamba including subchronic, chronic toxicity and reproduction studies showed no treatment-related effects on spleen and thymus weights and histopathology parameters that would suggest the potential for immunotoxicity. Under the HED guidance, if the TDAR assay is negative and evaluation of observational endpoints from all available toxicology database provide no evidence of immunotoxicity, the test article is considered negative for immunotoxicity, and evaluation of NK cells activity is not necessary.

**Under conditions of this study, the NOAEL for immunotoxicity in male rats is 4000 ppm (307 mg/kg/day), the highest dose tested. A LOAEL was not established.**

This 4-week dietary immunotoxicity study in the rat is **acceptable/guideline** and satisfies the guideline requirement for an immunotoxicity study (OPPTS 870.7800).

#### **A.5.9 Special Studies: Toxicity of Dicamba Metabolites or Amine Salts**

##### **870.3050 DCGA 28-Day Oral Study in Rats**

In a 28 day dietary toxicity test (MRID 47899506) groups of 10 rats/sex/group were exposed to DCGA (MON 52724) (Purity 98.1% Lot/batch No GLP-0904-19809-T) at dietary concentrations of 0, 500, 3000, 6000, or 12000 ppm. The average test substance consumption over the entire study was 0, 40, 240, 474, and 956 mg/kg/day for males and 0, 45, 265, 519, and 1063 mg/kg/day for females. All animals were observed twice daily for moribundity and mortality, clinical examinations were performed daily,

and individual body weights were recorded weekly. Food consumption, functional observational battery (FOB) and motor activity were recorded twice weekly.

All animals survived to the scheduled necropsy. There were no adverse test substance related clinical observations, effects on organ weights or histological, or macroscopic findings. FOB and motor activity were unaffected by treatment. Body weights were decreased 9% in males and 6% in females (not statistically significant).

**The NOAEL was 474 mg/kg/day and the LOAEL was 956 mg/kg/day based upon decreased body weight in males.**

This study is classified as acceptable/guideline, and it satisfies the guideline requirement for a 28-day oral toxicity study in rodents (OECD 407, OPPTS 870.3050).

### **870.3100 DCSA 90-Day Oral Study in Rats**

In a 90 day dietary study (MRID 47899507), Sprague-Dawley (CrI:CD®[SD]) (10 rats/ sex/group) were exposed to MON 52708 (purity 97.9%; Lot/batchGLP-0603-16958-T) for 90-days. Final dietary concentrations were 500, 3000, 6000 and 12000 ppm. Due to potential problems with palatability observed in a previous range finding study, rats in the higher dose groups received slowly increasing doses during the first 1 to 2 weeks. Group 4 rats received the 3000 ppm diet during week 0 and the 6000 ppm diet during weeks 1 through 12. Group 5 rats received the 3000 ppm diet during week 0, the 6000 ppm diet during week 1 and the 12000 ppm diet during weeks 2 through 12.) The control group (Group 1) received the basal diet only throughout the study. The average test substance consumption over the entire study was 0, 32, 195, 362, or 659 mg/kg/day for males and 0, 37, 222, 436, or 719 mg/kg/day for females.

All animals were observed twice daily for mortality and morbidity. Clinical observations were made daily and detailed physical exams conducted weekly. Body weights and food consumption were measured weekly. Functional observational battery (FOB), locomotor activity and ophthalmic examination data were recorded prior to beginning exposure to MON 52708 and at the end of the study (week 12). Hematology, serum chemistry and urinalysis assessments were conducted during study week 13. Complete necropsies were conducted on all animals at study week 13. Selected organs were weighed at necropsy and selected tissues from all animals were examined microscopically. Lower body weights were noted in the 12000 ppm group males and females throughout the study after dose ramping was concluded and final dosing levels were achieved (end of study week 2). Terminal mean body weights for the 12000 ppm males and females were 28.1% and 29.7% lower than controls, respectively. Body weights and food consumption in the 6000 ppm group females were also statistically significantly lower compared to controls during the first few weeks of the study after ramping was concluded and generally remained lower but were not statistically significantly different for the rest of the study.

Food consumption in 12000 ppm males and females was decreased from the end of week 2 until approximately midway through the study. After approximately week 7, food consumption was increased in 12000 ppm males compared to controls and in 12000 ppm females was comparable to controls.

In the functional observation battery, there were no treatment-related effects noted during home cage, handling, open field, sensory, neuromuscular, or physiological observations. For the motor activity assessment, ambulatory counts were increased in 12000 ppm males by 59% ( $p < 0.005$ ), compared to controls, during the first 15-minute interval. Ambulatory counts were increased for that group in 2 other intervals, but not with statistical significance.

Hematological effects were noted in the 12000 ppm group. Effects included decreased red blood cell count, haemoglobin, MCHC, and hematocrit, and were more pronounced in females than in males. Liver enzymes, including alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase, were increased in the 12000 ppm group. Relative liver weights were higher in the 12000 ppm group compared to controls, but absolute liver weights were not statistically different. There were no microscopic findings in the liver.

Microscopic lesions included an increase of bone marrow depletion in the sternum of the 12000 ppm group males and 6000 and 12000 ppm group females and hyperplasia of the epithelium in the glandular stomach of 12000 ppm group males and females. There were also four erosions in the glandular stomach, one each in males from the 6000 and 12000 ppm groups and two in females from the 12000 ppm group.

**The NOAEL is 362 mg/kg/day and the LOAEL is 659 mg/kg/day based on decreased body weight, increased motor activity, decreased hematological parameters, and increased liver enzymes.**

This study is classified as acceptable/guideline and satisfies the guideline requirement for a 90-day feeding study in the rat (EPA OPPTS guideline 870.3100 and OCED guideline Section 408).

#### **870.3100 Dicamba BAPMA 90-Day Oral Study in Rats**

In a 90-day oral toxicity study (MRID 49441801), Dicamba BAPMA Salt (69.5% a.i. Dicamba acid; batch#: 1781-6) was administered to 10 Wistar rats/sex/dose in the diet at dose levels of 0, 4317, 8633, or 17266 ppm (equivalent to 0, 257, 513, and 1027 mg/kg bw/day in males and 0, 294, 589, and 1178 mg/kg bw/day in females). The test diets were equivalent to 0, 3000, 6000, and 12000 ppm Dicamba acid (equivalent to 0, 178, 357, and 714 mg/kg bw/day in males and 0, 205, 409, and 819 mg/kg bw/day in females). Evaluated parameters included mortality, clinical signs, body weight, food consumption, ophthalmological examinations, functional observational battery (FOB), clinical pathology, organ weight, and gross and histopathological examination.

There were no treatment-related effects on mortality, clinical signs, FOB, body weights, food consumption, ophthalmoscopy, urine parameters, macroscopic findings, or histopathology. Treatment-related increased absolute and relative kidney weights were noted in males of the high-dose study group (absolute weight 15% greater than controls [n.s.] and relative weight 20% greater than controls). Total bilirubin levels were significantly decreased 41-79% in all treated animals, and the changes were considered related to treatment, but were not considered adverse. In males of the high-dose group, prolonged prothrombin time (9.5%) and increased incidence of urine triple phosphate crystals were observed. In females, creatinine levels were significantly increased 33% at the high-dose. In both sexes at the high-dose, total protein and globulin levels were significantly decreased 5-16%. **Therefore,**

**under the conditions of this study, the LOAEL of Dicamba BAPMA Salt is 17266 ppm (1027 mg/kg bw/day in males and 1178 mg/kg/day in females; corresponding to 714 and 819 mg/kg bw/day Dicamba Acid in males and females, respectively), based on kidney effects and altered hematology (increased prothrombin time in males) and clinical chemistry (increased creatinine levels in females and decreased total protein and globulin levels in both sexes) parameters. The NOAEL is 8633 ppm (513 mg/kg bw/day in males and 589 mg/kg/day in females; corresponding to 357 and 409 mg/kg bw/day Dicamba Acid in males and females, respectively).**

This 90-day oral toxicity study in the rat is **Acceptable / Guideline** and satisfies the guideline requirement for a 90-day oral toxicity study (OCSPP 870.3100; OECD 408).

#### **870.3150 DCSA 90-Day Oral Study in Dogs**

In a 90-day oral capsule study (MRID 48358002), Beagle dogs (5 animals/sex/group) were treated with MON 52708 (purity 97.7%; Lot/batchGLP-0603-16958-T) for 90 days with doses of 0, 15, 50 and 150 mg/kg/day.

All animals were observed twice daily for mortality and morbidity. Clinical observations were performed daily and detailed physical exams were conducted weekly. Body weights were measured weekly. Food consumption was recorded daily and reported weekly. Clinical pathology evaluations included hematology, coagulation, serum chemistry and urinalysis and were conducted prior to initiation of dosing and during study weeks 6 and 13. Ophthalmic examinations were conducted prior to initiation of dosing and during study week 12. Complete necropsies were conducted on all animals during study week 13. Selected organs were weighed at necropsy and selected tissues were examined microscopically.

One female in the 150 mg/kg/day dose group was euthanized in extremis on day 50 of the study. Death was associated with repeated emesis, electrolyte imbalance, and severe dehydration. All other animals survived to the scheduled necropsy.

Statistically significant decreases were observed in cumulative body weight gains in both males and females in the 150 mg/kg/day groups. Absolute mean body weights in these groups were about 11% lower than controls at the end of the study, though the differences were not statistically significant. Decreased food consumption was observed in females in the 150 mg/kg/day group during study weeks 1 -2 and 3-4. Male food consumption was not different from controls. Abnormal excreta and emesis were present in the 150 mg/kg/day male and female groups. Abnormal excreta began on study day 0; emesis began on study day 2. Both effects persisted to the end of the study.

Coagulation effects were observed in both males and females: APTT values were higher in males in the 150 mg/kg/day at study week 13 and in females in the 150 mg/kg/day group at study week 6. Liver weights relative to body weights were higher in males and females in the 150 mg/kg/day groups. Hypertrophy of periportal hepatocytes was observed in the livers of both sexes in the 150 mg/kg/day groups.

**The NOAEL is 50 mg/kg/day and the LOAEL is 150 mg/kg/day based on mortality, decreased body weight, clinical signs (abnormal excreta and emesis), and increased clotting time.**

This study is classified as acceptable/guideline and satisfies the guideline requirement (EPA OPPTS guideline 870.3150 and OCED guideline Section 409) for a 90-day dog study.

#### **870.3200 Dicamba DGA 21-Day Dermal Study in Rabbits**

In a 21-day dermal toxicity study (MRID No. 43554206) New Zealand White rabbits [5/sex/dose] were given repeated dermal applications of the diglycolamine (DGA) salt (59%) of dicamba at 0, 100, 500 or 1000 mg/kg, 6 hours/day, 5 days/week for a total of 15 applications during a 3-week period. No treatment-related dermal reactions or histopathological dermal lesions were seen. No systemic toxicity was seen; treatment had no adverse effect on survival, clinical signs, mean body weights, body weight gains, hematology, clinical chemistry, organ weights or gross and histopathology. **A NOAEL of 1000 mg/kg/day (Limit-Dose) was established for both dermal irritation and systemic toxicity. A LOAEL was not established for either end-point.**

This study is classified as Core Guideline and satisfies the data requirement [§82-2] for a 21-day dermal toxicity study in rabbits and is acceptable for regulatory purposes.

#### **870.3200 Dicamba IPA 21-Day Dermal Study in Rabbits**

In a 21-day dermal toxicity study (MRID No. 43554207) New Zealand White rabbits [5/sex/dose] were given repeated dermal applications of the isopropylamine (IPA) salt (41%) of dicamba at 0, 100, 500 or 1000 mg/kg, 6 hours/day, 5 days/week for a total of 15 applications during a 3-week period. No treatment-related dermal reactions or histopathological dermal lesions were seen. No systemic toxicity was seen; treatment had no adverse effect on survival, clinical signs, mean body weights, body weight gains, hematology, clinical chemistry, organ weights or gross and histopathology. **A NOAEL of 1000 mg/kg/day (Limit-Dose) was established for both dermal irritation and systemic toxicity. A LOAEL was not established for either end-point.**

This study is classified as **Core Guideline** and satisfies the data requirement [§82-2] for a 21-day dermal toxicity study in rabbits and is acceptable for regulatory purposes.

#### **870.3465 Dicamba BAPMA 28-Day Inhalation Study in Rats**

In a nose-only inhalation toxicity study (MRID 49441803), four groups of Crl:WI(Han) rats (10/sex/group; ~10 weeks of age) were administered Dicamba BAPMA Salt [84.7%, equivalent to 69.5% Dicamba acid (Batch No. 1781-6)] as a dust aerosol at target exposure concentrations of 0, 0.0014, 0.0072, or 0.036 mg/L (respective actual concentrations of 0, 0.0015, 0.0070, and 0.0352 mg/L) for 28 days.

There were no mortalities or clinical signs observed at any exposure concentration. No substance-related adverse findings were observed on body weight, ophthalmology examinations, food consumption, or clinical pathology parameters in blood. Plasma concentrations of Dicamba acid after 22 days of exposure increased with exposure concentration, but not proportionally to the 5-fold

increase in exposure between the mid- and high-exposure concentrations. The respective mean values of female animals were higher than those of the males. Microscopic examination of tissues showed that the test substance was a respiratory tract irritant with adverse effects on the nasal cavity, larynx, trachea, lungs, and the lung-associated lymph nodes. **Nasal cavity:** In Level I, focal degeneration/regeneration of the respiratory and/or transitional epithelium was observed in 1 male and 1 female from the mid exposure group (minimal severity), and in 8 males and 5 females from the high exposure group (minimal to slight). Two males and two females at the high concentration showed minimal focal squamous cell metaplasia of the respiratory epithelium in the septum. In Level II, one female at the high concentration showed an ulcer in the epithelium of the septum. **Larynx:** Ulcers in epithelial tissues were observed in males at incidences of 2/10, 5/10, and 8/10, respectively, in the low-, mid-, and high-exposure groups. Minimal focal inflammation was observed in Level I or Level II in 3 males at the low concentration, 1 male and 1 female at the mid concentration, and in 1 male and 3 females at the high concentration. Single or multi-focal hyperplasia's were observed in Level I and/or Level II in 5 males and 4 females at the low concentration, 8 males and 7 females at the mid concentration, and in 7 males and 7 females at the high concentration. **Trachea:** Minimal or slight focal degeneration/regeneration of the respiratory epithelium was observed in 2 males at the mid concentration, and in 5 males and 1 female at the high concentration. **Lung:** Minimal to slight inflammation was observed in bronchi and/or alveoli in most to all of the males and females at the mid- and high-concentration. Minimal multifocal bronchiolo-alveolar hyperplasia was observed in 2 males at the high concentration and in 1 female at the mid concentration. Minimal hypertrophy of single terminal bronchi was observed in 6 males and 3 females at the high concentration. The incidence of minimal or slight multifocal alveolar histiocytosis increased in males from all three exposed groups and in females from the mid- and high-concentration groups. The incidence of minimal or slight alveolar macrophage aggregates was increased in males at the mid- and high-concentration and in females from all three exposed groups.

Tracheobronchial and mediastinal lymph nodes: Minimal to slight lympho-reticulocellular hyperplasia in one or both of these lymph nodes was observed in males at the mid- and high-exposure concentrations and in females at all three concentrations. Macrophage aggregates were observed in both sexes at the mid- and high-exposure concentrations.

**The LOAEL in Wistar rats was 0.0014 mg/L based on ulcers in epithelial tissues of the larynx and single/multi-focal hyperplasia's in the larynx. A NOAEL was not identified.**

This inhalation toxicity study is classified as **Acceptable (Guideline)** and satisfies the guideline requirement for 4-week inhalation toxicity study in rats (OCSP 870.3465).

#### **870.3650 BAPMA Base OECD 422 Developmental-Reproduction Study**

In a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test, N,N-Bis(3-aminopropyl)methylamine (99.6% a.i., Batch No. O2903) was administered to 10 Wistar rats/sex/dose by gavage in deionized water at dose levels of 0, 25, 100, or 500 mg/kg bw/day for at least 14 days prior to mating, throughout mating, and up to and including the day prior to sacrifice. Terminal sacrifices took place after 28 days of treatment in males and after 56 days of treatment in females. Evaluated parameters in the parental animals included functional observational battery (FOB),

motor activity, hematology, clinical chemistry, urinalysis, organ weights, macroscopic examination, and histopathology

In the high-dose group, there was 100% mortality (both sexes) within the first four days of treatment. One male was found dead on study day 3 and one female was found dead on study day 1. Due to clinical signs including labored respiration, piloerection, unsteady gait, hypothermia, semiclosed eyelids, and abdominal position, all animals of the high-dose group were sacrificed *in extremis* between study days 1 and 4. Treatment-related post mortem findings in these animals included red discoloration and lesions of the gastrointestinal track including extensive areas of erosion and/or ulceration, hemorrhagic inflammation, and blunting and fusion of villi. Tubular necrosis of the kidney was also observed.

No treatment-related mortality or clinical signs were observed in the low- and mid-dose groups. There were no treatment-related effects on mean body weight, food consumption, clinical pathology, or gross and microscopic necropsy findings of the low- and mid-dose groups. Motor activity was decreased by 24% at 100 mg/kg/day. Body weight loss was observed in the mid-dose group (-2.2 g vs. 4.6 g in control) during lactation but was not considered adverse because it did not affect mean body weights. Water consumption was decreased by 22-47% during pre-mating through GD 14 and was significantly decreased by 19% in females of the mid-dose group at the end of gestation (GD 19-20). In the absence of correlated effects on clinical signs, clinical pathology, organ weights, and/or gross or microscopic findings, the toxicological significance of the decreased water consumption is unclear.

**Deaths occurred in the dams at 500 mg/kg bw/day. Therefore, the parental systemic NOAEL is 25 mg/kg bw/day, and the LOAEL is 100 mg/kg/day based on decreased motor activity and water consumption, results from the surviving animals.**

No animals in the high-dose groups were mated due to excessive toxicity and mortality during the pre-mating period. No evidence of reproductive toxicity was found. Maternal treatment did not result in decreased *in utero* or postnatal survival, altered growth, abnormal clinical signs, or an increased incidence of gross abnormalities of the offspring. **Therefore, the reproductive/developmental LOAEL is not identified, and the reproductive/developmental NOAEL is 100 mg/kg bw/day.** However, it must be noted that there were only six and seven litters with live fetuses in the low- and mid-dose groups, respectively. Although the low numbers of litters are not treatment-related, they still limit the sensitivity of this study to detect effects on pregnancy, maternal and suckling behavior, and growth and development of the F<sub>1</sub> offspring from conception to day 4 post-partum.

This study is **Acceptable/ Non-Guideline** and does satisfy the guideline requirement for a reproductive/developmental toxicity screening study (OCSP 870.3650; OECD 422) in the rat.

#### **870.3700a Dicamba BAPMA- Prenatal Developmental Toxicity Study in Rats**

In a developmental toxicity study (MRID 49441802), Dicamba BAPMA salt [84.7% w/w Dicamba BAPMA; 69.5% w/w Dicamba (acid equivalent), batch# 1781-6] was administered to 25 female Wistar rats/dose in 1% aqueous carboxymethylcellulose suspension by oral gavage at dose levels of 0, 29, 86, or 288 mg/kg bw/day (corresponding to 20, 60, or 200 mg/kg bw/day Dicamba acid) on gestation days

(GDs) 6 through 19, inclusive. Body weights and food consumption were monitored regularly until sacrifice on GD 20. Dams were necropsied, and gravid uterine weight, numbers of corpora lutea, and numbers and distribution of live and dead fetuses and early and late resorptions were recorded. Fetuses were sexed, weighed, and investigated for external findings; approximately one-half of the fetuses of each litter were examined for soft tissue findings and the remaining fetuses for skeletal findings (inclusive of cartilage). Individual placental weights also were recorded.

At 86 and 288 mg/kg bw/day, maternal toxicity was characterized by increased incidences of adverse clinical signs, including unsteady gait, convulsions, and ataxia (occurrences/affected animals at 86 mg/kg/day: 114/24, 3/2 and 4/2; at 288 mg/kg/day: 74/20, 187/25 and 63/20, respectively, out of 25 total animals for both groups). Observations in the mid-dose females began after dosing and persisted for a maximum of 3 hours, with the earliest observations recorded on GD 6 (unsteady gait) or GDs 12-13 (convulsions/ataxia), while those in the high-dose females began after dosing, persisted for a maximum of 4 hours, and were first noted on GDs 6-7. Also, in the 288 mg/kg/day females, body weight gain and food consumption was significantly reduced compared to controls during intervals at the beginning of treatment, and non-statistically significantly reduced for the overall treatment period as follows: body weight gain: -20% during GDs 6-13, -8% during GDs 6-19; food consumption: -8% during GDs 6-10, -7% during GDs 6-19. The corrected (for gravid uterine weight) body weight gain was significantly lower in the high dose group by 16%, indicating that the decreased weight gain was a maternal effect. No maternal toxicity was apparent at the low dose of 29 mg/kg/day. No treatment-related effects on maternal cesarean section parameters were noted at any dose level for this study.

**The maternal LOAEL for Dicamba BAPMA salt in rats is 86 mg/kg bw/day (corresponding to 60 mg/kg bw/day Dicamba acid equivalent), based on adverse clinical signs of unsteady gait, ataxia, and convulsions. The maternal NOAEL is 29 mg/kg bw/day (corresponding to 20 mg/kg bw/day Dicamba acid equivalent).**

No developmental toxicity was evident as a result of maternal treatment with up to 288 mg/kg/day of Dicamba BAPMA salt. Fetal weights, fetal sex ratios, post implantation loss and numbers of viable fetuses, implantation sites, resorptions, and corpora lutea in all dose groups were comparable to the control group. The infrequent occurrence and nature of fetal malformations observed in the study were not considered treatment-related, and visceral and skeletal variations were comparable to controls and/or did not exhibit a dose-response relationship.

**The developmental LOAEL for Dicamba BAPMA salt in rats was not determined. The developmental NOAEL is greater than or equal to 288 mg/kg bw/day (200 mg/kg bw/day Dicamba acid equivalent).**

The developmental toxicity study in the rat is classified **Acceptable/Guideline** and satisfies the guideline requirement for a developmental toxicity study (OCSPP 870.3700; OECD 414) in the rat.

#### **870.3700a DCSA- Prenatal Developmental Toxicity Study in Rats**

In a prenatal developmental toxicity study (MRID 47899519) groups of 25 bred female Crl:CD (SD) rats were administered MON 52708 (purity 97.9%; Lot/batch# GLP-0603-16958-T) by oral gavage at doses

of 0, 10, 30 and 100 mg/kg/day from gestation days 6 through 19. The doses for this study were based on a previous prenatal developmental toxicity dose range-finding study (MRID47899518).

All animals were observed twice daily for mortality and moribundity, and individual clinical observations were recorded from gestation days 0 through 20. Animals were also observed for signs of toxicity approximately 1 hour following dose administration. Body weights and food consumption were recorded on gestation days 0 and 6-20. On gestation day 20, a laparohysterectomy was performed on each female. The uteri, placentae and ovaries were examined, and the numbers of fetuses, early and late resorptions, total implantations and corpora lutea were recorded. Gravid uterine weights were recorded, and net body weights and net body weight changes were calculated. The fetuses were weighed, sexed and examined for external, visceral and skeletal malformations and developmental variations.

All females survived to the scheduled necropsy on gestation day 20; there were no test article-related clinical or macroscopic findings at any dose level. Mean maternal body weights, body weight gains, net body weights, net body weight gains, gravid uterine weights and food consumption in all test article-treated groups were generally similar to those in the control group.

No test article-related effects on intrauterine growth, survival or fetal morphology were observed at any dose level.

Doses in this study were based upon toxicity in a pilot study (MRID47899518, see Appendix). In the pilot study clinical observations at 200 mg/kg/day included salivation, red and/or clear material around the mouth and/or nose, and yellow or brown material around the genital area. Fetal body weights were decreased 14% in the 200 mg/kg/day group compared to controls.

**The maternal and developmental NOAELs are both 100 mg/kg/day, the highest dose tested. A LOAEL was not determined.**

This study is classified **totally reliable (acceptable/guideline) when considered in conjunction with the range-finding study** (MRID47899518) and satisfies the guideline requirements (EPA OPPTS guideline 870.3700 and OCED guideline 414).

#### **DCSA Range-Finding Study for Prenatal Developmental Study**

In a prenatal development toxicity range finding test (MRID47899518) groups of 8 bred female Crl:CD(SD) rats were administered by MON 52708 (purity 97.9%; Lot/batch no GLP-0603-16958-T) by oral gavage at doses of 0, 50, 200, 500 or 1000 mg/kg/day from gestation days 6-19.

All animals were observed twice daily for mortality and moribundity, and individual detailed clinical observations were recorded from gestation days 0 through 20. Animals were also observed for signs of toxicity at the time of dose administration and approximately 1 hour following dose administration. Body weights and food consumption were recorded on gestation days 0 and 6-20. On gestation day 20, a laparohysterectomy was performed on each surviving female. The fetuses were weighed, sexed and examined for external malformations and developmental variations.

In the 1000 mg/kg/day group, 7 of the females were found dead and 1 female was euthanized *in extremis* on gestation day 7, 8 or 9. In the 500 mg/kg/day group, 2 females were found dead, 1 each on gestation days 8 and 10. All other females survived to the scheduled necropsy.

Clinical findings for surviving females in the 200 and 500 mg/kg/day groups included salivation and red and/or clear material around the mouth and/or nose. In addition, in the 500 mg/kg/day group, excessive pawing and wiping of the mouth on the cage were noted.

Mean maternal body weight losses and/or lower mean body weight gains and lower food consumption, mean gravid uterine weights, net body weights and/or net body weight gains (relative to the control group) were generally noted in the 200 and 500 mg/kg/day groups throughout the treatment period. Body weight gain for the 200 mg/kg/day group was 92 g vs 117 g in controls. Body weights were also reduced in the 500 mg/kg/day, though this was in part due to the 100% resorptions at that dose.

At the scheduled necropsy, no remarkable macroscopic findings were noted in the surviving dams at any dose level. Mean absolute liver weights in the 200 and 500 mg/kg/day groups were 7.0% and 19.0% lower than the control group value, respectively. In addition, slightly higher mean absolute spleen and kidney weights (16.7% and 11.6%, respectively) were noted in the 500 mg/kg/day group when compared to the control group values.

Evaluation of laparohysterectomy parameters in the 1000 mg/kg/day group was precluded by the death of all females in this group. Surviving females in the 500 mg/kg/day group had early resorptions of all litters. In the 200 mg/kg/day group, mean fetal weight was decreased 14% compared to controls. No malformations or developmental variations were noted in any fetuses in the control or test article-treated groups following an external examination.

Because this range finding study was not intended to fulfill a guideline requirement, NOAELs and LOAELs are not assigned. This study is suitable for use in dose selection for a definitive guideline study.

#### **870.3700a DCGA- Prenatal Developmental Toxicity Study in Rats**

In a dose range-finding toxicity study (MRID 47899520) four groups of eight bred female CrI:CD(SD) rats per dose group were exposed to MON 52724 (Purity 96.3%; Lot/batch No GLP-0903-19699-T ) by gavage with corn oil at doses of 0, 50, 200, 500, and 1000 mg/kg/day. Animals were observed twice daily for moribundity and mortality and individual detailed clinical observations were recorded from day 0 through gestation day 20. Body weights and food consumption were recorded from gestation days 0 and 6-20. On gestation day 20, a laparohysterectomy was performed on each of the surviving animals and the uteri, placentae, ovaries were examined, and the number of fetuses, early and late resorptions, total implantations and corpora lutea were recorded. Fetuses received an external examination but not a soft tissue or skeletal examination.

Mean body weights were 4.0% to 6.6% lower during gestation days 13-20 in the 500 mg/kg/day group and 4.4% to 12.1% lower during gestation days 12-20 in the 1000 mg/kg/day group. Five of the eight females in the 1000 mg/kg/day group died or were euthanized *in extremis* during gestation days 12-19. Clinical findings in dams included rales and red or clear material on body surfaces at doses of 200

mg/kg/day and above. There were no effects observed on uterine growth, survival, external malformations or variations.

Because this range finding study was not intended to fulfill a guideline requirement, NOAELs and LOAELs are not assigned. This study is suitable for use in dose selection for a definitive guideline study.

#### **870.3700b DCSA- Prenatal Developmental Study in Rabbits**

In a developmental toxicity study (MRID 47899522), groups of twenty-five mated female New Zealand white rabbits were exposed to DCSA (MON 52708) (Purity 97.7%; Lot/batch No GLP-0603-16958-T ) by gavage from gestation days 6-28 at doses of 0, 10, 25, or 65 mg/kg/day. All animals were observed twice daily for moribundity and mortality and individual detailed clinical observations, body weights, and food consumption were recorded. On gestation day 29, a laprohysterectomy was performed on each surviving females and the uteri, placentae, ovaries were examined, and the number of fetuses, early and late resorptions, total implantations and corpora lutea were recorded.

One control female and one female in the 65 mg/kg/day group died with cause of death undetermined. One female in the 10 mg/kg/day group aborted. All treatment groups had decreased defecation. There were no toxicologically significant test substance related effects observed on survival, clinical signs, body weight, food consumption, intrauterine growth, pup survival, external malformations or morphology of fetuses.

Although no toxicity occurred in this study at the high dose of 65 mg/kg/day, the does could not have tolerated a much higher dose because 100 mg/kg/day was found to be a maternally lethal dose in the range finding study (MRID 47899521).

**The maternal and developmental NOAELs are 65 mg/kg/day, the highest dose tested. The maternal and developmental LOAELs were not determined.**

Therefore, this study is classified **as acceptable/guideline when considered in conjunction with the range finding study** and satisfies the guideline requirements for a developmental toxicity study in rabbits (OPPTS 870.3700, OECD 414).

#### **870.3800 DCSA- Reproduction and Fertility Effects in Rats**

In a dietary two-generation reproductive toxicity study (MRID 47899517) DCSA (MON 52708) (purity 97.7%, Lot/Batch no., GLP-0603-16958-T) was administered continuously in the diet to groups of male and female Crl:CD(SD) rats (30/sex/group) at dose levels of 0, 50, 500 and 5000 ppm. One litter per dam was produced in each generation.

Mean test substance consumption for the F0 males was 4, 37 and 362 mg/kg/day and for F0 females was 4, 43 and 414 mg/kg/day during the pre-mating period, 3, 34 and 323 mg/kg/day during gestation and 8, 78 and 610 mg/kg/day during lactation, for the 50, 500, and 5000 mg/kg/day groups, respectively.

Because all surviving offspring of the F0 animals in the 5000 ppm group were euthanized on PND 21 due to pup mortality and a high incidence of total litter loss among the dams, no offspring of the F0 animals in the 5000 ppm group were selected for the F1 generation. Mean test substance consumption for the F1 males was 4 and 41 mg/kg/day and for F1 females was 5 and 52 mg/kg/day during the pre-mating period, 3 and 34 mg/kg/day during gestation and 8 and 79 mg/kg/day during lactation, for the 50 and 500 mg/kg/day groups, respectively.

Three additional groups of female rats (10/group) were included in this study for evaluation of clinical and histological pathology parameters. These non-mated satellite animals were administered either basal diet or the test substance in the diet for at least 90 consecutive days; dietary concentrations were 0, 50 and 500 ppm. No differences in clinical pathology or histological parameters were observed when comparing control and test substance-treated animal data. Mean test substance consumption for the satellite phase females in the 50 and 500 ppm groups was 4 and 42 mg/kg/day, respectively.

F0 and F1 parental survival was unaffected by test diet administration at all exposure levels. No remarkable clinical findings were noted at any exposure level tested in the F0 or F1 generations. Parental body weight and food consumption parameters were not adversely affected at exposure levels of 50 and 500 ppm in either generation. At an exposure level of 5000 ppm (evaluated only in the F0 generation), test substance-related reductions in mean body weight gain, food consumption and food efficiency were noted during the first month of test diet exposure, which resulted in lower mean body weights throughout the pre-mating period (females) or entire generation (males). Lower mean food consumption was also noted for the 5000 ppm group females throughout gestation and lactation.

There were no indications of adverse effects on reproductive performance in either the F0 or F1 generations. Male and female mating and fertility indices, male copulation indices, female conception indices, pre-coital intervals, spermatogenic endpoints, lengths of the estrous cycle and gestation, and live litter size were similar in all exposure groups. No test substance-related effects in gross pathology, organ weights or histopathology were noted in F0 or F1 parental animals. Additionally, ovarian follicle counts for the test substance-exposed F0 (5000 ppm, high-dose group) and F1 (500 ppm, high-dose group) females were similar to the control group values.

Test substance-related effects on pre-weaning offspring were noted at an exposure level of 5000 ppm (F1 pups) and included decreased pup survival during PND 0-1, 1-4 (pre-selection), 7-14 and 14-21 (due primarily to 7 females with total litter loss), clinical signs of toxicity (pale body, blackened ventral abdominal area, distended abdomen, uneven hair growth and desquamation) and lower body weights and weight gains during PND 1-21.

As a result of pup mortality and a high incidence of total litter loss among the F0 dams at 5000 ppm, all surviving offspring of the F0 animals in the 5000 ppm group were euthanized on PND 21; therefore, a dosage level of 5000 ppm group was not evaluated in the F1 generation.

At 500 ppm, mean F<sub>1</sub> male and female pup body weights on postnatal days 14 and 21 were reduced approximately -6% to -9% of controls; female pup body weight was also reduced at week 18 (-7%). Hyperkeratosis was noted upon histological evaluation of the F1 pups in the 5000 ppm group that had gross skin lesions or clinical findings of desquamation or uneven hair loss/hair growth.

No test substance-related effects on offspring survival, general physical condition, body weights, macroscopic pathology and organ weights were noted at exposure levels of 50 ppm for F1 or F2 pups. Mean ages and body weights on the day of attainment of balanopreputial separation and vaginal patency were unaffected by treatment in any group.

**The parental NOAEL is 37 mg/kg/day and the parental LOAEL is 362 mg/kg/day based upon decreased body weight.**

**No reproductive toxicity was noted and the reproductive NOAEL is 362 mg/kg/day; the reproductive LOAEL was not attained.**

**The offspring NOAEL is 4 mg/kg/day and the offspring LOAEL is 37 mg/kg/day based upon decreased pup body weight in F<sub>1</sub> pups on postnatal days 14 and 21 (both sexes) and at week 18 (females only).**

This study is classified as acceptable/guideline and satisfies the guideline requirement for a reproduction study (OECD 416, OPPTS 870.3800, PMRA DACO 4.5.1).

#### **870.4200a DCSA- Combined Chronic Toxicity/Carcinogenicity in the Rat**

In this combined chronic toxicity/carcinogenicity study (MRID 47899516, chronic toxicity and MRID 48358003, carcinogenicity), Sprague Dawley (CrI:CD®[SD]) rats were exposed to MON 52708 (purity 97.4% - 97.7%; Lot/batch no GLP-0603-16958-T) in the diet. Dietary concentrations were 0, 10, 100, 300, 1000 or 3000 ppm. Doses for the chronic toxicity phase were 0.6, 5.6, 16.9, 56.9, and 171.2 mg/kg/day for males and 0, 0.7, 6.9, 20.5, 68.2, and 206.2 mg/kg/day for females. Doses for the carcinogenicity phase were 0.5, 5.0, 14.6, 48.8, and 150.1 mg/kg/day in males and 0.6, 6.1, 18.4, 60.9, and 181.5 mg/kg/day in females. There were 50 male and 50 female rats in the 24-month carcinogenicity study and 20 male and 20 female rats in the 12-month chronic toxicity study.

All animals were observed twice daily for mortality and moribundity. Clinical examinations were performed daily, and detailed physical examinations were performed weekly. Individual body weights and food consumption were recorded at least weekly for the first 13 weeks of the study, and at least once every four weeks thereafter. Ophthalmic examinations were performed during study weeks 2 and 51. Clinical pathology parameters were evaluated for the last 10 surviving animals/sex/group: hematology and serum chemistry were evaluated during study weeks 12 and 25, and at the scheduled necropsy (study week 52); coagulation parameters were evaluated only at the scheduled necropsy (study week 52); and urinalysis parameters were analyzed during study week 25 and at the scheduled necropsy (study week 52). Complete necropsies were conducted on all animals, and selected organs were weighed at the scheduled necropsy. Selected tissues were examined microscopically from animals in the control and 3000 ppm groups. Tissue masses (when present), pituitary glands, and gross lesions (when present) were examined from all animals.

There were no toxicologically significant treatment related effects on mortality, clinical signs, body weight, food consumption, ophthalmology, clinical chemistry, hematology, coagulation, urinalysis, or organ weights. There were no toxicologically significant effects noted for gross or microscopic pathology.

**No significant toxicity occurred in this study and the NOAEL is 150 mg/kg/day, (1000 ppm dietary concentration) the highest dose tested. A LOAEL was not determined.**

**This study is classified acceptable/non-guideline.**

## Mutagenicity

### Gene Mutation

Guideline No./Study Type/MRID/Classification	Doses/Results
870.5100, DCSA: Bacterial Reverse Mutation Test: <i>S. typhimurium</i> (TA1535, TA1537, TA98, and TA100) and <i>E. Coli</i> (WP2uvrA) MRID 47899509 Acceptable/Guideline	Preliminary Cytotoxicity Assay: 6.67, 10, 33.3, 66.7, 100, 333, 667, 1000, 3330 or 5000 µg/plate (±S9) Mutation Assay: 0, 33.3, 100, 333, 1000, 2500 or 5000 µg/plate (±S9) Vehicle Control/Solvent: DMSO Positive Controls: +S9: 2-Aminoanthracene, Benzo[a]pyrene; -S9: 2-Nitrofluorene, ICR-191, Sodium azide, 4-nitroquinoline-N-oxide Results: Not Mutagenic
870.5100, DCGA: Bacterial Reverse Mutation Test: <i>S. typhimurium</i> (TA1535, TA1537, TA98, and TA100) and <i>E. Coli</i> (WP2uvrA) MRID 47899514 Acceptable/Guideline	Initial Trial: 0, 1.6, 5, 16, 50, 160, 500, 1600, 5000 µg/plate (±S9) Confirmatory Trial: +S9: 0, 33.3, 100, 333, 1000, 2500, 5000; -S9 (Salmonella): 0, 3.33, 10, 33.3, 100, 333, 1000, 2500; -S9 ( <i>E. coli</i> ): 0, 10, 33.3, 100, 333, 1000, 2500, 5000 µg/plate Vehicle Control/Solvent: DMSO Positive Controls: +S9: 2-Aminoanthracene, Benzo[a]pyrene; -S9: 2-Nitrofluorene, ICR-191, Sodium azide, 4-nitroquinoline-N-oxide Results: Not Mutagenic
870.5100, DMA Salt: Bacterial Reverse Mutation Test: <i>S. typhimurium</i> (TA1535, TA1537, TA1538, TA98, and TA100) MRID 43310301 Acceptable/Guideline	Preliminary Cytotoxicity Assay: 6.7, 10, 33, 67, 100, 333, 667, 1000, 3333 or 5000 µg/plate (±S9) Mutation Assay: 100, 333, 1000, 3333 or 5000 µg/plate (±S9) Vehicle Control/Solvent: Deionized Distilled Water Positive Controls: +S9: 2-Aminoanthracene; -S9: 2-Nitrofluorene, 9-Aminoacridine, Sodium azide Results: Not Mutagenic
870.5100, IPA Salt: Bacterial Reverse Mutation Test: <i>S. typhimurium</i> (TA1535, TA1537, TA1538, TA98, and TA100) MRID 43310303 Acceptable/Guideline	Preliminary Cytotoxicity Assay: 6.7, 10, 33, 67, 100, 333, 667, 1000, 3333 or 5000 µg/plate (±S9) Mutation Assay: 100, 333, 1000, 3333 or 5000 µg/plate (±S9) Vehicle Control/Solvent: Deionized Distilled Water Positive Controls: +S9: 2-Aminoanthracene; -S9: 2-Nitrofluorene, 9-Aminoacridine, Sodium azide Results: Not Mutagenic
870.5100, Dicamba BAPMA: Bacterial Reverse Mutation Test: <i>S. typhimurium</i> (TA1535, TA1537, TA98, and TA100) and <i>E. Coli</i> (WP2uvrA) MRID 48718001 Acceptable/Guideline	Trial 1: 100, 333, 1000, 3333, 5200, 10,400 µg/plate (±S9) Trial 2: 100, 333, 1000, 3333, 5200, 10,400 µg/plate (±S9) Vehicle Control/Solvent: DMSO Positive Controls: +S9: 2-Aminoanthracene; -S9: 4-nitroquinoline-N-oxide, 9-Aminoacridine, 4-nitro-o-phenylenediamine, N-methyl-N-nitro-N-nitrosoguanidine Results: Not Mutagenic

870.5300, DCSA- <i>In vitro</i> Mammalian Cell Gene Mutation Assay in CHO Cells MRID 47899512 Acceptable/Guideline	Preliminary Cytotoxicity Assay: 0, 78.5, 157, 313, 625, 1250, or 2500 µg/mL (±S9) Mutation Assay: Initial Trial: +S9: 0, 200, 400, 500, 600, 700, 800, 1000, 1200; -S9: 0, 200, 400, 600, 800, 1000, 1200, 1400, 1600 µg/mL Confirmatory Trial: +S9: 0, 500, 600, 700, 800, 900, 1000, 1100, 1200; -S9: 0, 800, 900, 1000, 1100, 1200, 1300, 1400, 1500, 1600 µg/mL Vehicle Control/Solvent: DMSO Positive Control: +S9: 3-Methyl-cholanthrene; -S9: 5-Bromo-2' deoxyuridine Results: Not Mutagenic
870.5300, Dicamba BAPMA- <i>In vitro</i> Mammalian Cell Gene Mutation Assay in CHO Cells MRID 48718002 Acceptable/Guideline	Trial 1: 650, 1300, 2600, 5200, 10,400 µg/mL (±S9) Trial 2: +S9: 2000, 4000, 8000, 10400; -S9: 500, 1000, 2000, 4000, 8000, 10400 µg/mL Trial 3: 62.5, 125, 250, 500, 1000, 2000, 4000, 8000 µg/mL (-S9) Vehicle Control/Solvent: DMSO Positive Control: +S9: Methyl-cholanthrene; -S9: Ethyl methane-sulfonate Results: Not Mutagenic
870.5300, DMA Salt: <i>In vitro</i> Mammalian Cell Gene Mutation Assay in Mouse Lymphoma (L5178Y) Cells MRID 43310304 Acceptable/Guideline	Preliminary Cytotoxicity Assay: 0.5, 1, 5, 10, 50, 100, 500, 1000 or 5000 µg/mL (±S9). Mutation Assay: 900, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000 µg/mL (±S9) Vehicle Control/Solvent: Deionized Distilled Water Positive Control: +S9: Dimethylbenzanthracene; -S9: Ethyl methane-sulfonate Results: Not Mutagenic
870.5300, IPA Salt: <i>In vitro</i> Mammalian Cell Gene Mutation Assay in Mouse Lymphoma (L5178Y) Cells MRID 43310306 Acceptable/Guideline	Preliminary Cytotoxicity Assay: 0.5, 1, 5, 10, 50, 100, 500, 1000 or 5000 µg/mL (±S9). Mutation Assay: 900, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000 µg/mL (±S9) Vehicle Control/Solvent: Deionized Distilled Water Positive Control: +S9: Dimethylbenzanthracene; -S9: Ethyl methane-sulfonate Results: Not Mutagenic

### Cytogenetics

Guideline No./Study Type/MRID/Classification	Doses/Results
870.5375, Dicamba BAPMA: <i>In Vitro</i> Mammalian Chromosome Aberration Test in Human Lymphocytes MRID 48718003 Acceptable/Guideline	Trial 1: 650, 1,300, 2,600, 5,200, 10,400 µg/mL (±S9) Trial 2: 2600, 5200, 7800, 10,400 µg/mL (±S9) Vehicle Control: DMSO Positive Control: +S9: Cyclophosphamide; -S9: Ethyl methane-sulfonate Results: Positive for clastogenic activity
870.5385, DCSA: <i>In Vivo</i> Mammalian Chromosome Aberration Assay in Rats MRID 47899513 Acceptable/Guideline	0, 400/300, 800/600, 1600/1200 mg/kg (M/F) Vehicle Control/Solvent: Corn Oil Positive Control: Cyclophosphamide (60 mg/kg) Results: Not Mutagenic

870.5385, DCSA: <i>In Vivo</i> Mammalian Chromosome Aberration Assay in Rats MRID 47899515 Acceptable/Guideline	0, 375, 750, 1500 mg/kg Vehicle Control/Solvent: Corn Oil Positive Control: Cyclophosphamide (60 mg/kg) Results: Not Mutagenic
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### Other Genotoxicity

Guideline No./Study Type/MRID/Classification	Doses/Results
870.5395, DCSA- <i>In Vivo</i> Mammalian (mouse) Erythrocyte Micronucleus Assay MRID 47899511 Acceptable/Guideline	0, 250, 500, 1000 mg/kg Vehicle Control/Solvent: Corn Oil Positive Control: Cyclophosphamide (80 mg/kg) Results: Negative for clastogenic or aneugenic effects
870.5395, Dicamba BAMPA- <i>In Vivo</i> Mammalian (mouse) Bone Marrow Micronucleus Assay MRID 48718004 Acceptable/Guideline	500, 1000, 2000 mg/kg Vehicle Control/Solvent: Deionized Distilled Water Positive Control: Cyclophosphamide (20 mg/kg), Vincristine Sulfate (0.15 mg/kg) Results: Negative for clastogenic or aneugenic effects
870.5395, IPA Salt- <i>In Vivo</i> Mammalian (mouse) Bone Marrow Micronucleus Assay MRID 43354334 Acceptable/Guideline	500, 1000, 2000 mg/kg Vehicle Control/Solvent: Deionized Distilled Water Positive Control: Cyclophosphamide (40 mg/kg) Results: Not Mutagenic
870.5395, DMA Salt- <i>In Vivo</i> Mammalian (mouse) Bone Marrow Micronucleus Assay MRID 43354332 Acceptable/Guideline	450, 900, 1800 mg/kg Vehicle Control/Solvent: Deionized Distilled Water Positive Control: Cyclophosphamide (40 mg/kg) Results: Not Mutagenic

### 870.7485 DCSA- Metabolism

In a metabolism and pharmacokinetic study (MRID 47899502), a mixture of radiolabelled and unlabelled DCSA (5,560 dpm/ $\mu$ g) as a suspension in corn oil was administered by oral gavage individually to six male rats (Sprague-Dawley Crl:CD® (SD)) as a single dose at a target dose level of 100 mg/kg bw.

[<sup>14</sup>C]DCSA was extensively absorbed by the rat and rapidly excreted with very little retention in tissues. Urinary excretion was the major route of elimination accounting for approximately 95% of the administered dose. Levels of radioactivity in the tissues after 7 days were very low with kidney containing the highest levels of the dose. Limited metabolism of DCSA occurred in the rat *via* glucuronidation at either the carboxylic acid or phenol moiety. Unchanged DCSA represented approximately 82% of the dose.

**This study is classified totally reliable (acceptable/guideline) and satisfies the guideline requirement for a metabolism/pharmacokinetic study when evaluated with MRID 47899503.**

In a metabolism and pharmacokinetics study (MRID 47899503), unlabelled DCSA was administered in the diet for 14 days followed by a single oral gavage dose on the 15<sup>th</sup> day of [<sup>14</sup>C]DCSA in corn oil to male and female rats (Sprague-Dawley CrI:CD® (SD)) at target dose levels of 42, 125, 250, 375, or 500 mg/kg bw.

There was a plateau in plasma C<sub>max</sub> values following the [<sup>14</sup>C]DCSA dose at dose levels above 125 mg/kg bw. Clearance of the dose is also limited, especially in females, even at the 125 mg/kg bw dose level, as evidenced by higher than dose-proportional increases in AUC<sub>0-∞</sub> values with increasing dose. This leads to an increase in 24-h plasma concentration values at dose levels above 125 mg/kg bw. It appears that the breakpoint for the change in pharmacokinetic behaviour of DCSA occurs between the 125 and 250 mg/kg bw dose levels.

Following repeated dosing of males and females at 125 or 500 mg/kg bw, a single oral gavage dose of DCSA was well-absorbed and rapidly excreted, primarily in urine. While significant changes in pharmacokinetic parameters were observed with increasing dose level, only minor differences were observed in the metabolism and elimination of DCSA between dose levels or genders. Elimination at the high dose was somewhat slower than the low dose, likely due to delayed/saturated absorption at the high dose. Limited metabolism of DCSA occurred *via* glucuronidation at either the carboxylic acid or phenolic moieties. DCSA phenolic glucuronide and DCSA carboxyl glucuronide constituted 10-15% and 1.5-16% of the administered dose in the excreta, respectively. No other metabolite exceeded 1% of the administered dose. The excretion pattern and metabolite profiles obtained in this study following repeated dosing at 125 or 500 mg/kg bw of both males and females are very similar to those obtained in the DCSA rat ADME study described in point 5.8.1 in which males only were dosed by single oral gavage with [<sup>14</sup>C]DCSA at a 100 mg/kg bw dose level.

**This study is classified totally reliable (acceptable/guideline) and satisfies the guideline requirement for a metabolism/pharmacokinetic study and should be evaluated with MRID 47899502.**

## A.6 Statistical Analysis of the Dicamba Acid Reproduction Study Pup Body Weights

### A.6.1 Mean and Standard Deviation of litter-specific average pup weight (males and females combined results)

Dose (ppm)	N	Mean (SD) (grams)					
		PND 0	PND 4	PND 8	PND 12	PND 16	PND 21
0	25	6.29 (0.62)	10.07 (1.67)	19.05 (2.66)	30.35 (3.37)	41.53 (4.18)	59.65 (6.24)
500	28	6.29 (0.70)	9.89 (1.94)	18.63 (3.39)	29.33 (3.99)	40.01 (4.26)	57.75 (6.37)
1500	29	6.31 (0.60)	10.26 (2.02)	19.10 (2.91)	29.68 (3.83)	40.14 (5.02)	57.30 (7.09)
5000	26	5.87 (0.58)	9.09 (1.55)	16.00 (2.92)	24.43 (4.31)	33.61 (6.02)	45.41 (8.56)

Table A.6.1.2. Mean and Standard Deviation of Litter-Specific Average Pup Weight of F2 Generations								
Age	Dose (ppm)	N	Mean (SD) (grams)					
			PND 0	PND 4	PND 8	PND 12	PND 16	PND 21
F2A	0	15	6.59 (0.63)	11.59 (1.23)	21.56 (1.79)	33.06 (2.80)	44.49 (3.57)	64.95 (4.09)
	500	17	6.43 (0.64)	10.75 (2.04)	20.18 (3.44)	31.12 (4.23)	42.62 (4.63)	62.48 (6.89)
	1500	12	6.40 (0.67)	10.41 (2.11)	19.43 (3.46)	30.23 (3.62)	40.68 (4.43)	58.44 (6.42)
	5000	19	6.10 (0.67)	10.38 (1.67)	18.06 (2.90)	26.63 (3.73)	34.06 (4.46)	47.89 (6.77)
F2B	0	14	6.56 (0.64)	10.61 (1.76)	20.05 (3.38)	31.45 (4.09)	43.30 (5.32)	61.76 (6.86)
	500	16	6.61 (0.73)	10.49 (1.68)	19.13 (3.33)	30.40 (4.60)	41.69 (5.63)	59.77 (7.22)
	1500	14	6.69 (0.60)	10.21 (1.24)	18.16 (2.80)	27.56 (4.62)	37.55 (5.79)	52.87 (8.42)
	5000	19	6.12 (0.68)	9.69 (1.98)	16.27 (2.90)	23.82 (4.04)	30.50 (3.95)	43.22 (6.33)

#### Pup Body Weight Statistical Analysis Compared to the MARTA (Middle Atlantic Reproduction and Teratology Association) Historical Control Database

The results show that the PND 0 pup body weights for the MARTA historical control mean of 6.33 grams are statistically different than the 95% confidence intervals for F1 generation at 5000 ppm and F2B generation at 1500 ppm. However, only in the F1 generation at 5000 ppm is the pup body weight considered adverse at PND 0 since it is a decrease of 7.2%, before the lactation phase. In the F2B generation at 1500 ppm, the pup body weight is above the historical control average, thus not considered adverse. The concurrent control PND 0 pup body weights in the dicamba acid study were statistically identical to the MARTA historical control data base PND 0 values.

The results show that the PND 21 pup body weights for the MARTA historical control mean of 49.33 grams is statistically different than the 95% confidence intervals for all doses except the F2A generation at 5000 ppm and F2B generation at 1500 ppm. The pup body weights are only considered adverse in the F1 and F2B generations at 5000 ppm, since the pup body weights are both decreased by over 5% (i.e. -7.9% and -12.4%, respectively) and statistically significant, relative to the MARTA historical control data.

At the 5000 ppm dose, there were adverse decreases in the F1 pup body weights at PND 0 before the lactation phase. The WIL Research Laboratories historical control database supported the MARTA database conclusions that the dicamba acid reproduction study pup body weights were still above average values at the 500 ppm and 1500 ppm doses and only below average weights at the 5000 ppm dose (DCSA reproduction study, MRID 47899517).

## PND 0

Mean of historical control means	6.33
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Generation	Group	sample size	Dicamba group mean	Dicamba group SD	95% CI		p-value
F1	Control	25	6.29	0.62	6.03	6.55	> 0.05
F1	500	28	6.29	0.7	6.02	6.56	> 0.05
F1	1500	29	6.31	0.6	6.08	6.54	> 0.05
F1	5000	26	5.87	0.58	5.64	6.10	< 0.05
F2A	Control	15	6.59	0.63	6.24	6.94	> 0.05
F2A	500	17	6.43	0.64	6.10	6.76	> 0.05
F2A	1500	12	6.4	0.67	5.97	6.83	> 0.05
F2A	5000	19	6.1	0.67	5.78	6.42	> 0.05
F2B	Control	14	6.56	0.64	6.19	6.93	> 0.05
F2B	500	16	6.61	0.73	6.22	7.00	> 0.05
F2B	1500	14	6.69	0.6	6.34	7.04	< 0.05
F2B	5000	19	6.12	0.68	5.79	6.45	> 0.05

## PND 21

Mean of historical control means	49.33
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Generation	Group	Dicamba sample size	Dicamba group mean	Dicamba group SD	95% CI		p-value
F1	Control	25	59.65	6.24	57.07	62.23	< 0.05
F1	500	28	57.75	6.37	55.28	60.22	< 0.05
F1	1500	29	57.3	7.09	54.60	60.00	< 0.05
F1	5000	26	45.41	8.56	41.95	48.87	< 0.05
F2A	Control	15	64.95	4.09	62.69	67.21	< 0.05
F2A	500	17	62.48	6.89	58.94	66.02	< 0.05
F2A	1500	12	58.44	6.42	54.36	62.52	< 0.05
F2A	5000	19	47.89	6.77	44.63	51.15	> 0.05
F2B	Control	14	61.76	6.86	57.80	65.72	< 0.05
F2B	500	16	59.77	7.22	55.92	63.62	< 0.05
F2B	1500	14	52.87	8.42	48.01	57.73	> 0.05
F2B	5000	19	43.22	6.33	40.17	46.27	< 0.05

### A.6.2 Statistical Report: Dicamba- a reproduction study – Analysis of litter-specific average pup weights versus study concurrent control groups

#### Statistical methods

Repeated-Measures Analysis of Variance (mixed-effects models) was used to analyze the litter-specific average pup weight of F1 and F2 generations on a per dam basis. (Litters of F1 generation were

identified by the F0 dams' identification numbers, and litters of F2 generation were identified by the F1 dams' identification numbers.)

Since the individual pup body weights were not provided in the registrant's submission and the body weight of each of pups may be affected by the number of pups in a given dam's litter, the number of live pups in a dam on each measurement day was included in the model as covariate. Also, the number of pups in a dam's litter was standardized on post-natal day 4, so number of pups on day 0 (i.e., number of live pups born) was used as covariate for the measurement on post-natal day 4. (Results show that for each pup increase in the number of live pups in a litter, the F1 litter-specific average pup weight decreases by 0.082 grams and F2 litter-specific average pup weight decreases by 0.090 grams).

In the analysis of F1 litter-specific average pup weight, the model incorporates dose, day, interaction between dose and day, and number of live pups in the litter on the measurement day. To account for the correlation between measurements on different post-natal days of same litter, an unstructured (UN) covariance matrix was selected (which has smaller Akaike Information Criterion or AIC value compared to compound symmetric (CS) covariance matrix and autoregressive lag(1) correlation matrix (AR(1))).

In the analysis of F2 litter-specific average pup weight, the final model includes age (young: first litter/having pups at young age and old: second litter/having pups at an older age), dose, day, interaction between dose and day, interaction between age and day, and number of live pups in each specific litter on the measurement day. The three-way interaction "age-day-dose" and two-way interaction between "age-dose" were not significant and were not kept in the final model. Multiple covariance matrices were considered (UN@UN (not convergence), UN@CS, UN@AR(1), and heterogeneous/different UN for each Age). The heterogeneous covariance matrices (i.e., different UN covariance for each age) were selected based the criterion of lower AIC value.

### Results:

Table A.6.2.a presents the results of comparison of the F1 litter-specific average pup weight. The F1 litter-specific average pup weight associated with the **high dose** (5000 ppm) was significantly lower than the **control** on post-natal days 0, 4, 8, 12, 16, and 21 (-6.4%, -9.4%, -16.2%, -19.6%, -19.2%, and 24%, respectively). The **mid-** and **low-** dose groups (1500 ppm and 500 ppm, respectively) did not differ significantly from the **control** group. Figure 1 presents the predicted curves and observed means of litter-specific average pup weight. As can be seen and was confirmed with the Dunnett's test, the average pup weight in the high-dose group differs significantly from that of the control group.

In the analysis of F2 litter-specific average pup weight data in which dams gave birth at both "young" or F2A and "old" or F2B ages, the interaction "dose\*age" was not significant (p-value > 0.05 and this term was thus not kept in the final model); this indicates that the dose effect (of same dose level on same given post-natal day) on litter-specific average pup weight was not affected by the dam's age. Therefore, there is a single common dose effect on litter-specific average pup weight (on a specific post-natal day) and this can be used to appropriately represent the dose effect (on a specific post-natal day) at either age ("young" vs. "old") of the dam. However, the significant "dose\*day" interaction indicates that dose effects on litter-specific average pup weight were different between post-natal days. Therefore, it is necessary for the dose effects to be estimated --- and evaluated -- separately on

each post-natal day. (The significant age\*day interaction indicates that the effects of post natal day on litter-specific average pup weight varied between the two ages of the dam (young and old). Note that this day effect is not related to dose effect).

Table A.6.2.b presents the results of comparisons of common litter-specific average pup weight between the dosed groups and control group. The litter-specific average pup weight in **mid-dose** group was not significantly different from the control group on post-natal days 0, 4, and 8; however, the litter-specific average pup weight in **mid-dose** group was significantly lower compared to the control group on post-natal days 12, 16, and 21 (-9.3%, -9.9%, and -11.2%, respectively). The litter-specific average pup weight in **high dose** group was significantly lower than the control on post-natal days 0, 4, 8, 12, 16, and 21 (-7.8%, -9.2%, -17.1%, -21.5%, -26.1%, and -27.4%, respectively). No significant difference was seen on any post-natal day for the **low** dose group compared to the control.

<b>_Name_</b>	<b>DOSE</b>	<b>day0</b>	<b>day4</b>	<b>day8</b>	<b>day12</b>	<b>day16</b>	<b>day21</b>
LSMean (SE)	0	6.60 (0.10)	10.38 (0.32)	18.88 (0.60)	30.18 (0.78)	41.36 (0.98)	59.47 (1.42)
	500	6.63 (0.09)	10.23 (0.31)	18.44 (0.56)	29.14 (0.73)	39.82 (0.93)	57.56 (1.35)
	1500	6.75 (0.10)	10.69 (0.30)	18.93 (0.55)	29.51 (0.72)	39.97 (0.91)	57.13 (1.32)
	5000	6.18 (0.10)	9.40 (0.32)	15.83 (0.58)	24.26 (0.76)	33.43 (0.96)	45.21 (1.40)
Diff (SE)	500 vs.0	0.02 (0.13)	-0.16 (0.44)	-0.43 (0.82)	-1.04 (1.07)	-1.53 (1.35)	-1.91 (1.96)
	1500 vs.0	0.15 (0.13)	0.31 (0.44)	0.05 (0.81)	-0.67 (1.06)	-1.38 (1.34)	-2.34 (1.94)
	5000 vs.0	-0.42 (0.13)	-0.98 (0.45)	-3.05 (0.83)	-5.92 (1.09)	-7.93 (1.38)	-14.26 (1.99)
Percent (%)	500 vs.0	0.36	-1.51	-2.30	-3.44	-3.71	-3.21
	1500 vs.0	2.24	2.98	0.27	-2.22	-3.35	-3.94
	5000 vs.0	-6.39	-9.43	-16.16	-19.60	-19.17	-23.98
raw p-value	500 vs.0	0.851	0.726	0.597	0.334	0.259	0.332
	1500 vs.0	0.241	0.484	0.949	0.530	0.304	0.230
	5000 vs.0	0.001	0.033	0.000	0.000	0.000	0.000
Dunnett p-value	500 vs.0	0.995	0.970	0.909	0.640	0.527	0.638
	1500 vs.0	0.497	0.819	1.000	0.860	0.597	0.478
	5000 vs.0	0.004	0.083	0.001	< 0.001	< 0.001	< 0.001

<b>_Name_</b>	<b>DOSE</b>	<b>day0</b>	<b>day4</b>	<b>day8</b>	<b>day12</b>	<b>day16</b>	<b>day21</b>
LSMean (SE)	0	6.92 (0.09)	11.42 (0.28)	20.56 (0.55)	32.01 (0.73)	43.57 (0.86)	62.88 (1.21)
	500	6.91 (0.09)	10.86 (0.27)	19.34 (0.52)	30.31 (0.68)	41.76 (0.81)	60.59 (1.14)
	1500	6.80 (0.10)	10.69 (0.30)	18.89 (0.58)	29.05 (0.77)	39.27 (0.92)	55.86 (1.29)
	5000	6.38 (0.08)	10.37 (0.25)	17.05 (0.48)	25.13 (0.64)	32.19 (0.76)	45.66 (1.06)
Diff (SE)	500 vs.0	-0.02 (0.12)	-0.56 (0.38)	-1.22 (0.75)	-1.71 (0.99)	-1.82 (1.17)	-2.29 (1.65)
	1500 vs.0	-0.12 (0.13)	-0.73 (0.41)	-1.67 (0.80)	-2.96 (1.05)	-4.30 (1.25)	-7.02 (1.76)
	5000 vs.0	-0.54 (0.12)	-1.06 (0.37)	-3.51 (0.73)	-6.88 (0.96)	-11.38 (1.14)	-17.22 (1.60)
Percent	500 vs.0	-0.22	-4.90	-5.91	-5.33	-4.17	-3.65
	1500 vs.0	-1.75	-6.41	-8.11	-9.26	-9.87	-11.16
	5000 vs.0	-7.78	-9.24	-17.05	-21.49	-26.12	-27.39

<u>_Name_</u>	<u>DOSE</u>	<u>day0</u>	<u>day4</u>	<u>day8</u>	<u>day12</u>	<u>day16</u>	<u>day21</u>
raw p-value	500 vs.0	0.901	0.146	0.105	0.084	0.122	0.165
	1500 vs.0	0.344	0.074	0.037	0.005	0.001	0.000
	5000 vs.0	0.000	0.005	0.000	0.000	0.000	0.000
Dunnett p-value	500 vs.0	0.999	0.327	0.244	0.200	0.279	0.363
	1500 vs.0	0.657	0.177	0.093	0.014	0.002	< 0.001
	5000 vs.0	0.000	0.013	< 0.001	< 0.001	< 0.001	< 0.001

### Supplemental Tables and Figures

Table A.6.2.c: SAS output table Type 3 Tests of Fixed Effects of the model analyzing F1 litter-specific average pup weight.

<u>Effect</u>	<u>Num DF</u>	<u>Den DF</u>	<u>F Value</u>	<u>Pr &gt; F</u>
<b>Dose</b>	3	104	14.46	<.0001
<b>Day</b>	5	104	1584.91	<.0001
<b>Dose*Day</b>	15	104	13.42	<.0001
<b>npup</b>	1	104	79.25	<.0001

repeated Day/subject=Dam type=un; [IDEALLY – if individual pup weights were available-- THE SUBJECT WOULD NOT BE LITTER-SPECIFIC, BUT PUP NESTED WITHIN LITTER-SPECIFIC.

Table A.6.2.d.: Statistical Analysis Software (SAS) output table Type 3 Tests of Fixed Effects of the model analyzing F2 litter-specific average pup weight.

<u>Effect</u>	<u>Num DF</u>	<u>Den DF</u>	<u>F Value</u>	<u>Pr &gt; F</u>
<b>Day</b>	5	380	1979.95	<.0001
<b>Dose</b>	3	76	30.38	<.0001
<b>Age</b>	1	45	8.71	0.0050
<b>Dose*Day</b>	15	380	23.67	<.0001
<b>Age* Day</b>	5	225	2.85	0.0161
<b>npup</b>	1	649	112.11	<.0001

repeated Day/subject=dam type= un group = age;

### A.6.3 Dicamba – a reproduction study analysis of F1 body weight post-weaning period

#### Background

Table A.6.3.a below presents the available data of individual F1 generation pup body weight and the time that the data were collected.

- The data analysis was done separately for the lactation period and post-weaning period because:
  - body weight data were reported differently for the lactation period and post-weaning period and could not be combined (i.e., averaged male and female pup body weight per

- litter for the lactation period and individual body weights for each gender, but no litter information, for the post-weaning period)
- For the statistics done for the lactation period, litter was the experimental subject, and number of live pups per litter was incorporated as a covariate into the analysis of lactation period; however – for the post-weaning period -- each individual pup served as the experimental subject (no litter and no number of live pups per litter information was made available)
  - The individual body weight data of female pups and male pups in post-weaning period should not be pooled together into one single analysis because there were two pups (1 male and 1 female) selected from each litter but the information to identify which pups were from the same litter was not available. In order to do a single analysis of both males and females, the litter information must be available to account for the litter effects in the model. Table 1 below summarizes the key features of both data set available for the lactation period and for the post-weaning period.

Table A.6.3.a: Available Data of F1 Pup Body Weight and The Time Data Were Collected.		
	Lactation Period (Post-Natal Day)	Post-Weaning Period (Post-Natal Week)
	0, 4, 8, 12, 16, and 21	4, 5, 6, 7, 8, and 9
Available data	Average pup body weight per litter (all males and females together)	Individual body weight of 1 male and 1 female per litter, but no litter information was available The pups have median body weight within each litter were selected

**Caution:** Since pups for the post-weaning period were not selected randomly but instead purposely selected as the pup closest to the median of body weight within each litter, there are limitations in the interpretation of the results from the analysis using post-weaning body weight data. An effect that is statistically “not significant” at a given dose level does not necessarily mean that the dose had no significant effect on the pup body weight in general. It may be that the animal with the lowest weight in a litter which was not selected for collecting body weight data during the post-weaning period might be the animal that is most affected by the dose level.

## Statistical Methods

Linear mixed-effects models were used to analyze the repeated-measures body weight data of the pups collected during post-weaning period. The model included Dose, Week (linear term), Week\*Week (quadratic term), Week\*Week\*Week (cubic term), and interaction between Dose and Week. The quadratic Week\*Week and cubic Week\*Week\*Week terms allow the models to properly account for the curvature in growth curves of the animals. Based on the AIC criterion (smaller is better), the selected models included random intercept (different pups had different body weight at beginning), random coefficient of week (different pups have different linear growth rate), and random coefficient of week\*week (different pups have different curvatures between their growth curves).

## Results

During post-weaning period, the F1 pups body weight of both median male and female in each litter in the mid dose and low dose were not significantly different from the control. However, this does not

mean that the average pup body weight per litter (as in lactation period) in the mid dose and low dose were not different from the control during the post-weaning period.

The median body weight of both male and female in each litter in the high dose group was significantly lower than the control during the post-weaning period, except for the median body weight female in high dose group on week 9. Table A.6.3.b presents the mean and standard deviation of each group by week and gender. Table A.6.3.c and A.6.3.d present the body weight comparisons between the treated groups and the control group for male and female F1 pups, respectively. These comparisons were conducted using linear mixed-effects models.

Gender	Dose	Mean (SD) (grams)					
		Week 4	Week 5	Week 6	Week 7	Week 8	Week 9
Female	0	91.93 (12.96)	132.46 (17.55)	170.96 (18.27)	200.43 (22.39)	229.50 (26.57)	255.32 (31.74)
	500	91.11 (10.78)	134.61 (12.65)	173.68 (14.22)	203.07 (17.40)	231.96 (20.40)	254.21 (23.66)
	1500	89.93 (11.48)	132.29 (13.53)	171.07 (17.17)	201.11 (19.05)	227.89 (19.98)	254.93 (20.57)
	5000	75.64 (9.82)	114.79 (12.32)	155.32 (15.02)	186.86 (17.23)	216.00 (21.17)	241.29 (24.61)
Male	0	94.82 (16.78)	151.39 (23.04)	215.64 (27.06)	281.54 (32.25)	341.68 (34.98)	394.96 (40.08)
	500	100.14 (12.00)	159.50 (17.92)	224.14 (19.92)	292.64 (24.37)	359.32 (27.84)	415.14 (30.58)
	1500	100.39 (13.10)	157.37 (19.34)	228.74 (24.13)	297.64 (31.75)	362.29 (38.38)	419.71 (45.69)
	5000	79.71 (16.49)	129.21 (22.37)	190.79 (28.79)	254.21 (35.77)	311.21 (46.56)	372.41 (42.88)

_Name_	DOSE	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9
LSMean (SE)	0	94.60 (2.80)	150.55 (3.75)	214.38 (4.78)	280.50 (5.86)	343.32 (6.99)	397.24 (8.17)
	500	100.56 (2.80)	158.80 (3.75)	224.93 (4.78)	293.34 (5.86)	358.45 (6.99)	414.67 (8.17)
	1500	99.70 (2.80)	159.30 (3.75)	226.79 (4.78)	296.57 (5.86)	363.04 (6.99)	420.61 (8.17)
	5000	79.58 (2.80)	131.50 (3.75)	191.31 (4.78)	253.41 (5.86)	312.21 (6.99)	362.11 (8.17)
Diff (SE)	500 vs.0	5.96 (3.96)	8.25 (5.27)	10.55 (6.74)	12.84 (8.28)	15.13 (9.87)	17.43 (11.47)
	1500 vs.0	5.10 (3.96)	8.75 (5.27)	12.41 (6.74)	16.06 (8.28)	19.72 (9.87)	23.37 (11.47)
	5000 vs.0	-15.02 (3.96)	-19.04 (5.27)	-23.07 (6.74)	-27.09 (8.28)	-31.11 (9.87)	-35.13 (11.47)
Percent	500 vs.0	6.30	5.48	4.92	4.58	4.41	4.39
	1500 vs.0	5.39	5.81	5.79	5.73	5.74	5.88
	5000 vs.0	-15.88	-12.65	-10.76	-9.66	-9.06	-8.84
raw p-value	500 vs.0	0.133	0.118	0.119	0.122	0.126	0.130
	1500 vs.0	0.198	0.098	0.067	0.053	0.047	0.042
	5000 vs.0	<0.001	<0.001	0.001	0.001	0.002	0.002
Dunnett p-value	500 vs.0	0.305	0.275	0.275	0.282	0.290	0.298
	1500 vs.0	0.429	0.231	0.163	0.133	0.117	0.108

<u>_Name_</u>	<u>DOSE</u>	<u>Week 4</u>	<u>Week 5</u>	<u>Week 6</u>	<u>Week 7</u>	<u>Week 8</u>	<u>Week 9</u>
	5000 vs.0	0.001	0.001	0.002	0.003	0.005	0.007

<u>_Name_</u>	<u>DOSE</u>	<u>Week 4</u>	<u>Week 5</u>	<u>Week 6</u>	<u>Week 7</u>	<u>Week 8</u>	<u>Week 9</u>
LSMean (SE)	0	92.00 (2.18)	134.32 (2.47)	170.76 (2.93)	202.27 (3.48)	229.83 (4.11)	254.39 (4.79)
	500	90.61 (2.18)	133.45 (2.47)	170.41 (2.93)	202.45 (3.48)	230.53 (4.11)	255.61 (4.79)
	1500	90.07 (2.18)	132.73 (2.47)	169.51 (2.93)	201.37 (3.48)	229.28 (4.11)	254.18 (4.79)
	5000	74.75 (2.18)	117.87 (2.47)	155.10 (2.93)	187.42 (3.48)	215.77 (4.11)	241.13 (4.79)
Diff (SE)	500 vs.0	-1.39 (3.07)	-0.87 (3.44)	-0.35 (4.08)	0.18 (4.89)	0.70 (5.80)	1.22 (6.76)
	1500 vs.0	-1.93 (3.07)	-1.59 (3.44)	-1.24 (4.08)	-0.90 (4.89)	-0.56 (5.80)	-0.21 (6.76)
	5000 vs.0	-17.25 (3.07)	-16.45 (3.44)	-15.65 (4.08)	-14.86 (4.89)	-14.06 (5.80)	-13.26 (6.76)
Percent	500 vs.0	-1.51	-0.65	-0.20	0.09	0.30	0.48
	1500 vs.0	-2.10	-1.18	-0.73	-0.45	-0.24	-0.08
	5000 vs.0	-18.75	-12.25	-9.17	-7.34	-6.12	-5.21
raw p-value	500 vs.0	0.651	0.801	0.932	0.971	0.904	0.857
	1500 vs.0	0.530	0.645	0.761	0.854	0.924	0.975
	5000 vs.0	<0.001	<0.001	<0.001	0.003	0.016	0.051
Dunnett p-value	500 vs.0	0.942	0.989	>0.999	>0.999	0.999	0.996
	1500 vs.0	0.865	0.939	0.981	0.996	0.999	>0.999
	5000 vs.0	<0.001	<0.001	<0.001	0.007	0.042	0.127

In the scatter-plot of observed group means and predicted curves of each group for F1 male and F1 female, the observed group means of each dose group were close to the group predicted curve. This result indicates that the selected model was very good in its ability to accurately characterize and describe the growth of body weight of the animals during the post-weaning period.

### Supplemental Tables and Figures

<u>Effect</u>	<u>Dose</u>	<u>Estimate</u>	<u>Stand. Error</u>	<u>DF</u>	<u>t Value</u>	<u>Pr &gt;  t </u>
Intercept		61.5338	13.0441	108	4.72	<.0001
Week		-48.5249	6.3657	108	-7.62	<.0001
Week*Week		17.9273	0.9861	111	18.18	<.0001
Week*Week*Week		-0.9323	0.05021	332	-18.57	<.0001
Dose	500	-3.2160	4.7512	332	-0.68	0.4990
Dose	1500	-9.5165	4.7528	332	-2.00	0.0461

Effect	Dose	Estimate	Stand. Error	DF	t Value	Pr >  t
Dose	5000	1.0696	4.7516	332	0.23	0.8220
Dose	0	0	.	.	.	.
Week*Dose	500	2.2935	1.6641	332	1.38	0.1691
Week*Dose	1500	3.6541	1.6642	332	2.20	0.0288
Week*Dose	5000	-4.0227	1.6641	332	-2.42	0.0162
Week*Dose	0	0	.	.	.	.

Note: the linear growth rate of mid dose was significantly higher than the control and the linear growth rate of high dose was significantly lower than the control.

Effect	Num DF	Den DF	F Value	Pr > F
Week	1	108	58.46	<.0001
Week*Week	1	111	330.50	<.0001
Week*Week*Week	1	332	344.85	<.0001
Dose	3	332	2.01	0.1127
Week*Dose	3	332	8.15	<.0001

Effect	Dose	Estimate	Stand. Error	DF	t Value	Pr >  t
Intercept		-155.24	12.8583	108	-12.07	<.0001
Week		80.6063	6.2118	108	12.98	<.0001
Week*Week		-5.3386	0.9758	111	-5.47	<.0001
Week*Week*Week		0.1599	0.04982	334	3.21	0.0015
Dose	500	-3.4838	4.9228	334	-0.71	0.4796
Dose	1500	-3.3088	4.9219	334	-0.67	0.5019
Dose	5000	-20.4414	4.9219	334	-4.15	<.0001
Dose	10000	0	.	.	.	.
Week*Dose	500	0.5229	1.1028	334	0.47	0.6357
Week*Dose	1500	0.3440	1.1027	334	0.31	0.7552
Week*Dose	5000	0.7979	1.1027	334	0.72	0.4698
Week*Dose	10000	0	.	.	.	.

Note: the growth curve of high dose was significantly lower (shifted down) than the control.

Effect	Num DF	Den DF	F Value	Pr > F
Week	1	108	172.18	<.0001
Week*Week	1	111	29.93	<.0001
Week*Week*Week	1	334	10.31	0.0015
Dose	3	334	7.03	0.0001
Week*Dose	3	334	0.18	0.9073

## Appendix B. Physical/Chemical Properties.

Table B.1. Physicochemical Properties of the Technical Grade Test Compound: Dicamba.			
Parameter	Value	Reference	
Melting point	114-116 EC (Pure Active Ingredient) 90-100 EC (87% Technical Grade Active Ingredient)	Residue Chemistry Chapter of the Dicamba RED (D317699, C. L. Olinger, 20-DEC-2005).	
pH	2.5-3.0 (87% TGAI)		
Density	1.57 g/mL at 25 EC (87% TGAI)		
Water solubility	0.5 g/100 mL at 25 EC (PAI)		
Solvent solubility	<u>g/100 mL at 25 EC (PAI)</u>		
	dioxane		118.0
	ethanol		92.2
	isopropyl alcohol		76.0
	methylene chloride		26.0
	acetone		17.0
	toluene		13.0
Vapor pressure	xylene	7.8	
	heavy aromatic naphthalene	5.2	
Vapor pressure	3.4 x 10 <sup>-5</sup> mm Hg at 25 EC (PAI)		
Dissociation constant, pK <sub>a</sub>	1.97 (PAI)		
Octanol/water partition coefficient, Log(K <sub>ow</sub> )	0.1 (PAI)		
UV/visible absorption spectrum	neutral:	511 (275 nm)	
	acidic (pH 0-1):	1053 (281 nm)	
	basic (pH 13-14):	469 (274 nm)	

## Appendix C. Review of Human Research

It is HED policy to use the best available data to assess exposure. Several sources of generic data were used in this assessment as surrogate data in the absence of chemical-specific data, including Pesticide Handlers Exposure Database Version 1.1 (PHED 1.1); the Agricultural Handler Exposure Task Force (AHETF) database; and the Outdoor Residential Exposure Task Force (ORETF) database. Some of these data are proprietary, and subject to the data protection provisions of the *Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)*. For certain studies, the ethics review may have included review by the Human Studies Review Board. Descriptions of data sources, as well as guidance on their use, can be found at the Agency website<sup>21</sup>.

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<sup>21</sup> <https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data> and <https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-post-application-exposure>

## Appendix D. Summary of US and International Tolerances and Maximum Residue Limits.

Table D.1. Summary of US and International Tolerances and Maximum Residue Limits.					
<i>Residue Definition:</i>					
US	Canada			Mexico	Codex
40 CFR 180.227: (a) <i>General</i> . (1) Compliance with the tolerance levels is to be determined by measuring only the sum of the residues of dicamba (3,6-dichloro-2-methoxybenzoic acid), and its metabolites 3,6-dichloro-5-hydroxy-2-methoxybenzoic acid, and 3,6-dichloro-2-hydroxybenzoic acid, calculated as the stoichiometric equivalent of dicamba	All food crops except dry soybeans: benzoic acid,3,6-dichloro-2-methoxy including the metabolite benzoic acid, 2,5-dichloro-3-hydroxy-6-methoxy-				Dicamba
	<i>Tolerance (ppm)/Maximum Residue Limit (mg/kg)</i>				
Commodity <sup>1</sup>	US Established	HED-Recommended	Canada	Mexico <sup>1</sup>	Codex
Asparagus	4.0	5			5
Barley, grain	6.0	7			7
Barley, hay	2.0	2			
Barley, straw	15.0	15			50 barley straw and fodder, dry
Corn, field, forage	3.0	6			
Corn, field, grain	0.1	0.1	0.1		0.01 (*)
Corn, field, stover	3.0	20			0.6 maize fodder dry
Corn, pop, grain	0.1	0.1			
Corn, pop, stover	3.0	3			1
Corn, sweet, forage	0.50	0.5			
Corn, sweet, kernel + cob with husks removed	0.04	0.04	0.04		0.02 sweet corn (kernels)
Corn, sweet, stover	0.50	0.5			
Cotton, gin byproducts	70	70			
Cotton, undelinted seed	3.0	3			0.04
Grain, aspirated fractions	1000	1000			
Grass, forage, fodder & hay, group 17, forage	125.0	125			
Grass, forage, fodder & hay, group 17, hay	200.0	200			30 hay or fodder (dry) of grasses
Millet, proso, forage	90.0	90			
Millet, proso, grain	2.0	2	7		
Millet, proso, hay	40.0	40	7		
Millet, proso, straw	30.0	30			
Oat, forage	90.0	90			

Oat, grain	2.0	2			
Oat, hay	40.0	40			
Oat, straw	30.0	30			
Rye, forage	90.0	90			
Rye, grain	2.0	2			
Rye, straw	30.0	30			
Sorghum, grain, forage	3.0	3			
Sorghum, grain, grain	4.0	4			4
Sorghum, grain, stover	10.0	10			8 sorghum straw and fodder, dry
Sugarcane, cane	0.3	1			1
Sugarcane, molasses	5.0	5			
Soybean, forage	60	60			
Soybean, hay	100	100			
Soybean, hulls	30.0	30			
Soybean, seed	10.0	10	10		10
Teff, forage	90.0	90			
Teff, grain	6.0	6			
Teff, hay	40.0	40			
Teff, straw	30.0	30			
Wheat, forage	90.0	90			
Wheat, grain	2.0	2			2
Wheat, hay	40.0	40			
Wheat, straw	30.0	30			50 wheat straw and fodder, dry
<b>Summary of US and International Tolerances and Maximum Residue Limits.</b>					
<i>Residue Definition:</i>					
US	Canada		Mexico	Codex	
40 CFR 180.227: (2) Compliance with the tolerance levels is to be determined by measuring only the residues of dicamba (3,6-dichloro-2-methoxybenzoic acid), and its metabolite 3,6-dichloro-2-hydroxybenzoic acid, calculated as the stoichiometric equivalent of dicamba.	Food and crops, same as above.			Sum of dicamba and DCSA expressed as dicamba. The residue is not fat-soluble.	
Commodity <sup>1</sup>	<i>Tolerance (ppm)/Maximum Residue Limit (mg/kg)</i>				
	US Established	HED-Recommended	Canada	Mexico <sup>1</sup>	Codex
Cattle, fat	0.3	0.3			0.07 mammalian fats except milk fats
Cattle, kidney	25.0	25			0.7 edible offal mammalian

Cattle, meat	0.25	0.25			0.03 meat from mammals other than marine mammals)
Cattle, meat byproducts, except kidney	3.0	3			0.7 edible offal mammalian
Goat, fat	0.3	0.3			0.07 mammalian fats except milk fats
Goat, kidney	25.0	25			0.7 edible offal mammalian
Goat, meat	0.25	0.25			0.03 meat from mammals other than marine mammals)
Goat, meat byproducts, except kidney	3.0	3			0.7 edible offal mammalian
Hog, fat	0.3	0.3			0.07 mammalian fats except milk fats
Hog, kidney	25.0	25			0.7 edible offal mammalian
Hog, meat	0.25	0.25			0.03 meat from mammals other than marine mammals)
Hog, meat byproducts, except kidney	3.0	3			0.7 edible offal mammalian
Horse, fat	0.3	0.3			0.07 mammalian fats except milk fats
Horse, kidney	25.0	25			0.7 edible offal mammalian
Horse, meat	0.25	0.25			0.03 meat from mammals other than marine mammals)
Horse, meat byproducts, except kidney	3.0	3			0.7 edible offal mammalian
Milk	0.2	0.2			0.2
Sheep, fat	0.3	0.3			0.07 mammalian fats except milk fats
Sheep, kidney	25.0	25			0.7 edible offal mammalian
Sheep, meat	0.25	0.25			0.03 meat from mammals other than marine mammals)
Sheep, meat byproducts, except kidney	3.0	3			0.7 edible offal mammalian
Completed using Global MRL. 03-JAN-2025					