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

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

ELECTRONIC MAIL

October 19, 2022

John Reilly
UPL NA Inc.
630 Freedom Business Center, Suite 402
King of Prussia, PA 19406

Fred Trudwig, Jr.
Aceto Life Sciences, LLC
4 Tri Harbor Court
Port Washington NY 11050

SUBJECT: Dodine Waiver Request for Data Requirement 870.3465 in GDCI-044301-1686

Dear Mr. Reilly and Mr. Trudwig,

The Agency has completed its review of the waiver request submitted by UPL NA Inc. (previously Arysta LifeScience) dated May 14, 2019, for data requirement 870.3465 (90-day inhalation toxicity study) in response to GDCI-044301-1686. See the enclosed memo for the Agency's review of the waiver request. The Agency concluded that a waiver for 870.3465 is supported if all end-use product labels are amended with the addition of PF10 respirators for several occupational handler scenarios. Therefore, the Agency is requiring adding a respirator statement to mitigate potential inhalation exposure risks to occupational handlers for pesticides covered by the Worker Protection Standard (WPS),[1] and proposes adding any associated fit test, training, and medical evaluation requirements[2] for the following scenarios:

- Mixing and loading dry flowable or water dispersible granular products with dodine for aerial application to orchard[3] and high-acreage field crops[4]
- Mixing and loading dry flowable or water dispersible granular products with dodine for groundboom application to high-acreage field crops
- Mixing, loading, and applying dry flowable/water dispersible granular or liquid products with dodine for mechanically pressurized handgun applications to orchard crops

Table 1 lists the dodine end use products that need to be amended with the appropriate PF10 respirators for a waiver to be granted for data requirement 870.3465. Table 2 specifies the labeling changes for the dodine end use products.

[1] 40 C.F.R. pt. 170.
[2] Pursuant to 40 C.F.R. pt. 170, EPA requires fit testing (29 C.F.R. § 1910.134), training (29 C.F.R. § 1910.134(k)(1)(i)-(vi)), and medical evaluations (29 C.F.R. § 1910.134)—conducted in accordance with the cited OSHA regulations—for all handlers that are required to wear respirators and whose work falls within the scope of the WPS. Label Review Manual at Ch. 10, App. A, https://www.epa.gov/pesticide-registration/label-review-manual.
[3] Almonds, apple, apricot, banana, cherries (sweet & sour), nectarines, peaches, pecans, pears, plums, and walnuts.
[4] Peanut.

Table 1. Current Dodine End Use Products Subject to Registration Review Pre-Decision Mitigation[1]	
EPA Registration Number	**Product Name**
2749-625	AG33037 B 3.4FL Fungicide
70506-611 (previously 55260-06)	Syllit Flow Fungicide
70506-614 (previously 55260-11)	Syllit 65WG
[1] These are the active dodine registrations for end-use products as of October 12, 2022. New registrations would need to conform with the requirement for the PF10 respirator for the waiver to be continuously applicable.	

Table 2. Required Labeling Changes for Dodine End Use Products		
Description	**Required Label Language for Dodine End Use Products**	**Placement on Label**
Requirement for the Use of a PF10 Respirator Applies to products formulated as **dry flowable** or **water dispersible granule**. Applies to products with the following orchard crops - **Almonds, Apple, Apricot, Banana, Cherries (sweet & sour), Nectarines, Peaches, Pecans, Pears, Plums, and Walnuts**	**Aerial Applications** "Mixers and loaders of products formulated as dry flowable or water dispersible granules for aerial applications to [*CHOOSE APPLICABLE CROP(S): Almonds, Apple, Apricot, Banana, Cherries (sweet & sour), Nectarines, Peaches, Pecans, Pears, Plums, Walnuts*] must wear a [*CHOOSE THE APPROPRIATE RESPIRATOR LANGUAGE FOR YOUR PRODUCT; SEE "PF10 Respirator Language" ROW*]."	In the Personal Protective Equipment (PPE) within the Precautionary Statements
Requirement for the Use of a PF10 Respirator Applies to products formulated as **dry flowable** or **water dispersible granule**.	**Aerial Applications** "Mixers and loaders of products formulated as dry flowable or water dispersible granules for aerial applications to peanuts must wear a [*CHOOSE THE APPROPRIATE RESPIRATOR LANGUAGE FOR YOUR PRODUCT; SEE "PF10 Respirator Language" ROW*]." **Groundboom Applications** "Mixers and loaders of products formulated as dry flowable or water dispersible granules for groundboom applications to peanuts must wear a [*CHOOSE THE APPROPRIATE RESPIRATOR LANGUAGE FOR YOUR PRODUCT; SEE "PF10 Respirator Language" ROW*]."	

Applies to products with use on **Peanuts**		
Requirement for the Use of a PF10 Respirator Applies to products formulated as **dry flowable, water dispersible granule, or liquid**. Applies to products with the following orchard crops - **Almonds, Apple, Apricot, Banana, Cherries (sweet & sour), Nectarines, Peaches, Pecans, Pears, Plums, and Walnuts**	**Mechanically Pressurized Handgun Applications** "Mixers, loaders, and applicators of products formulated as dry flowable, water dispersible granules, or liquid for applications using a mechanically pressurized handgun to [*CHOOSE APPLICABLE CROP(S): Almonds, Apple, Apricot, Banana, Cherries (sweet & sour), Nectarines, Peaches, Pecans, Pears, Plums, Walnuts*] must wear a [*CHOOSE THE APPROPRIATE RESPIRATOR LANGUAGE FOR YOUR PRODUCT; SEE "PF10 Respirator Language" ROW*]."	In the Personal Protective Equipment (PPE) within the Precautionary Statements
PF10 Respirator Language	• If your end-use product requires **protection from particulates only** (low volatility), use the following language: "Wear a minimum of a NIOSH-approved particulate filtering facepiece respirator with any N*, R or P filter; OR a NIOSH-approved elastomeric particulate respirator with any N*, R or P filter; OR a NIOSH-approved powered air purifying respirator with HE filters." *Drop the "N" option if there is oil in the product's formulation and/or the product is labeled for mixing with oil-containing products. • For respiratory **protection from organic vapor and particulates (or aerosols)**, use the following language: "Wear a minimum of a NIOSH-approved elastomeric half mask respirator with organic vapor (OV) cartridges and combination N*, R, or P filters; OR a NIOSH-approved gas mask with OV canisters; OR a NIOSH-approved powered air purifying respirator with OV cartridges and combination HE filters." *Drop the "N" option if there is oil in the product's formulation and/or the product is labeled for mixing with oil-containing products. • For products requiring **protection for organic vapor only**, use the following language:	In the Personal Protective Equipment (PPE) within the Precautionary Statements

	"Wear a minimum of a NIOSH-approved elastomeric half mask respirator with organic vapor (OV) cartridges; OR a NIOSH-approved full face respirator with OV cartridges; OR a gas mask with OV canisters; OR a powered air purifying respirator with OV cartridges." *Drop the "N" option if there is oil in the product's formulation and/or the product is labeled for mixing with oil-containing products.	

The data requirement 870.3465 (90-day inhalation toxicity study) cannot be waived until all end use product labels are received, reviewed, and approved by the agency. In the absence of revised labeling, the dodine data requirement for a 90-day inhalation toxicity study (870.3465) remains a data gap.

Each registrant needs to submit amended product labels within 30 days of receipt of this letter. Registrants must submit a cover letter, a completed Application for Registration (EPA form 8570-1), and electronic copies of the amended product labels by November 19, 2022. Two copies for each label must be submitted, a clean copy and an annotated copy with changes. In order for the application to be processed, registrants must include the following statement on the Application for Registration (EPA form 8570-1):

"I certify that this amendment satisfies the requirements of the EPA regulations at 40 C.F.R. Section 152.44, and no other changes have been made to the labeling of this product. I understand that it is a violation of 18 U.S.C. Section 1001 to willfully make any false statement to EPA. I further understand that if this amendment is found not to satisfy the requirements of 40 C.F.R. Section 152.44, this product may be in violation of FIFRA and may be subject to regulatory and/or enforcement action and penalties under FIFRA."

Within the required timeframe, registrants must submit the required documents to the Registration Review section of EPA's Pesticide Submission Portal (PSP), which can be accessed through EPA's Central Data Exchange (CDX) at https://cdx.epa.gov/.

If you have any questions, please feel free to contact Susan Bartow of my staff at 202-566-2280 or by e-mail at bartow.susan@epa.gov.

Sincerely,

Linda Arrington, Branch Chief
Risk Management and Implementation Branch 4
Pesticide Re-Evaluation Division
Office of Pesticide Programs

Enclosure: *Dodine: Summary of Hazard and Science Policy Council (HASPOC) Meeting on April 14th, 2022: Recommendations on the Need for Subchronic Inhalation Toxicity Study.* Dated April 15, 2022.

Cc: Nathan Mellor, PM 21, Registration Division (RD)

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION
WASHINGTON, D.C. 20460

ELECTRONIC MAIL

May 21, 2024

Lael Jimenez
UPL NA Inc.
PO Box 12219
Research Triangle Park, NC 27709-2219

Fred Trudwig, Jr.
Aceto Life Sciences, LLC
4 Tri Harbor Court
Port Washington, NY 11050

SUBJECT: Required Labeling Changes for Dodine End Use Products (Corrected)

Dear Lael Jimenez and Fred Trudwig,

The Agency has discovered that several orchard crops were inadvertently left off from Table 2 (Required Labeling Changes for Dodine End Use Products) in our letter dated October 19, 2022. This letter is intended to correct Table 2 for the dodine end use products that are subject to Registration Review pre-decision mitigation.

As previously stated, in the October 19, 2022, letter, the Agency concluded that a waiver for 870.3465 is supported if all end-use product labels are amended with the addition of PF10 respirators for several occupational handler scenarios. Therefore, the Agency is requiring adding a respirator statement to mitigate potential inhalation exposure risks to occupational handlers for pesticides covered by the Worker Protection Standard (WPS),[1] and proposes adding any associated fit test, training, and medical evaluation requirements[2] for the following scenarios:

- Mixing and loading dry flowable/water dispersible granular products for aerial application to orchard/vineyard crops[3]
- Mixing, loading, and applying dry flowable/water dispersible granular or liquid products for mechanically pressurized handgun applications to orchard/vineyard crops

[1] 40 C.F.R. pt. 170.
[2] Pursuant to 40 C.F.R. pt. 170, EPA requires fit testing (29 C.F.R. § 1910.134), training (29 C.F.R. § 1910.134(k)(1)(i)-(vi)), and medical evaluations (29 C.F.R. § 1910.134)—conducted in accordance with the cited OSHA regulations—for all handlers that are required to wear respirators and whose work falls within the scope of the WPS. Label Review Manual at Ch. 10, App. A, https://www.epa.gov/pesticide-registration/label-review-manual.
[3] Orchard/Vineyard crops: includes Bananas, Olives, Pome Fruit Group 11-10, Stone Fruit Group 12-12, and Tree Nut Group 14-12

Table 1 lists the dodine end use products that need to be amended with the appropriate PF10 respirators for a waiver to be granted for data requirement 870.3465. Table 2 specifies the labeling changes for the dodine end use products.

Table 1. Current Dodine End Use Products Subject to Registration Review Pre-Decision Mitigation[1]	
EPA Registration Number	**Product Name**
2749-624[2]	AG33037 A 3.4FL Fungicide
2749-625	AG33037 B 3.4FL Fungicide
2749-626	AG33037 C 3.4FL Fungicide
70506-611 (previously 55260-06)	Syllit Flow Fungicide
70506-614 (previously 55260-11)	Syllit 65WG

[1] These are the active dodine registrations for end-use products as of May 07, 2024. New registrations would need to conform with the requirement for the PF10 respirator for the waiver to be continuously applicable.

[2] The stamped approved product label already includes the pre-decision mitigation and does not need to be resubmitted to the Agency.

Table 2. Required Labeling Changes for Dodine End Use Products		
Description	**Required Label Language for Dodine End Use Products**	**Placement on Label**
Requirement for the Use of a PF10 Respirator Applies to products formulated as **dry flowable/ water dispersible granule**. Applies to products with the following orchard/vineyard crops – **Bananas, Olives, Pome Fruits- Crop Croup 11-10, Stone Fruits- Crop Group 12-12, and Tree Nuts- Crop Group 14-12.**	**Aerial Applications** "Mixers and loaders of products formulated as dry flowable/water dispersible granules for aerial applications to [*CHOOSE APPLICABLE CROP(S): Bananas, Olives, Pome Fruits- Crop Croup 11-10, Stone Fruits- Crop Group 12-12, and Tree Nuts- Crop Group 14-12]* [*CHOOSE THE APPROPRIATE RESPIRATOR LANGUAGE FOR YOUR PRODUCT; SEE "PF10 Respirator Language" ROW*]."	In the Personal Protective Equipment (PPE) within the Precautionary Statements
Requirement for the Use of a PF10 Respirator Applies to products formulated as **dry flowable/ water dispersible granule, or liquid**.	**Mechanically Pressurized Handgun Applications** "Mixers, loaders, and applicators of products formulated as dry flowable/water dispersible granules or liquid for applications using a mechanically pressurized handgun to [*CHOOSE APPLICABLE CROP(S): Bananas, Olives, Pome Fruits- Crop Croup 11-10, Stone Fruits- Crop Group 12-12, and Tree Nuts- Crop Group 14-12*] must wear a [*CHOOSE THE APPROPRIATE RESPIRATOR LANGUAGE FOR YOUR PRODUCT; SEE "PF10 Respirator Language" ROW*]."	In the Personal Protective Equipment (PPE) within the Precautionary Statements

Applies to products with the following orchard/vineyard crops – **Bananas, Olives, Pome Fruits- Crop Croup 11-10, Stone Fruits- Crop Group 12-12, and Tree Nuts- Crop Group 14-12.**		
PF10 Respirator Language	• If your end-use product requires **protection from particulates only** (low volatility), use the following language: "Wear a minimum of a NIOSH-approved particulate filtering facepiece respirator with any N*, R or P filter; OR a NIOSH-approved elastomeric particulate respirator with any N*, R or P filter; OR a NIOSH-approved powered air purifying respirator with HE filters." *Drop the "N" option if there is oil in the product's formulation and/or the product is labeled for mixing with oil-containing products. • For respiratory **protection from organic vapor and particulates (or aerosols)**, use the following language: "Wear a minimum of a NIOSH-approved elastomeric half mask respirator with organic vapor (OV) cartridges and combination N*, R, or P filters; OR a NIOSH-approved gas mask with OV canisters; OR a NIOSH-approved powered air purifying respirator with OV cartridges and combination HE filters." *Drop the "N" option if there is oil in the product's formulation and/or the product is labeled for mixing with oil-containing products. • For products requiring **protection for organic vapor only**, use the following language: "Wear a minimum of a NIOSH-approved elastomeric half mask respirator with organic vapor (OV) cartridges; OR a NIOSH-approved full face respirator with OV cartridges; OR a gas mask with OV canisters; OR a powered air purifying respirator with OV cartridges." *Drop the "N" option if there is oil in the product's formulation and/or the product is labeled for mixing with oil-containing products.	In the Personal Protective Equipment (PPE) within the Precautionary Statements

The data requirement 870.3465 (90-day inhalation toxicity study) cannot be waived until all end use product labels are received, reviewed, and approved by the agency. In the absence of revised labeling, the dodine data requirement for a 90-day inhalation toxicity study (870.3465) remains a data gap.

Registrants who have already submitted their labels to the Agency through CDX need to submit amended product labels within 30 days of receipt of this letter via email to carr.caleb@epa.gov and reference their original CDX submission number. If the product labels have not already been submitted through CDX, each

registrant needs to submit amended product labels within 30 days of receipt of this letter to the Registration Review section of EPA's Pesticide Submission Portal (PSP), which can be accessed through EPA's Central Data Exchange (CDX) at https://cdx.epa.gov/.

Registrants must submit a cover letter, a completed Application for Registration (EPA form 8570-1), and electronic copies of the amended product labels by **June 21, 2024**. Two copies for each label must be submitted, a clean copy and an annotated copy with changes. In order for the application to be processed, registrants must include the following statement on the Application for Registration (EPA form 8570-1):

"I certify that this amendment satisfies the requirements of the EPA regulations at 40 C.F.R. Section 152.44, and no other changes have been made to the labeling of this product. I understand that it is a violation of 18 U.S.C. Section 1001 to willfully make any false statement to EPA. I further understand that if this amendment is found not to satisfy the requirements of 40 C.F.R. Section 152.44, this product may be in violation of FIFRA and may be subject to regulatory and/or enforcement action and penalties under FIFRA."

If you have any questions, please feel free to contact Caleb Carr of my staff at 202-566-0636 or by e-mail at carr.caleb@epa.gov.

Sincerely,

Linda Arrington, Branch Chief
Risk Management and Implementation Branch 4
Pesticide Re-Evaluation Division
Office of Pesticide Programs

Enclosure: *Dodine: Summary of Hazard and Science Policy Council (HASPOC) Meeting on April 14th, 2022: Recommendations on the Need for Subchronic Inhalation Toxicity Study.* Dated April 15, 2022.

Cc: Stephanie Suarez, PM 21, Registration Division (RD)

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

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

DATE: 4/15/2022

SUBJECT: **Dodine**: Summary of Hazard and Science Policy Council (HASPOC) Meeting on April 14th, 2022: Recommendations on the Need for Subchronic Inhalation Toxicity Study

PC Code: 044301
Decision No.: N/A
Petition No.: N/A
Risk Assessment Type: N/A
TXR No.: 0058258
MRID No.: N/A

DP Barcode: N/A
Registration No.: N/A
Regulatory Action: N/A
Case No.: N/A
CAS No.: 2439-10-3
40 CFR: N/A

FROM: Adrian Britt, Executive Secretary Adrian Britt
HASPOC
Health Effects Division (7509T)

THROUGH: Joshua Godshall, Co-Chair
HASPOC
Health Effects Division (7509T)

TO: Sarah Dobreniecki, Biologist
Michael Metzger, Branch Chief
Risk Assessment Branch V/VII (RABV/VII)
Health Effects Division (7509T)

MEETING ATTENDEES:

HASPOC Members: Joshua Godshall*, Sarah Dobreniecki, Krystle Yozzo, Michael Metzger, Cassi Walls, Kelly Lowe, Elizabeth Mendez, Jacqueline Meadows, Brian VanDeusen, Angela Gonzales, Anwar Dunbar, Hannah Pope-Varsalona, Moana Appleyard, Monique Perron, Jeffery Dawson

* HASPOC Chairs

Presenter: Sarah Dobreniecki

Other Attendees: Adrian Britt**, Cynthia Browning, Melantha Jackson, Destiny Carter, Alexandra Turley, Jessie Wozniak, David Nadrchal, Susan Bartow, Yonqui Li, Jorrell Fredericks, Megan Stallard, Julie Javier, Melanie Biscoe, Harold Cooper, John Patrick Rodgers, Nicholas Thomas, Heriberto Deleon, Linda Arrington

** HASPOC Secretary

I. PURPOSE OF MEETING

The recommendation on the requirement for a subchronic inhalation toxicity study for dodine was previously discussed by the Hazard and Science Policy Council (HASPOC) in 2013 and 2016. Both meetings recommended that a subchronic inhalation toxicity study should not be waived based on the irritating properties of dodine and occupational exposure estimates indicating inhalation risks are of concern using the HASPOC target of 10X higher than the level of concern (LOC) (margins of exposure (MOEs) <1,000) (K. Rury, TXR 0056498, 02/08/2013 and U. Habiba, TXR 0057429, 07/27/2016). A generic data call-in (GDCI) was issued in 2019, and in response to the GDCI, the dodine registrant submitted a waiver request (MRID 50851301) which suggests that the inhalation toxicity study is not needed because the scenarios that are of concern can be mitigated by requiring the use of respiratory protection. Due to the differences in the use and exposure patterns this waiver is only considering the need for a subchronic inhalation toxicity study for dodine (conventional pesticide) and does not address the need for a DGH (antimicrobial pesticide) inhalation route-specific study. Dodine is registered for occupational use on a variety of agriculture crops while there are residential exposures to DGH from its use as a preservative in paint. Therefore, the need for an inhalation route specific study for the occupational use and exposure to dodine is being addressed at this time. The HASPOC met on April 14th, 2022, to determine if the subchronic inhalation toxicity study is necessary to support the registrations for dodine.

II. SUMMARY OF USE PROFILE, EXPOSURE, AND HAZARD CONSIDERATIONS

a. Use and Exposure Profile

Dodine (N-dodecylguanidine acetate) is a pesticide belonging to the guanidine fungicide class that is used as a foliar protectant against disease on fruits and nuts. It is specifically useful for the control of scab on apples and pears, leafspot on cherries, foliar diseases of bacterial leafspot on peaches, and leaf blight of sycamores and black walnuts. The pesticidal mode of action (MOA) for dodine is through the disruption of cell membranes. Dodine is formulated as a wettable powder (WP) containing 65% active ingredient (ai), a water dispersible granule (WDG) containing 65% ai, and a flowable concentrate (FC) containing 39.6% ai. Applications are made as a foliar spray via ground or aerial equipment. Treatments can be made at a variety of crop development stages, which include dormant, delayed dormant, pre-bloom, early bloom, bloom, petal fall, mature fruit growth, as well as post-harvest to trees. Dodine can be applied at maximum rates which range from 1.3 to 2.6 lb ai/A/application with a pre-harvest interval (PHI) designated between 5 to 15 days. Permanent tolerances are established under 40 CFR 180.172(a) on a number of fruit and nut crop commodities.

Exposure to dodine can occur through food and drinking water from application of the pesticide to growing crops. There are no proposed or registered residential and/or non-agricultural uses for dodine, so there are not likely to be exposures in non-occupational settings other than dermal (adults and children) and incidental oral (children only) exposures from spray drift. 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.

b. Toxicity Profile

The toxicity data for dodine, as well as the dodecylguanidine hydrochloride (DGH) antimicrobial pesticide, are considered together since dodine and DGH are both salts of the same chemical (see Figure A.1. for chemical structures). The Agency has previously determined that the two chemicals are toxicologically equivalent, based on the following: the cationic species from both dodine and DGH are identical; the no observed adverse effect level (NOAEL)/lowest observed adverse effect level (LOAEL) values for both dodine and DGH are similar when comparing similar studies; the adverse effects of both chemicals are the same, and the acute toxicity profiles (Toxicity Categories) for dodine and DGH are similar.

Dodine
A definitive target organ was not identified for dodine in the available toxicology data. The most common effects observed in subchronic and chronic studies in rats and dogs were decreases in food consumption, body weight, and/or body weight gain. When allometric scaling (3/4 power of body weight ($BW_{3/4}$)) is used to adjust to a human equivalent dosage, the dog was found to be the most sensitive species for this endpoint. There was no evidence of progression of toxicity with time and no indication that the observed toxic effects were a consequence of unpalatability of the food. No evidence of neurotoxicity was noted across the database.

In a subchronic dermal toxicity study in the rat, no systemic toxicity was noted; histopathological alterations were limited to dermal lesions. Decreased maternal body weight gain and food consumption were the only effects observed in a rat developmental toxicity study. In a rabbit developmental toxicity study, does demonstrated decreased food consumption. No treatment-related effects were observed in fetuses in the developmental studies in rats or rabbits. There was no evidence of increased susceptibility to fetuses in these studies.

Dodine did not adversely affect reproductive parameters in rats over two generations. However, at the highest dose of 53 mg/kg/day, decreases in parental body weight, body weight gain, and food consumption were noted in both generations of rats. Furthermore, the offspring of both generations demonstrated decreased body weight after post-natal day 4 which continued through pre-mating. There was no evidence of increased susceptibility to offspring in this study. Offspring effects (decreased pup weight) were observed in the presence of comparable maternal effects (decreased body weight).

Dodine is a severe eye irritant (Toxicity Category I), causes severe dermal irritation (Toxicity Category I), and is not a skin sensitizer. Dodine is Toxicity Category II *via* the inhalation route based on an LC_{50} = 0.45 mg/L.

DGH

Similar to study results observed with dodine, the toxicology data on DGH did not identify a definitive target organ but show similar effects after administration (decreased body weight and/or weight gain, decreased food consumption, and salivation). In the developmental toxicity study in rats with DGH, excessive salivation and moist rales were observed in maternal animals. This could be due to the irritancy of the test chemical. There was no developmental toxicity observed at any dose level in this study.

In the 90-day oral toxicity study in dogs, decreased body weights and clinical signs (thin/emaciated, excessive salivation, emesis) were observed in dogs at 35 mg/kg/day. In the 21-day dermal toxicity study, there were no systemic effects observed. Dermal irritation, including erythema, desquamation, fissuring, and edema, was observed at all doses tested.

DGH is a severe eye irritant (Toxicity Category I), causes severe dermal irritation (Toxicity Category I), and is not a skin sensitizer. DGH is Toxicity Category II *via* the inhalation route based on an LC_{50} = 0.2 mg/L.

III. STUDY WAIVER REQUESTS

a. Subchronic Inhalation Study

When considering the scientific information available to waive (or not waive) an inhalation study, in the past, OPP has used a set of criteria involving 1) the potential for irritation and corrosivity, 2) the potential for volatilization, 3) aerosol particle size, 4) the acute inhalation toxicity category, and 5) an extrapolated MOE (e.g., MOEs 10 times higher than the target). In 2009, OPP developed an issue paper on risk assessment approaches for semi-volatile pesticides[1]. As part of that issue paper, an analysis was conducted on a comparison of oral and inhalation experimental toxicology studies. In general, this analysis showed that the degree to which oral points of departure (PODs) were protective of potential inhalation toxicity varied. In many cases the oral POD was protective, but in some, the inhalation PODs were significantly more sensitive. Currently, OPP uses a weight of the evidence (WOE) approach discussed below which builds upon experience using the previously-used criteria listed above and informed by the 2009 SAP[1]. As approaches for route-to-route extrapolation evolve and improve in the future, OPP may, if appropriate, bring additional considerations into the WOE analysis. Thus, the considerations listed below are not exhaustive but rather provide an outline of what may be considered in the WOE analysis.

Inhalation exposure can be to vapors, droplets, and/or particles/dusts. The form of this exposure is determined by a number of factors including physical-chemical properties, use pattern, and exposure scenario. This interim WOE approach considers:

1. **Physical-chemical properties:** Vapor pressure and Henry's law constant are key considerations with respect to volatilization after sprays have settled. The vapor pressure for dodine is 1.5 x 10^{-7} mm Hg at 25°C and the Henry's law constant is 9.01 x 10^{-11} atm-

[1] Scientific Issues Associated with Field Volatilization of Conventional Pesticides (https://wwwregulations.gov/document?D=EPA-HQ-OPP-2009-0687-0006)

m^3/mole, so it is not expected to volatilize. However, vapor pressure and/or Henry's law constant does not preclude exposure to droplets or particles/dusts.

2. **Use pattern & exposure scenarios:** Any application scenario that leads to inhalation exposure to droplets needs to be considered in the WOE analysis for an inhalation toxicology study waiver request. It is, however, acknowledged that air blast and aerial applications are more likely to lead to higher occupational handler inhalation exposure, particularly to droplets; and may also contribute to spray drift. In the case of the dodine, occupational applicators may be exposed while handling the pesticide prior to application as well as during application, with airblast and aerial application exposure scenarios plausible. There's also the potential for dermal (adults and children) and incidental oral (children only) exposures resulting from spray drift following applications to various crops using aerial and airblast equipment.

3. **Margins of Exposure (MOEs):** The size of the MOEs for inhalation scenarios calculated using an oral toxicity study should be considered in the WOE analysis for an inhalation toxicology study waiver request. In the past, OPP has used MOEs of approximately 10 times higher than LOC as a benchmark for waiver requests. The 2009 analysis suggests this is ample for most pesticides, but not all. As a result, MOEs 10X over the LOC will be considered in combination with other factors discussed here.

   In the case of dodine, there are no conventional uses of dodine registered for use in residential settings. Occupational handler inhalation MOEs calculated using an oral POD of 8.75 mg/kg/day (LOAEL= 35 mg/kg/day) from a subchronic toxicity study in the dog with DGH are based on decreased body weight and range from 1,000 to 310,000, assuming the use of a PF10 respirator for certain scenarios (which are not currently required on the labels) [LOC= 100; 10X for intraspecies variation and 10X for interspecies extrapolation]. The following scenarios represent inhalation risk estimates with no respirator, and would require a PF10 respirator in order for the MOEs to be greater than 10X the LOC (i.e., MOE $\geq$ 1,000):

   a) Mixing/loading dry flowable/water dispersible granular dodine for aerial application to orchard and high-acreage field crops (MOEs = 170 and 100, respectively)
   b) Mixing/loading dry flowable/water dispersible granular dodine for groundboom application to high-acreage field crops (MOE = 600)
   c) Mixing/loading/applying dry flowable/water dispersible granular or liquid dodine for mechanically pressurized handgun applications to orchard crops (MOE = 900)

   See Appendix A (Table A.3) for a summary of the inhalation risk estimates.

4. **Inhalation toxicity:** Dodine is a severe eye irritant (Toxicity Category I), causes severe dermal irritation (Toxicity Category I), and is not a skin sensitizer. Dodine is Toxicity Category II *via* the inhalation route based on an LC_{50} = 0.45 mg/L.

   In an acute inhalation toxicity study with dodine technical (MRID 46621302), rats were exposed nose-only to 0, 0.25, 0.34 or 0.51 mg/L. A number of clinical signs were

observed at all doses tested including, but not limited to, exaggerated breathing, noisy respiration, and gasping. Gross necropsy revealed treatment related effects at the mid- and high-dosed groups including, but not limited to, congestion of the lungs, small dark focus on lung, distended stomach, and distended intestines. Mortality was also noted at the two highest concentrations (see Table A.4 for complete study results).

An acute inhalation toxicity study with DGH (MRID 40756803) dosed five male and female rats once for four hours at 0.01, 0.035, 0.13, 0.15, 0.3, or 1.6 mg/L (correction made for the percent active ingredient (35%)). All animals exposed to the top three dose levels died and mortality was observed in 20-30% of the rats exposed to the three lowest dose levels. Death occurred on the day of exposure through post exposure day 4. Macroscopic lesions observed in the dead animals included discoloration of the lungs, liver, kidneys, and spleen; clear or foamy white fluid in the lungs, thoracic cavity, and trachea; perioral, perinasal, and periocular encrustation; and congested blood vessels of the intestines. Ocular and respiratory irritation were observed in rats of all exposure groups on the day of exposure and for the first week postexposure. Additional clinical signs observed in the top three dose levels included ataxia, prostration, slow surface-righting reflex, absence of toe and tail pinch reflexes, decreased respiratory rate, hypoactivity, and hypothermia.

5. **Evidence of inhalation toxicity from related chemicals:** For considering a waiver request for an inhalation toxicity study, the Agency will evaluate the toxicity database of the chemical under review as well as other pesticides which share the same MOA and/or have structural similarity. These pesticides can provide important information regarding potential inhalation toxicity. Specifically, if other similar pesticides show inhalation toxicity studies to be more sensitive than the oral POD, an inhalation toxicity study may be required, depending on the exposure profile. Other toxicological considerations may include, but are not limited to, oral absorption, dose spread, temporal effects and evidence of life stage susceptibility. Irritating or corrosive compounds will be considered in the context of exposure estimates and the likelihood that irritation effects may be more sensitive than a systemic effect.

   A search was conducted using ChemIDplus[2] for pesticides with >60% structural similarity to dodine. This search did not return any pesticides that fit the search criteria.

   A search was also conducted using the Compendium of Pesticide Common Names[3]. Dodine was labeled as an aliphatic nitrogen fungicide and there were six other chemicals within this class. Four chemicals are not registered with the Agency (dodicin, guazatine, iminoctadine, and seboctylamine), one chemical is canceled with no active registrations (butylamine), and one chemical is currently registered (cymoxanil). For cymoxanil, HASPOC recommended that a developmental inhalation toxicity study be required because of increased qualitative and quantitative pre- and post-natal susceptibility observed in oral studies and MOEs for selected occupational use patterns that were below 1,000 using an oral endpoint (D. Dotson, D441918, 06/04/2018). However, if the

[2] https://chem nlm nih.gov/chemidplus/
[3] https://pesticidecompendium.bcpc.org/

registrant agrees to additional mitigation on registered labels (i.e., use of PF10 respirators as appropriate), the Agency will consider waiving the requirement for an inhalation study for cymoxanil.

HASPOC Recommendation: Based on the inhalation exposure/risk profile for dodine, the addition of a PF10 respirator to the label directions for 1) mixing/loading dry flowable/water dispersible granular dodine for aerial application to orchard and high acreage field crops, 2) mixing/loading dry flowable/water dispersible granular dodine for aerial application to high acreage field crops, and 3) mixing/loading/applying dry flowable/water dispersible granular or liquid dodine for mechanically pressurized handgun applications to orchard crops would mitigate concerns for the MOEs that fall below 10X the LOC. In that case, an inhalation study would not be needed for the occupational uses of dodine, and HED could recommend waiving the need for the subchronic inhalation study, pending finalization of modified labels to include the additional PPE. However, a 10X database uncertainty factor will be applied for assessing risk for inhalation scenarios until modified labels are finalized or an acceptable subchronic inhalation study is submitted.

IV. HASPOC CONCLUSIONS

Given the registrant's waiver request addressed the use of PF10 respirators to mitigate the potential occupational risks identified for dodine, the Agency assumes the dodine registrant will amend the labels to include this requirement. The inclusion of a PF10 respirator requirement on the label, would obviate the need for the route-specific studies as MOEs for all exposure scenarios would be ≥ 1000. Hence, the HASPOC recommends the inhalation toxicity study be waived **once amended labels requiring PF10 respirators are submitted to and approved by the Agency.**

V. APPENDIX A

Table A.1. Summary of Toxicological Doses and Endpoints for Dodine for Use in Dietary and Non-Occupational Human Health Risk Assessments				
Exposure/ Scenario	**Point of Departure**	**Uncertainty/FQPA Safety Factors**	**RfD, PAD, Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Acute Dietary (General Population, including Infants and Children)	N/A	N/A	N/A	No appropriate endpoint identified resulting from a single exposure
Acute Dietary (Females 13-49 years of age)	N/A	N/A	N/A	No appropriate endpoint for females aged 13-49 identified resulting from a single exposure
Chronic Dietary (All Populations)	NOAEL = 2 mg/kg/day	UF_A=10X UF_H=10X FQPA SF = 1X	Chronic RfD = 0.02 mg/kg/day cPAD = 0.02 mg/kg/day	Chronic toxicity – dog (dodine) (MRID 44246101) LOAEL = 10 mg/kg/day based on marked body weight loss and food consumption in individual females
Incidental Oral Short-Term (1-30 days) Incidental Oral Intermediate-Term (1-6 months)	NOAEL = 8.75 mg/kg/day	UF_A=10X UF_H=10X FQPA = 1X	Residential LOC =100	Subchronic toxicity – dog (DGH) (MRID 41316903) LOAEL = 35 mg/kg/day based on decreased body weight
Dermal **systemic** Short-Term (1-30 days) Dermal **systemic** Intermediate-Term (1-6 months)	N/A	N/A	N/A	No endpoint for systemic toxicity from dermal exposure was identified in the database for Dodine or DGH
Cancer (oral, dermal, inhalation)	No Evidence of Carcinogenicity			

UF = uncertainty factor, UF_{DB} =10X for lack of an inhalation toxicity study, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level,), MOE = margin of exposure, LOC = level of concern, NA = Not Applicable

Table A.2. Summary of Toxicological Doses and Endpoints for Dodine for Use in Occupational Human Health Risk Assessments				
Exposure/ Scenario	**Point of Departure**	**Uncertainty Factors**	**Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Dermal Short-Term (1-30 days) Dermal Intermediate-Term (1-6 months)	N/A	N/A	N/A	No endpoint for systemic toxicity from dermal exposure was identified in the database for Dodine or DGH
Inhalation Short-Term (1-30 days) Inhalation Intermediate-term (1-6 months)	NOAEL = 8.75 mg/kg/day	UF_A=10X UF_H=10X UF_{DB}=10X	Occupational LOC = 1,000	Subchronic toxicity – dog (DGH) (MRID 41316903) LOAEL = 35 mg/kg/day based on decreased body weight
Cancer (oral, dermal, inhalation)	No Evidence of Carcinogenicity			

UF = uncertainty factor, UF_{DB}=10X for lack of an inhalation toxicity study, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level,), MOE = margin of exposure, LOC = level of concern, NA = Not Applicable

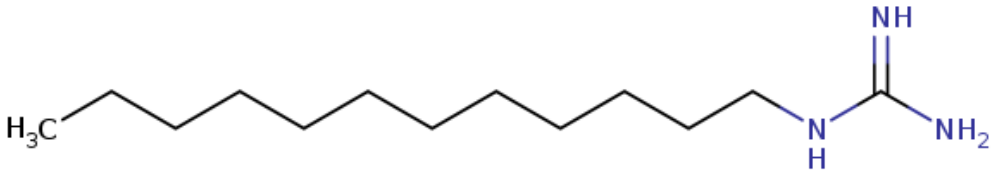
Table A.3. Short-/Intermediate-Term Occupational Exposure and Risk Estimates for Dodine.						
Exposure Scenario	**Crop or Target**	**Inhalation Unit Exposure (µg/lb ai)[1] Mitigation Level = no respirator unless indicated otherwise**	**Maximum Application Rate[2] (lb ai/A)**	**Area Treated or Amount Handled Daily[3]**	**Inhalation**	
					Dose (mg/kg/day)[4]	**MOE[5] (LOC = 100)**
Mixer/Loader						
Mixing/Loading Water Dispersible Granular/ Dry Flowable for Aerial Application	Orchard*	8.96	1.3	350 Acres	0.051	170
		0.896 Respirator (PF10)			0.0051	1,700
	Peanut	8.96	0.65	1200 Acres	0.0874	100
		0.896 Respirator (PF10)			0.00874	1,000
Mixing/Loading Water Dispersible Granular/ Dry Flowable for Groundboom Application	Peanut	8.96	0.65	200 Acres	0.0145	600
		1.792 Respirator (PF10)			0.005291	6,000
Mixing/Loading Dry Flowable for Airblast Application	Orchard*	0.219	1.3	40 Acres	0.00583	1,500
Mixing/Loading liquids for Aerial Application	Peanut		0.65	1,200 Acres	0.00214	4,100
	Orchard*		1.3	350 Acres	0.00125	7,000
Mixing/Loading liquids for Groundboom Application	Peanut		0.65	200 Acres	0.000356	25,000
Mixing/Loading Liquids for Airblast Application	Orchard*		1.3	40 Acres	0.000143	61,000
			0.65		0.0000711	120,000
Applicator						
Applying Sprays via Groundboom Equipment	Orchard*	0.34	1.3	80 Acres	0.000221	40,000
	Peanut		0.65	200 Acres	0.000553	16,000
Applying Sprays via Aerial Equipment	Orchard*	0.0049 EC	1.3	350 Acres	0.000028	310,000
			0.65	1,200 Acres	0.0000478	180,000
Applying Sprays via Airblast Equipment		4.71	1.3	40 Acers	0.00306	2,900
Flagger						
Flagger for aerial spray application	Orchard*	0.35	1.3	350 Acres	0.00199	4,400
			0.65		0.000995	8,800
Mixer/Loader/Applicator						
Water Dispersible Granular via Mechanically-pressurized Handgun & Liquids via Mechanically-pressurized Handgun	Orchard*	8.68	0.09 lb ai/Gal	1,000 Gal	0.00976	900
		1.74 Respirator (PF10)			0.00196	9,000

1) Based on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table"; Level of mitigation: Baseline, PPE (respirator only).
2) Based on registered labels.
3) Exposure Science Advisory Council Policy #9.2.
4) Inhalation Dose = Inhalation Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled (A or gal/day) ÷ BW (80 kg).
5) Inhalation MOE = Inhalation NOAEL (8.75 mg/kg/day) ÷ Inhalation Dose (mg/kg/day).

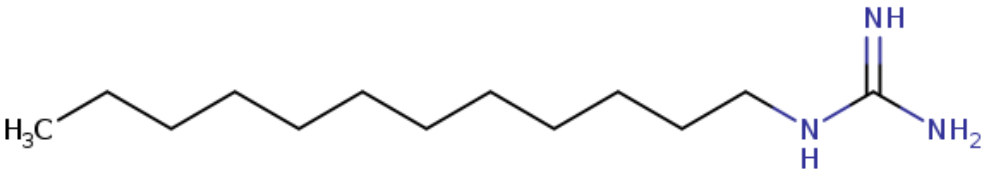
* Orchard Crops: Almonds, Apple, Apricot, Banana, Cherries (sweet & sour), Nectarines, Olives, Peaches, Pecans, Pears, Plums, Walnuts @ 1.3 lb ai/A (except Apple and Banana @ 0.65 lb ai/A)

Table A.4. Complete Study Results of Acute Inhalation Toxicity Testing with Dodine Technical (MRID 46621302)			
Dose mg/L	**Time of Death**	**Clinical Observations**	**Gross Necropsy Observations**
0.25	N/A	Fur/skin soiled w/excreta, exaggerated breathing, noisy respiration, gasping, brown staining of snout/jaws/body, wet fur, swollen abdomen, brown crusty staining of snout/jaws	No observable abnormalities noted
0.34	1/10 on day 2	Fur/skin soiled w/excreta, wet fur, exaggerated breathing, noisy respiration, brown staining of snout/jaw/body, staggering, gasping, matted fur, brown crusty staining snout/jaws, lethargic swollen abdomen, alopecia	Congested lungs, pale liver, distended stomach, distended cecum, distended intestines, small dark focus on lung
0.51	1/10 at 1 hr. 1/10 at 2 hrs. 3/10 on day 1 1/10 on day 4 1/10 on day 5	Fur/skin soiled w/excreta, wet fur, lethargic, whole body cold to touch, piloerection, slow breathing rate, brown staining of snout/jaws, gasping, noisy respiration, immobile, exaggerated breathing, brown crusty staining snout/jaw, matted fur, ataxia, unsteady gait	Congested lungs, small spleen, enlarged heart, distended stomach/cecum/large intestines/small intestines, congested intestines

Figure A.1: Select Chemical Structures

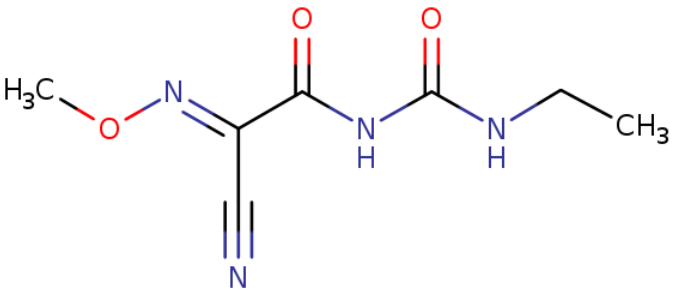


Dodine



HCl

DGH



Cymoxanil

All tables are based on the most up-to-date information available at the time of the HASPOC meeting and are subject to change.