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

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

January 24, 2008

MEMORANDUM

SUBJECT: Dodine: Human Health Risk Assessment for Proposed Use Bananas and Peanuts.
PC Code: 044301, Petition No: 7F7185DP Barcode: D338147

Regulatory Action: Section 3 Registration Action
Risk Assessment Type: Single Chemical Aggregate

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1.0 Executive Summary

Dodine is a general use pesticide belonging to the guanidine fungicide class. It is used as a foliar protectant against various diseases on fruits and nuts, specifically for control of scab on apples and pears, leafspot on cherries, foliar diseases of strawberries, bacterial leafspot on peaches, and leaf blight of sycamores and black walnuts. The mode of action is through disruption of cell membranes. Currently, dodine is registered for use on apple, cherry, peach, pear, pecan, strawberry, and walnut. AGRIPHAR SA, through their agent Ceres International LLC, has submitted a petition, PP#7F7185, proposing the establishment of tolerances for residues of dodine (dodecylguanidine acetate) in/on bananas and peanuts. The Reregistration Eligibility Decision (RED) for dodine was issued September 2005.

HUMAN HEALTH RISK ASSESSMENT:

Toxicology/Hazard

Technical dodine has moderate toxicity via the acute oral, dermal and inhalation routes of exposure (Category III). It is a severe eye irritant (Category I) and causes severe dermal irritation (Category I); it is not a skin sensitizer.

A definitive target organ has not been identified for dodine. The most common effects observed in subchronic and chronic studies were decreases in food consumption, body weight and/or body weight gain. Possible neurological clinical signs (excessive salivation and hunched posture/hypoactivity) were observed in chronic studies in rats and mice but were not dose-related or statistically significant. Excessive salivation in the chronic study in dogs showed a treatment-related dose response; however, it was not consistent with a neurological adverse effect since it was seen prior to dosing and was a persistent finding throughout the study. Therefore, there is no evidence of neurotoxicity. A developmental neurotoxicity (DNT) study is not warranted at this time.

In a rat 28-day dermal study, no mortality or clinical signs were observed in males or females. No treatment-related effects were observed on body weight, body weight gain, food consumption, hematology and clinical chemistry. Histopathological alterations were limited to dermal lesions.

Decreased maternal body weight gain and food consumption were observed in a rat developmental toxicity study at 45 mg/kg/day. In a rabbit developmental toxicity study, dams demonstrated decreased food consumption at 80 mg/kg/day. No treatment-related effects were observed in fetuses in the developmental studies in rats or rabbits.

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 is no evidence of increased susceptibility (quantitative or qualitative) in pups versus adults based on rat and rabbit developmental studies and the rat multi-generation reproduction study. In rat and rabbit prenatal developmental studies, there was no toxicity identified in the fetuses up to the highest dose tested. In the two generation reproduction study, decreases in body weight gain and food consumption were seen in pups at the same dose at which maternal toxicity (decreased body weight, body weight gain and food consumption) was observed. Consequently, there is no concern for pre- or postnatal toxicity resulting from exposure to dodine; therefore, from the toxicity perspective and taking into account the exposure component of the risk assessment, the FQPA safety factor can be reduced (1X).

A weight of evidence evaluation of the carcinogenic potential of dodine was performed, and based on the results it was concluded that there is no evidence of carcinogenicity after exposure to dodine (D323607, J. Morales).

All toxicological endpoints chosen for risk assessment were based on body weight effects plus, in the case of inhalation, reduced food consumption.

Dietary Exposure (Food/Water)

A chronic aggregate dietary (food and drinking water) exposure and risk assessment was conducted using the Dietary Exposure Evaluation Model DEEM-FCID™, Version 2.03 which uses food consumption data from the U.S. Department of Agriculture's Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. The analysis was performed to evaluate requested new uses of dodine on bananas and peanuts and the Agency has sufficient data to assess these uses.

The chronic assessment is based on tolerance-level residues and incorporates percent crop treated information for pome fruit, stone fruit, strawberry, pecan, and walnut, and assumes 100% crop treated for bananas and peanuts. Default processing factors from DEEM 7.78 were used for all processed commodities. An estimate of dodine residue in water was incorporated directly into the analysis. Based on these input parameters and assumptions, the chronic dietary risk estimate for the U.S. population is 3% of the chronic population-adjusted dose (cPAD). The highest risk estimate is for children 1-2 years of age at 20% of the cPAD. Therefore, the risk estimates for all population subgroups are below HED's level of concern (i.e., < 100% of the cPAD). Given the use of percent crop treated estimates, the dietary risk estimates should be considered to be moderately refined.

Residential (Non-occupational) Exposure

There are no registered residential and/or non-agricultural uses for dodine, and no new such uses are being proposed. However, a related chemical, dodecylguanidinium hydrochloride (DGH), is registered as an antimicrobial pesticide with potential residential and non-occupational exposures from its incorporation in paint and disposable diapers. Dodine and DGH have similar chemical compositions and properties (i.e, both are salts of dodecylguanidine). In the 1987 Registration Standard for Dodine, dodine and DGH were reviewed as bio-equivalents. Because both dodine and DGH are expected to be almost completely dissociated under most environmental

conditions, and certainly under physiological conditions, the two anions are expected to have negligible effect on the dodecylguanidinium moiety, so data for dodine can also be considered representative of DGH data, and vice versa. This should be especially true for toxicological data (D323607, J. Morales). The residential uses associated with DGH were previously assessed by the Antimicrobial Division (AD). The DGH assessment has also been incorporated into the dodine RED. Since AD did not assess incidental ingestion of paint chips as part of their assessment, HED has included an assessment for the scenario.

Handlers

Dermal and inhalation exposures and risks to the residential handlers (painters) were assessed by AD, using the Pesticide Handler Exposure Database (PHED) and the Agency's standard values. Since residential painters typically paint on an intermittent basis, only the short-term exposure duration (1 -30 days) was necessary to assess. All inhalation, dermal, and total MOEs of painters were greater than 100 and do not exceed the Agency's level of concern for residential uses.

Post-application

Post-application dermal contact with wet paint was not assessed because the paint is expected to dry within a day, so any potential exposure is expected to be negligible. DGH has a low vapor pressure (i.e., $<1x10^{-7}$ mmHg @25°C), therefore it is not likely to generate sufficient vapor to cause an inhalation concern to residential populations performing post-application tasks or occupying recently treated areas. Thus, there are no risk concerns and inhalation post-application exposures were not quantitatively evaluated.

The incidental ingestion of paint chips from uses of DGH was assessed using the HED's Residential Standard Operating Procedures (SOP). The short-term oral MOE is greater than 100 and; therefore, is not of concern.

DGH is also incorporated as a bacteriostat in the manufacturing of the absorbent material used in disposable diapers. Residential dermal exposures and risks to infants (< 1 year old) who wear DGH-impregnated diapers were estimated as part of this assessment. Since infants typically wear diapers on a continuous basis, short-, intermediate- and long-term exposure durations were assessed. No data on leaching or migration data of DGH to skin of infants were provided to support this use; therefore, all of the assumptions used for calculating the exposures in this assessment are based on the Agency's standard values.

For estimating the exposure of infants to DGH when used in diapers, AD used two transfer factors, 100% and 5%. A 100% transfer factor resulted in MOEs of concern for all exposure durations (MOE = 36). However, using a transfer factor of 5%, which is based on the default percent transfer factor for pesticide residues migrating from carpets to skin surfaces (Revisions to the Standard Operating Procedures (SOPs) for Residential Exposure Assessments; Policy 12; US EPA, 2001), the MOEs for all durations were greater than 100 and were not of concern (MOE = 714). In order to refine dermal exposure resulting from use of DGH-impregnated diapers and to fully answer the rate of migration of DGH to the skin of infants, AD indicated the

need for an impregnated diaper migration study as confirmatory data to support the lower transfer factor assumption.

For purposes of refining the dermal exposure resulting from use of diapers impregnated with DGH and incorporating this use into an aggregate risk (ie., dietary + drinking water + residential exposure) for the Dodine Human Health Risk Assessment, HED performed a back calculation to determine what transfer factor would be required to reach an MOE of 120 (for purposes of aggregate risk since an MOE of 100 for diaper exposure alone will not be sufficient). The calculations determined that a 30% transfer factor would be required to result in an MOE of 120.

HED believes that a transfer factor of 100% is an overestimate of exposure in determining the amount of DGH transferred to infants from diapers. Although using either 30% or 5 % transfer factors result in MOEs that are not of concern, HED has no means to confirm these estimates of exposure. Therefore, **HED concurs with AD's request for submission of an impregnated diaper migration study as confirmatory data.**

Aggregate Risk

In examining aggregate exposure, the HED aggregated exposures to dodine in food + water with exposures to DGH from residential uses. Accordingly, risk assessments for aggregate exposure (food + drinking water + residential) were considered only for the short-term for adults handling paints, and short-, intermediate-, and long-term for infants wearing diapers.

The aggregate MOEs for adult subpopulations are > 100 and therefore represent risk estimates which are not of concern to HED. The aggregate MOEs for infants wearing DGH-impregnated diapers range from 34 to 640 and indicate that there may be risks of concern, depending on what assumptions are made regarding the amount of DGH that is transferred from the diaper to the infant.

Occupational Exposure/Risk

HED's level of concern is for MOEs equal to or less than 100. Therefore, all MOEs greater than 100 are not of concern. Since the dermal and inhalation endpoints are based on the same effects, the dermal and inhalation exposures were added together to obtain a total MOE.

The petitioner has not submitted any product specific occupational exposure data; therefore, HED default values and PHED were used to estimate the exposures to pesticide handlers. The exposure estimates indicate that the risks from all handler scenarios are not of concern (MOEs ≥ 100) at baseline PPE (long-sleeve shirt, long pants, shoes, socks, and no respirator), with two exceptions. The mixer/loader scenarios at baseline resulted in risks of concern (Dermal MOEs=11 and 94). However, the addition of gloves resulted in MOEs (MOE > 100) that are not of concern. Furthermore, the label mandates use of chemical-resistant gloves for handlers under PPE.

Post-application exposures were estimated using default dermal transfer coefficients from the HED's Exposure SAC Policy No. 3.1. It should be noted that there was no transfer coefficient

data in Policy 3.1 for banana. Therefore, surrogate transfer coefficient values for bunch/bundle crop groups (i.e., hops and tobacco) were used to assess postapplication exposure and risk for bananas. All postapplication MOEs were greater than 100 on day 0 after application, and therefore are not of concern to HED.

Restricted Entry Interval (REI):

Dodine has moderate acute toxicity by oral, dermal, and inhalation routes (Categories III) and is not a skin sensitizer. However, it is a severe dermal and eye irritant (Toxicity Categories I). Chemicals classified as Toxicity Category I require a 48-hour REI in accordance with Worker Protection Standards (WPS) in addition to double layer clothing, chemical resistant footwear, gloves, respiratory device and protective eyewear. HED concurs with the 48-hour REI on the proposed product label.

ENVIRONMENTAL JUSTICE CONSIDERATIONS

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations" http://www.eh.doe.gov/oepa/guidance/justice/eo12898.pdf).

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 USDA under the Continuing Survey of Food Intakes by Individuals (CSFII) 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, season of the year, ethnic group, and region of the country. 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 postapplication are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

Review of Human Research

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These studies, which comprise the Pesticide Handlers Exposure Database (PHED), have been determined to require a review of their ethical conduct, and have received that review. The studies in PHED are considered appropriate (ethically conducted) for use in risk assessments.

ADDITIONAL DATA NEEDS/RECOMMENDATIONS

Occupational and Residential Exposure

- HED recommends a conditional registration based on submission of an impregnated diaper migration study as confirmatory data.

Regulatory Recommendations and Residue Chemistry Deficiencies

Directions for Use

- The proposed use on banana does not include a maximum seasonal rate. In addition, the crop field trial data from Hawaii do not reflect the proposed use pattern. The petitioner should modify the proposed label such that the use pattern on banana corresponds to the use pattern of the banana crop field trials: five applications at 0.71 lb ai/A/application, for a maximum seasonal rate of 3.6 lb ai/A, with a minimum retreatment interval of 6 days and a PHI of 0 days.

- The petitioner has indicated that the proposed tolerance for bananas is intended to apply to domestic bananas as well as imported bananas, but that the use directions for foreign countries have not yet been finalized. To allow HED to determine that the submitted crop field trial data adequately reflect the use of dodine on bananas in countries outside the U.S., when the use directions have been finalized, the petitioner should submit copies of product labels (with English translations, if needed) with use directions on bananas from all countries in which dodine is to be applied to bananas destined for import into the U.S. If the finalized use directions differ significantly from the use patterns of the submitted crop field trial data, additional data may be required.

Residue Analytical Methods

- Method METH1595.02 should be modified to remove the conversion of residue results to "dodine free base" (this calculation is made at the step in which standard solutions are prepared). Residue results must be calculated in terms of dodine, as N-dodecylguanidine acetate in order to correspond to the tolerance expresson. In addition, the typographical error in step 9.3.7 of the method should be corrected ["Repeat steps 9.2.3 to 9.2.6 two more times" should be changed to "Repeat steps 9.3.3 to 9.3.6 two more times"].

Proposed Tolerances

- The proposed tolerance for peanut should be revised from 0.03 ppm to 0.013 ppm.

Confined Accumulation in Rotational Crops

- Confined rotational crop data are required to support the proposed use on peanuts. A confined rotational crop study was required in the Revised RED Chapter (DP# 320758, 9/14/05, D. Soderberg). These data remain outstanding. HED recommends the

registration of the uses on peanuts be made conditional on the future submission of these data.

Field Accumulation in Rotational Crops

- The need for field rotational crop studies and/or rotational crop restrictions/tolerances will be determined when an adequate confined rotational crop study has been submitted.

Provided the above issues are addressed, HED recommends for the establishment of the tolerances specified in Table C.1.

2.0 Ingredient Profile

Dodine (n-dodecylguanidine acetate) is a non-systemic guanidine based fungicide registered for the control of certain fungal diseases on apples, cherries, peaches, pears, pecans, walnuts, strawberries, and ornamental trees. It is a white crystalline solid formulated as wettable powder and flowable concentrate. The proposed formulation is Syllit® FL Fungicide (EPA Reg. No. 55260-6), which is a liquid flowable containing 39.6% or 3.4 lb dodine/gallon as the sole active ingredient (ai).

The petitioner is proposing the addition of two new sites, banana and peanut to the registered uses of dodine. On banana, the recommended application rate is 0.64-1.3 lb ai/A for the first application followed by four applications at 0.64 lb ai/A at 7-15 day intervals. The product is applied using aerial equipment in 9-18 pints/A water plus 5-7 pints of mineral oil/A. The maximum seasonal rate is 3.83 lb ai/A. On peanut, three applications of Syllit® FL Fungicide are made at 0.64 lb ai/A/application at 10-14 intervals using ground equipment. The maximum seasonal rate is 1.91 lb ai/A.

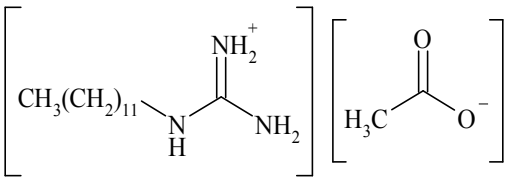
2.1 Summary of Proposed Uses

Table 2.1. Summary of Proposed Use Patterns for the End-Use Directions for Use of Dodine.

Applic. Timing, Type, and Equip.	Formulation [EPA Reg. No.]	Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI (days)	Use Directions and Limitations
Banana: Sigatoka						
Postemergence, Foliar, Aerial equipment	3.4 lb/gal FlC [55260-6]	0.64-1.3	5	Not specified (NS)	0	Applications may be made at up to 1.3 lb ai/A through first cover applications; subsequent applications to be made at 0.64 lb ai/A. A retreatment interval of 7-15 days is proposed. Applications are to be made in a mixture of 1.1-2.3 gal water/A and 0.6-0.9 gal mineral oil/A.

Table 2.1. Summary of Proposed Use Patterns for the End-Use Directions for Use of Dodine.						
Applic. Timing, Type, and Equip.	Formulation [EPA Reg. No.]	Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI (days)	Use Directions and Limitations
Peanut						
Postemergence Foliar Ground or aerial equipment	3.4 lb/gal FlC [55260-6]	0.64	3	1.9 (implied)	14	Applications are to begin when disease first appears (~35 days after planting) and to be repeated at retreatment intervals of 10-14 days. The feeding of hay and vines to livestock is prohibited.

2.2 Structure and Nomenclature

Table 2.2 Dodine Structure and Nomenclature.	
Chemical structure	
Common name	Dodine
Company experimental name	N/A
IUPAC name	1-dodecylguanidinium acetate
CAS name	dodecylguanidine monoacetate
CAS registry number	2439-10-3
End-use product (EP)	Syllit® FL Fungicide; EPA Reg. No. 55260-6; 3.4 lb/gal FlC formulation

2.3 Physical and Chemical Properties

Table 2.3 Physicochemical Properties of Dodine.		
Parameter	Value	Reference
Melting point/range	136-137 ºC	Product Chemistry Chapter of the Dodine Reregistration Standard (10/1/86)
pH	7.6 at 21 ºC (1% aqueous suspension) 7.0 at 25 ºC (saturated aqueous solution)	MRID 45322705
Density	0.55 kg/L unpacked; 0.64 kg/L packed	RD Memorandum, 9/13/88, A. Smith
Water solubility	0.07%	2001 Farm Chemicals Handbook
	0.104 g/100 mL at 21 ºC	RD Memorandum, 9/13/88, A. Smith

Table 2. 3 Physicochemical Properties of Dodine.		
Parameter	Value	Reference
Solvent solubility	Soluble in methanol and ethanol; practically insoluble in most organic solvents	2001 Farm Chemicals Handbook
	At 22 ºC 18.1 g/100 mL in methanol 7.8 g/100 mL in ethanol 0.003 g/100 mL in acetone 0.0006 g/100 mL in n-hexane Insoluble in toluene	RD Memorandum, 9/13/88, A. Smith
Vapor pressure	1.5×10^{-7} mm Hg at 25 ºC; No detectable vapor pressure at 50 ºC	Section C of PP#7F7185 RD Memorandum, DP# 273321, 6/18/01 H. Podall
Dissociation constant, pK_a	Completely dissociated	RD Memorandum, 9/13/88, A. Smith
Octanol/water partition coefficient, $Log(K_{OW})$	P = 5.77; Log P = 0.76 at 22 ºC	RD Memorandum, 9/13/88, A. Smith
UV/visible absorption spectrum	No color; No chromophore; No absorption between 300 - 540 nM	MRID 40975701

3.0 Hazard Characterization/Assessment

3.1 Hazard and Dose-Response Characterization

3.1.1 Database Summary

3.1.1.1 Sufficiency of studies/data

The database for dodine is complete and there are no datagaps. The available toxicity data are adequate to assess the chemical's hazard potential. The database contains the following toxicity studies: (i) a subchronic mouse toxicity study (ii) chronic rat, mouse, and dog toxicity studies, (iii) 28-day dermal and dermal penetration studies (rats), (iv) prenatal developmental studies (rats and rabbits), and (v) a reproduction study in rats. There are also acute LD50 studies, a metabolism study, and a complete mutagenicity battery.

3.1.1.2 Mode of action, metabolism, toxicokinetic data

Dodine is a fungi-toxic cationic surfactant that has a non-specific mode of action. Dodine acts by interfering with membrane structure, mainly by altering cell permeability to allow leakage of phosphorus and amino materials from poisoned cells.

3.1.2 Toxicological effects

Technical dodine has moderate toxicity via the acute oral, dermal and inhalation routes of exposure (Category III). It is a severe eye irritant (Category I) and causes severe dermal irritation (Category I); it is not a skin sensitizer.

A definitive target organ has not been identified for dodine. The most common effects observed in subchronic and chronic studies were decreases in food consumption, body weight and/or body weight gain. Possible neurological clinical signs (excessive salivation and hunched posture/hypoactivity) were observed in chronic studies in rats and mice but were not dose-related or statistically significant. Excessive salivation in the chronic study in dogs showed a treatment-related dose response; however, it was not consistent with a neurological adverse effect since it was seen prior to dosing and was a persistent finding throughout the study. Therefore, there is no evidence of neurotoxicity. A developmental neurotoxicity (DNT) study is not warranted at this time.

In a rat 28-day dermal study, no mortality or clinical signs were observed in males or females. No treatment-related effects were observed on body weight, body weight gain, food consumption, hematology and clinical chemistry. Histopathological alterations were limited to dermal lesions.

Decreased maternal body weight gain and food consumption were observed in a rat developmental toxicity study at 45 mg/kg/day. In a rabbit developmental toxicity study, dams demonstrated decreased food consumption at 80 mg/kg/day. No treatment-related effects were observed in fetuses in the developmental studies in rats or rabbits.

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 is no evidence of increased susceptibility (quantitative or qualitative) in pups versus adults based on rat and rabbit developmental studies and the rat multi-generation reproduction study. In rat and rabbit prenatal developmental studies, there was no toxicity identified in the fetuses up to the highest dose tested. In the two generation reproduction study, decreases in body weight gain and food consumption were seen in pups at the same dose at which maternal toxicity (decreased body weight, body weight gain and food consumption) was observed. Consequently, there is no concern for pre- or postnatal toxicity resulting from exposure to dodine; therefore, from the toxicity perspective, the FQPA safety factor can be reduced (1X).

There was equivocal evidence of carcinogenicity in rat and mouse carcinogenicity studies; however, a weight of evidence evaluation of the carcinogenic potential of dodine was performed, and based on the results it was concluded that there is no evidence of carcinogenicity after exposure to dodine (D323607, J. Morales).

3.1.3 Dose Response

For chronic dietary exposure, the chronic toxicity study in dogs was used to calculate the chronic reference dose (cRfD) of 0.02 mg/kg/day. The NOAEL of 2 mg/kg/day is based on changes in body weight in females at the LOAEL of 10 mg/kg/day; no appropriate endpoint was identified for acute dietary exposure. A 28-Day dermal toxicity study was used to select the dose and endpoint for occupational and residential dermal exposure (all durations). Although a LOAEL

was not established in the study, the NOAEL of 200 mg/kg/day is considered protective and appropriate for endpoint selection (see section 3.5.6). The developmental toxicity study in rats was used to select the dose and endpoint for occupational and residential short-term inhalation exposure. The NOAEL of 10 mg/kg/day is based on changes in body weight in females at the LOAEL of 45 mg/kg/day. Additionally, the 2-generation reproduction study was selected for incidental oral exposure. The developmental (offspring) NOAEL of 26 mg/kg/day is based on decreased pup weights at the LOAEL of 53 mg/kg/day.

3.2 Absorption, Distribution, Metabolism, Excretion (ADME)

Dodine was rapidly absorbed, distributed, metabolized and excreted at all dosing levels with no significant gender differences. Urine and feces were found to be major routes of excretion for dodine. At 120 hours (5 days) post-exposure, 40.55 to 45.35 % of the dose was excreted in the urine and 47.63 to 59.69 % was excreted in the feces in all dose groups. Total recovery at 120 hours ranged from 93.61 to 102.22 % of the administered dose. Tissues were collected and analyzed for radioactivity. Upon analysis, ≤ 3.35% of the administered dose was recovered in tissues. The highest amounts recovered were in the gastrointestinal tract (0.16-1.14% of the dose), muscle (0.02-0.61% of the dose) and skin (0.06-0.21%).

Urine and fecal samples from one animal/sex in each dose group were analyzed for metabolites. In urine, the unmetabolized parent compound was not identified; however, four metabolites were identified. The major metabolite was an alcohol of dodine, hydroxydodecylguanidine, and accounted for 10.98 to 23.52% of the administered dose. Females did have a slight increase in this metabolite when compared to males. Urea and two unidentified metabolites which appeared to be carboxylic acid products arising from oxidation of the alkane side chain account for the remaining metabolites. Parent compound was identified as the major metabolite in fecal samples, accounting for 0.17 to 4.17% of the dose.

The proposed metabolic pathway for dodine in rats is a ß-oxidation pathway similar to that for medium- and long-chain fatty acids. Oxidation takes place by forming intermediate products with shorter chain lengths which are eliminated in the urine. Urea is also formed in the liver from action on dodine or one of its metabolites.

3.3 FQPA Considerations

3.3.1 Adequacy of the Toxicity Data Base

The toxicology database is adequate for the evaluation of risks to infants and children. Acceptable studies include: developmental toxicity studies in rats and rabbits and a 2-generation reproduction study in rat.

3.3.2 Evidence of Neurotoxicity

Neurotoxicity studies are not available for dodine. Possible neurological clinical signs (excessive salivation and hunched posture/hypoactivity) were observed in chronic studies in rats and mice but were not dose-related or statistically significant. Excessive salivation in dogs showed a treatment related dose response; however, it was not consistent with a neurological

adverse effect since it was seen prior to dosing and was a persistent finding throughout the study. In addition, no evidence of neuropathology was observed in the available studies.

3.3.3 Developmental Toxicity Studies

In a rat developmental toxicity study, decreases in body weight gain and food consumption were observed at ≥ 45 mg/kg/day in maternal animals. No treatment-related effects were observed in fetuses up to 90 mg/kg/day.

In a rabbit developmental toxicity study, dams demonstrated decreased food consumption at 80 mg/kg/day; however, this finding was not considered adverse. No treatment-related effects were observed in fetuses up to 80 mg/kg/day.

In the rabbit developmental study, animals were not dosed up to the limit dose of 1000 mg/kg/day and no treatment-related effects were observed in the study up to the highest dose tested of 80 mg/kg/day. However, the rat (LOAEL =45 mg/kg/day) is considered the most sensitive species and is protective of potential developmental effects. Therefore, the developmental toxicity rabbit study is acceptable for risk assessment and data gathered from an additional study would not provide additional information.

3.3.4 Reproductive Toxicity Study

In a two-generation reproduction toxicity study in rats, decreases in parental body weight, body weight gain and food consumption were noted in both generations of rats at 53 mg/kg/day. Additionally at 53 mg/kg/day, the offspring of both generations demonstrated decreased body weight after post-natal day 4 which continued through pre-mating. No treatment-related effects were noted on reproduction parameters.

3.3.5 Additional Information from Literature Sources

The toxicological database for dodine, including all subchronic and chronic studies, was evaluated by an international peer review committee. The conclusions from that report can be found under the following reference:

JMPR Report. 2000. Pesticide Residues In Food 2000 : Dodine; First draft prepared by Virginia A. Dobozy, US Environmental Protection Agency, Washington DC, (4.10, page 79). http://www.fao.org/ag/AGP/AGPP/Pesticid/Default.html

3.3.6 Pre-and/or Postnatal Toxicity

3.3.6.1 Determination of Susceptibility

There is no concern for increased quantitative and/or qualitative susceptibility after *in utero* or postnatal exposure to dodine in developmental toxicity studies in rats and rabbits, or a reproduction study in rats.

3.3.6.2 Degree of Concern Analysis and Residual Uncertainties for Pre and/or Post-natal Susceptibility

The purpose of the Degree of Concern analysis are: (1) to determine the level of concern for the effects observed when considered in the context of all available toxicity data; and (2) to identify any residual uncertainties after establishing toxicity endpoints and traditional uncertainty factors to be used in the risk assessment. If residual uncertainties are identified, then HED determines whether these residual uncertainties can be addressed by a FQPA safety factor and, if so, the size of the factor needed.

There is no evidence (quantitative or qualitative) of increased susceptibility and no residual uncertainties with regard to pre- and/or postnatal toxicity following *in utero* exposure to rats or rabbits and pre and/or postnatal exposures to rats. Therefore, it is recommended that the FQPA safety factor be reduced to 1X and no additional safety factors are needed (section 3.4).

3.3.7 Recommendation for a Developmental Neurotoxicity Study

Possible neurological clinical signs (excessive salivation and hunched posture/hypoactivity) were observed in chronic studies in rats and mice but were not dose-related or statistically significant. Excessive salivation in the chronic study in dogs showed a treatment related dose response; however, it was not consistent with a neurological adverse effect since it was seen prior to dosing and was a persistent finding throughout the study. In addition, no evidence of neuropathology was observed in the available studies. Therefore, there is no evidence of neurotoxicity. Based on the weight of evidence, a developmental neurotoxicity (DNT) study is not warranted at this time.

3.4 Safety Factor for Infants and Children

HED recommends the FQPA SF be reduced to 1X because there is no evidence of increased susceptibility; there are no residual uncertainties with regard to pre- and/or postnatal toxicity; and the toxicological database for dodine is complete. After evaluating the toxicological and exposure data, the dodine risk assessment team recommends that the FQPA SF be reduced to 1X based on the following:

- The toxicity data showed no increase in susceptibility in fetuses and pups with *in utero* and post-natal exposure
- The dietary food exposure assessment is based on HED-recommended tolerance-level residues and health-protective modeling assumptions. Although percent crop treated estimates are used for crops with existing tolerances, the use of tolerance values for residue levels likely overestimate actual exposures.

- The dietary drinking water assessment is based on values generated by model and associated modeling parameters which are designed to provide conservative, health protective, upper-bound estimates of water concentrations.
- The residential exposure assessment utilizes reasonable high-end variables set out in HED's Residential Exposure SOPs. The aggregate assessment is based upon reasonable worst-case residential assumptions, and is also not likely to underestimate exposure/risk to any subpopulation, including those comprised of infants and children.

3.5 Hazard Identification and Toxicity Endpoint Selection

3.5.1 Acute Reference Dose (aRfD) - General Population and Females 13-49

No appropriate endpoint was identified for the general population or females age 13-49 that could be attributed to a single dose.

3.5.2 Chronic Reference Dose (cRfD)

Study Selected: Chronic Toxicity-Dog

MRID No: 44246101

Dose and Endpoint for Risk Assessment: NOAEL = 2 mg/kg/day

Uncertainty Factor: 100X (10X interspecies extrapolation, 10X intraspecies variability)

$$\textbf{Chronic RfD} = \frac{2\ mg/kg/day}{100\ (UF)} = \textbf{0.02 mg/kg/day}$$

Comments about Study/Endpoint/UF:

A chronic toxicity study in dogs was used to select the dose and endpoint for establishing the cRfD of 0.02 mg/kg/day. This study is the appropriate route and duration to establish a chronic dietary endpoint. The NOAEL of 2 mg/kg/day is based on weight loss in females observed at the LOAEL of 10 mg/kg/day. Uncertainty factors (100X) include: 10X interspecies extrapolation and 10X intraspecies variability.

This study is classified as **Acceptable /Guideline** and satisfies the requirements for a chronic toxicity study in dogs [870.4100b (§83-1)].

3.5.3 Incidental Oral Exposure (Short and Intermediate Term)

Study Selected: Reproduction and Fertility Effects - Rats

MRID No: 44246001

Dose and Endpoint for Risk Assessment: NOAEL = 26 mg/kg/day

Uncertainty Factor: 100X (10X interspecies extrapolation; 10X intraspecies variability)

Comments about Study/Endpoint/UF:

A 2-generation reproduction study in rats was used to select the dose and endpoint for short and intermediate term incidental oral exposure. Reductions in offspring body weight began as early as PND 4 indicating that the effect began before the pups had direct contact with the food. Therefore, since pup weight at birth was not affected and the effect was evident within a few days (days 4-21), the duration is appropriate for short-term oral exposure. Offspring body weight was also affected after the pups started eating the treated food. Therefore, this study is also applicable to intermediate term exposures because the rats continued to exhibit less weight than the control group during the premating of the F_1 generation. Although the rat prenatal developmental study demonstrated a lower NOAEL (10 mg/kg/day vs. 26 mg/kg/day in the reproduction study), the reproduction study is more relevant to this scenario since offspring effects were seen in the reproduction study at 53 mg/kg/day (doses tested were 0, 13, 26 and 53 mg/kg/day) indicating that the threshold dose is between 26 and 53 mg/kg/day. Note that no adverse effects were noted at a dose of 13 mg/kg/day in the reproduction study. The NOAEL of 10 mg/kg/day determined in the rat developmental study is likely a result of dose spacing. Therefore, based on the weight of evidence, a NOAEL of 26 mg/kg/day is adequately protective for this scenario and using the maternal NOAEL of 10 mg/kg/day from the prenatal developmental study in rats would lead to a very conservative estimation of risk. Uncertainty factors (100X) include: 10X interspecies extrapolation and 10X intraspecies variability.

3.5.4 Dermal Absorption

A dermal absorption study (MRID 46621303) is available for dodine where [^{14}C]- Dodine (n-dodecyl-^{14}C guanidine acetate) was administered to three groups of four male Sprague Dawley CD rats/dose to a 12 cm^2 dorsal area in a formulation and water dilution thereof at dose levels of 4.0 and 0.004 mg/ cm^2. The mean percent radioactivity remaining in the treated skin in the treatment groups (0.004 mg/ cm^2) were 36.6%, 49.5%, 45.2% and 40.3% at 8, 24, 48, 72 hours, respectively. Presumably, the [^{14}C]- Dodine remaining in the treated skin has the potential to be absorbed by the skin over time; however, this is not demonstrated by the study. In fact the radioactivity remaining at the application site increases slightly over time indicating that the maximum absorption is likely to happen after 72 hours. Therefore, approximately 1% (0.77%) of the dose applied to male rats was demonstrated to be absorbed in skin with the resulting radioactivity being found in the urine, feces, cagewash, carcass and untreated skin. Although eight to ten hours is considered most applicable to the typical worker and the doses used are the typical worker doses, it is appropriate to utilize the 72 hour/low dose dermal absorption value to be conservative in risk assessment. These values are considered conservative because a portion of the active ingredient was retained at the skin site and it is unlikely that all of the skin residues will become systemically available.

3.5.5. Dermal Exposure (Short-, Intermediate-, and Long-Term)

Study Selected: 28-Day Dermal Toxicity-Rat

MRID No: 46420701

Dose and Endpoint for Risk Assessment: NOAEL ≥ 200 mg/kg/day

Uncertainty Factor: 100X (10X interspecies extrapolation, 10X intraspecies variability)

Comments about Study/Endpoint/UF:

A 28 day dermal toxicity study in rats was used to select the dose and endpoint for establishing short-, intermediate-, and long-term dermal exposure. Although a definitive LOAEL associated with systemic toxicity was not identified, the weight of evidence suggests that increasing the dose (e.g. to more than 200 mg/kg/day) will ultimately result in similar (body weight effects) findings seen across the toxicology database. In addition, increased toxicity is not expected after extended treatment periods as demonstrated in oral studies with dodine. Therefore, an additional UF for extrapolating from a short- to long-term endpoint is not warranted.

3.5.6 Inhalation Exposure (Short-Term)

Study Selected: Developmental Toxicity-Rat

MRID No: 41900304

Dose and Endpoint for Risk Assessment: NOAEL = 10 mg/kg/day

Uncertainty Factor: 100X (10X for interspecies extrapolation, 10X for intraspecies extrapolation)

Comments about Study/Endpoint/UF: No appropriate inhalation toxicity studies are available for dodine. Two acute inhalation studies were submitted; however NOAELs were not identified in the studies. A developmental toxicity study in rats was used to select the dose and endpoint for establishing short-term inhalation exposure. The NOAEL of 10 mg/kg/day is based on weight loss observed in females at the LOAEL of 45 mg/kg/day. Uncertainty factors (100X) include: 10X interspecies extrapolation and 10X intraspecies variability.

3.5.7 Level of Concern for Margin of Exposure

Table 3.5.7 Summary of Levels of Concern for Risk Assessment

Route/Duration	Short-Term (1 - 30 days)	Intermediate-Term (1 - 6 months)	Long-Term (> 6 months)
Occupational (Worker) Exposure			
Dermal	100	100	N/A
Inhalation	100	100	N/A

Residential (Non-Dietary Exposure)			
Oral	100	N/A	N/A
Dermal	100	100	100
Inhalation	100	N/A	N/A

N/A = Not applicable

3.5.8 Recommendation for Aggregate Exposure Risk Assessments

As per 1996 FQPA, when there are potential residential exposures to the pesticide, aggregate risk assessment must consider exposures from three major sources: oral, dermal and inhalation exposures. All routes of exposure for all durations of exposure can be aggregated based on the common endpoint observed throughout the database (body weight effects). A cancer aggregate risk assessment is not required because there is no evidence of carcinogenicity (see cancer weight of evidence below).

3.5.9 Classification of Carcinogenic Potential

There was equivocal evidence of carcinogenicity. The following is a weight of evidence evaluation of the carcinogenic potential of dodine:

The rat and mouse carcinogenicity studies demonstrated that dodine was not associated with tumors in either sex in Sprague-Dawley rats or in male CD-1 mice. In female CD-1 mice fed with dodine at the highest dose tested (HDT) of 1500 ppm (see table 3.5.9 below), there was a statistically significant increase in the incidence of hepatocellular adenomas (0/60 vs 4/60 in HDT) and combined hepatocelluar adenomas and carcinomas (0/60 in control vs 5/60). There was an increased trend in adenomas, but there was no dose-related increase in the incidence of carcinomas. A positive trend ($p < 0.05$) with respect to dose rates was also observed in the combined tumor group. It should be noted that this positive trend was driven by the dose response in the adenomas (4/60 at HDT) and a spontaneous carcinoma (0/60 in the controls vs. 1/60 in both the low- and high- doses) seen in both the low- and high-dose group. The combined tumors (0 % in control and 8.3% at the HDT) were outside of the range for the historical control for Covance (the testing laboratory). However, when compared to the historical controls of Charles River (CR) (CD-1 mice supplier) the increase in incidence of combined tumors is marginal (8.3 % in female test animals vs. the 1-8 % range in female CR CD-1 mice). Charles River data indicate that more than one adenoma is reported in more than ½ of their studies. The following table is a summary of these findings:

Table 3.5.9	Female CD-1 mice			
Dosage	**0**	**200**	**750**	**1500**
Total examined (size of test group)	60	58	59	60

Table 3.5.9	Female CD-1 mice			
Dosage	**0**	**200**	**750**	**1500**
Adenoma	0	1 (1.7 %)	1 (1.7 %)	**4* (6.6 %)**
Carcinoma	0	1 (1.7 %)	0	1 (1.7 %)
Combined (Adenoma & Carcinoma)	0	2 (3.4 %)	1	**5** (8.3%)**
Combined Covance historical		3/395 (0.8 %)	3/395 (0.8 %)	6/395 (1.6 %)
Combined Charles River historical		(1.25- 2 %) (~3000 animals reported)	(1.25- 2 %) (~3000 animals reported)	(1- 8 %) (~3000 animals reported)

* Trend test significant at $p < 0.05$ in females
* * Significantly different from controls at $p < 0.05$

- There were no pre-neoplastic lesions that can be associated with the tumor response, and therefore, no evidence indicating that the high-dose was associated with further progression to carcinoma. No other test material related tumors were seen in the study.

  In mice, dosing at the highest dose (1500 ppm) was considered to be adequate, but not excessive, for carcinogenicity assessment. This was based on no treatment -related effects on survival, decreases in body weight (by 9 and 14% in males and females, respectively), and decreases in food consumption (by 6 and 19% in males and females, respectively). None of these effects is considered as evidence that the dose was excessive. It should be noted that on the first day of week 44, mice were inadvertently fed diets that were subsequently found to contain a level of dodine well in excess of the targeted 1500-ppm concentration. Furthermore, in a 13-week range finding study with dodine in mice, it was determined that the maximum tolerated dose (MTD) was considered to be higher than 1250 ppm but lower than 2500 ppm (pending MRID).

- There is no evidence of genotoxicity, and thus no mutagenicity concern.

- The structure activity relationship does not indicate a probable carcinogenic risk. Dodine belongs to the aliphatic and alicyclic fungicide class and consists of an alkyl carbon chain and a guanadine moiety. The alkyl carbon chain of dodine influences its toxic action. The 12-carbon homolog is the most effective.

- Dodine is a fungi-toxic cationic surfactant that has a non specific mode of action. Dodine acts by interfering with membrane structure, mainly by altering cell permeability to allow leakage of phosphorus and amino materials for poisoned cells.

Based on the weight of evidence it can be concluded that there is no evidence of carcinogenicity (D323607, J. Morales).

3.5.10 Summary of Toxicological Doses and Endpoints for Dodine Use in Dietary and Non-Occupational Human Health Risk Assessments

Table 3.5.10a Summary of Toxicological Doses and Endpoints for Dodine 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.
Acute Dietary (females 13-49 and general population)	N/A	N/A	N/A	No appropriate endpoint for females age 13-49.
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 LOAEL = 10 mg/kg/day based on body weight loss in females.
Incidental Oral Short-Term (1 - 30 days) Intermediate-Term (1 - 6 months)	NOAEL = 26 mg/kg/day	UF_A=10X UF_H=10X	Residential MOE =100	2-Generation Reproduction-rat Offspring LOAEL = 53 mg/kg/day based on decreased body weight.
Dermal Short-Term (1 - 30 days), Intermediate-term (1 - 6 months), and Long-Term (> 6 months)	NOAEL = 200 mg/kg/day (HDT)	UF_A=10X UF_H=10X	Residential MOE =100	28-Day Dermal Toxicity-rat LOAEL = not identified
Inhalation[a] Short-Term (1 - 30 days) Intermediate-Term[a] (1 - 6 months)	Developmental study Maternal NOAEL = 10 mg/kg/day IAF= 100%	UF_A=10X UF_H=10X	Residential MOE =100	Developmental toxicity study - rat Maternal LOAEL = 45 mg/kg/day based on decreased body weight gain and food consumption.
Cancer (oral, dermal, inhalation)	No Evidence of Carcinogenicity			

[a]IAF=inhalation absorption rate

Table 3.5.10b Summary of Toxicological Doses and Endpoints for Dodine Use in 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**
Dermal Short-Term (1 - 30 days) Intermediate-Term (1 - 6 months)	NOAEL = 200 mg/kg/day (HDT)	UF_A=10X UF_H=10X	Occupational MOE =100	28-Day Dermal Toxicity-rat LOAEL = not identified
Inhalation Short-Term[a] (1 - 30 days) Intermediate-Term[a] (1 - 6 months)	Developmental study Maternal NOAEL = 10 mg/kg/day	UF_A=10X UF_H=10X	Occupational MOE = 100	Developmental toxicity study - rat Maternal LOAEL = 45 mg/kg/day based on decreased body weight gain and food consumption.
Cancer (oral, dermal, inhalation)	No Evidence of Carcinogenicity			

[a] inhalation absorption rate = 100%, UF = uncertainty factor, FQPA SF = FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose, MOE = margin of exposure, LOC = level of concern, NA = Not Applicable.

3.6 Endocrine disruption

EPA is required under the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was a scientific basis for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP). In the available toxicity studies on dodine, there was no estrogen, androgen, and/or thyroid mediated toxicity.

When additional appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, dodine may be subjected to further screening and/or testing to better characterize effects related to endocrine disruption.

4.0 Public Health Data

Reference: *Review of Dodine and Dodecylguanidine hydrochloride Incident Reports*, DP Barcode D316590, Jerome Blondell, 05/10/2005

4.1 Incident Reports

Five databases were consulted for poisoning incident data. These include: OPP Incident Data System (IDS), Poison Control Centers, California Department of Pesticide Regulation, National Pesticide Telecommunications Network (NPTN), and National Institute of Occupational Safety and Health's Sentinel Event Notification System for Occupational Risks (NIOSH SENSOR). Of all poisoning incident data reported, there were almost no reports of ill effects concerning human poisoning or other adverse effects from exposure to dodine and dodecylguanidine hydrochloride.

5.0 Dietary Exposure/Risk Characterization

5.1 Pesticide Metabolism and Environmental Degradation

5.1.1 Metabolism in Primary Crops

The nature of the residue is adequately understood in fruiting and nut crops based on acceptable plant metabolism studies in apple, pecan and strawberry. These studies indicate that the residue of concern is dodine *per se*. In the Revised Residue Chemistry Chapter of the RED, HED concluded that no further plant metabolism studies are required (D320758, D. Soderberg). An additional study may be needed if any future uses are requested on crops such as leafy vegetables, root crops, or cereal grains.

5.1.2 Metabolism in Rotational Crops

No confined rotational crop data are available for dodine. A confined rotational crop study was required in the Revised Residue Chemistry Chapter of the RED; this data requirement remains outstanding. The need for rotational crop restrictions and/or tolerances will be determined when the confined rotational crop study has been submitted.

5.1.3 Metabolism in Livestock

The nature of the residue in livestock other than poultry is adequately understood based on a goat metabolism study. The residue of concern is dodine *per se*.

No poultry metabolism data have been submitted for dodine. Based on the fact that no detectable residues of dodine were observed in peanut meal processed from peanuts treated at 3x the proposed maximum rate, HED concludes that a poultry metabolism study will not be required to support the proposed use on peanuts. The petitioner should note that a poultry metabolism study may be required if any uses on crops with poultry feedstuffs are proposed in the future (D320758, D. Soderberg).

5.1.4 Analytical Methodology

Adequate enforcement methods are available for determining dodine residues in/on plant commodities. A colormetric method with spectrometric detection and various modifications is listed in PAM II as Methods I, I(a), I(b), and I(d). Additionally, a GLC method was submitted to the FDA in 1988 for inclusion in PAM II as Method II.

A GC/MSD method, Method 45137, has been proposed previously for use as an enforcement method for the determination of residues of dodine in/on plant commodities. HED has requested that the ACB evaluate GC/MSD Method 45137 to determine whether the method needs to be verified at ACB (DP# 323858, 1/18/06, D. Soderberg).

AGRIPHAR has proposed an LC/MS/MS method, METH1595.02, for the enforcement of tolerances for residues of dodine in/on banana and peanut commodities. AGRIPHAR submitted a copy of this method (as an appendix to MRID 47064901), as well as copies of previous versions METH1595-00.00 and METH1595.00.01. The validated limit of quantitation (LOQ) is 0.01 ppm and the limit of detection (LOD) is 0.003 ppm in each matrix. Although dodine reference standard is to be used to prepare all calibration and fortification solutions for the method, the method as written specifies that calibration and fortification standard concentration are to be calculated in term of "dodine free base" (presumed to be dodecylguanidine) instead of dodine (N-dodecylguanidine acetate), using a molecular weight conversion factor of 228.41/287.45. Therefore, residue results generated using this method are reported in terms of dodine free base.

LC/MS/MS method METH1595-00.00 was adequately validated using samples of banana fortified with dodine at 0.01 ppm, 0.10 ppm and 10 ppm, and samples of peanut and peanut oil fortified at 0.01 ppm, 0.10 ppm, and 1.0 ppm. Recoveries of dodine ranged 84-122% (mean ± SD = 105 ± 10%) from whole banana, 88-106% (98 ± 5.5%) from peanut, and 90-101% from peanut oil (100 ± 5.3%).

No validation data were included for peanut meal. However, adequate concurrent method recovery data were included with the peanut processing study submitted in conjunction with this petition. The concurrent method validation data in combination with the method validation data are sufficiently representative of the expected residue levels for the commodities included in the petition associated with this petition.

The LC/MS/MS method uses a single ion transition to quantitate residues of dodine in/on banana and peanut matrices (228.6→186.3 m/z), and specifies two additional parent-daughter ion transitions (228.6→85.3 m/z and 228.6→71.2 m/z) which may be used for analyte confirmation. No additional confirmatory analysis procedures will be required.

No radiovalidation data were submitted for LC/MS/MS method METH1595-00.00, METH1595-00.01, or METH1595.02. Adequate radiovalidation data have been submitted previously for a proposed enforcement method, GC/MS Method 45137 (DP# 320758, 9/14/05, D. Soderberg). The initial extraction procedures of GC/MSD Method 45137 are very similar to those of LC/MS/MS methods METH1595-00.00, METH1595-00.01, and METH1595.02. Therefore, HED concludes that the radiovalidation data for GC/MSD Method 45137 may be translated to support LC/MS/MS methods METH1595-00.00, METH1595-00.01, and METH1595.02.

Adequate independent laboratory validation data were submitted for the method using samples of banana, peanut, peanut meal, and peanut oil. Adequate recoveries were obtained for all matrices using the method as written. (D320758, D. Soderberg; D 338572/D342401. M. Doherty).

Conclusions: The submitted residue analytical method data are tentatively adequate to satisfy data requirements provided the method is revised as specified. Method METH1595.02 must be modified to remove the conversion of residue results to "dodine free base" (this calculation is made at the step in which standard solutions are prepared). Residue results must be calculated in terms of dodine, as N-dodecylguanidine acetate. In addition, the typographical error in step 9.3.7 of the method should be corrected ["Repeat steps 9.2.3 to 9.2.6 two more times" should be changed to "Repeat steps 9.3.3 to 9.3.6 two more times"].

LC/MS/MS method METH1595.02 does not require Agency method validation due to its similarity to existing, validated methods for dodine.

Due to the specifications of the method, all residue results for the crop field trial and processing studies associated with this petition were reported by the petitioner in terms of dodine free base. The study reviewer recalculated the residue results in terms of dodine using a molecular weight conversion factor of 1.258 (287.45/228.41). The recalculated LOQ was 0.013 ppm and the recalculated LOD was 0.004 ppm.

Because no tolerances are proposed or required for livestock commodities, no enforcement method for livestock commodities is needed at this time.

5.1.5 Environmental Degradation

Dodine is a water soluble (630 mg/L) salt of a strong base, and is completely dissociated to dodecylguanidinium ion and acetate in aqueous solutions under normal environmental conditions. In the field, dodine was almost exclusively confined to the 0-6 inch depth of bareground plots; it is immobile (K_{ads} = 2202 - 18,019 L/kg); is generally not expected to persist in aerobic soils (half-lives 17.5 - 22.3 d). The potential for dodine to reach drinking water sources is limited. With a low estimated vapor pressure of 1.5×10^{-7} torr for dodine (EPI Suite), volatilization is an unlikely route of dissipation; however, dodine may be transported off-site to drinking water sources as entrained sediment or via spray drift during aerial, airblast or ground spray applications. Once in aquatic environments, dodine is resistant to hydrolysis (half-lives 576-1198 d) and photolysis (641-770 d). In aerobic aquatic environments, dodine is likely to be moderately persistent to persistent (half-lives 38.9, 59.8, 227 d). In anaerobic aquatic environments, dodine is likely to be very persistent (half-life 2,492 d). Major degradates (excluding CO_2) were not identified in the available studies, but recovery of $^{14}CO_2$ from dodine radiolabeled in the guanidine moiety was approximately 90% in the aerobic soil study in the laboratory. Minor degradates of dodine expected in the environment are *n*-dodecylaminohydroxymethylamine, and guanidine. The former is formed at less than 5% of the total residue only after weathering for about a year, and is therefore not expected to be a significant part of exposure to dodine. In addition to being a very minor degradate, *n*-dodecylaminohydroxymethylamine was seen at significant levels in rat urine (above), so it is expected to be part of the total toxic exposure seen by the rats when they were dosed with dodine in the toxicology studies.

5.1.6 Comparative Metabolic Profile

The proposed metabolic pathway for dodine in rats is through a ß-oxidation pathway similar to medium- and long-chain fatty acids. Oxidation takes place by forming intermediate products with shorter chain lengths and these are eliminated in the urine. Urea is also formed in the liver.

In livestock and plants the metabolism of dodine appears to follow a similar metabolic route to that in rats. The terminal carbon on the dodecyl chain of dodine is oxidized to a carboxyl group and then the chain rapidly degrades, apparently 2 carbon atoms at a time, consistent with ß - oxidation until all that remains are the terminal metabolites: guanidine or urea. Thus, during metabolism of dodine in livestock, there is intermediate formation of dodecyl carboxylic acid guanidine, octyl carboxylic acid guanidine, and hexyl carboxylic acid guanidine in the tissues.

5.1.7 Toxicity Profile of Major Metabolites and Degradates of Concern

The major metabolites of dodine in foods in general are guanidine and urea - both common natural products with virtually no expected toxicity. In goat tissues, the n-alkyl carboxylic acid guanidine metabolites present a significant portion of the residue. These metabolites, however, are unlikely to share any of the biological effects of dodine since along with a quaternary amine they also have carboxylic groups at the distal end of the alkyl group.

5.1.8 Pesticide Metabolites and Degradates of Concern

Table 5.1.8 Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression

Matrix		**Residues included in Risk Assessment**	**Residues included in Tolerance Expression**
Plants	Primary Crop: bananas	Parent dodine	Parent dodine
	Primary Crop: bananas	Parent dodine	Parent dodine
	Rotational Crop*	N/A	NA
Livestock	Ruminant	Parent dodine	Parent dodine
	Poultry*	N/A	N/A
Drinking Water		Parent dodine	N/A

* study is not available

5.1.9 Drinking Water Residue Profile

The drinking water residues used in the dietary risk assessment were provided by the Environmental Fate and Effects Division (EFED) in the following memorandum: *Drinking Water Assessment for the Section 3 New Use Petitions for the Use of Dodine on Bananas and Peanuts*. (Marietta Echeverria, D338149, 16 OCT 2007) and incorporated directly into this

dietary assessment. Water residues were incorporated in the DEEM-FCID into the food categories "water, direct, all sources" and "water, indirect, all sources." The provided FIRST chronic surface water estimate of 0.004 ppm is greater than the groundwater estimate (< 0.00008 ppm; Table 5.1.9) and was used in the dietary assessment.

Table 5.1.9. Tier I estimated drinking water concentrations (EDWCs) resulting from applications of dodine.

Drinking water source (model)	Use (modeled rate)	Acute (ppb)	Chronic (ppb)
Surface water (FIRST)	Pecan, peach, walnut (13 lb/A/yr)	110	4.0
Groundwater (SCIGROW)		0.08	<0.08

5.1.10 Food Residue Profile

Insufficient use pattern information has been submitted to determine the adequacy of the banana crop field trial data. The petitioner has only submitted use pattern information for bananas grown in the U.S. The submitted crop field trial data are not in complete agreement with the proposed use directions (a total of 5 applications at 0.64-1.3 lb ai/A/application, with applications at 1.3 lb/A through first cover applications, and applications at 0.64 lb ai/A for subsequent application); the RTI and PHI of the field trials do agree with the proposed minimum RTI and PHI. Provided the petitioner modifies the proposed use on bananas to conform to the use pattern of the crop field trials, the submitted data are adequate to support use of dodine on bananas grown in the U.S. Additional use pattern information for banana importing countries is needed before HED may determine whether the submitted crop field trial data are adequate to support the proposed tolerance for bananas.

Based on the requirements identified in *NAFTA Guidance Document on Data Requirements for Tolerances on Imported Commodities in the United States and Canada* (December 2005), a total of 12 crop field trials are required to support an import tolerance for banana (approximately 99.7% of the banana consumed in the U.S. is imported, and banana accounts for 0.2-1.0% of the North American diet). Using the import values reported above, HED would require 3 trials with banana in each of Costa Rica, Ecuador, and Guatemala, 2 trials in Columbia, and 1 trial in Honduras. The petitioner conducted a total of 12 trials with bananas, in Colombia (1 trial), Costa Rica (3 trials), Ecuador (3 trials), Guatemala (1 trial), Hawaii (2 trials), Honduras (1 trial), and Martinique (1 trial). Although the submitted field trials do not conform exactly to the requirements, HED concludes that the number and location of banana crop field trials are adequate.

Provided the directions for use are modified to be in accord with the use patterns used in the field trials and the use patterns in the U.S. are the same as those being proposed for other banana-growing countries, the available data support the proposed tolerance (0.50 ppm) for residues of dodine in/on banana.

The submitted peanut crop field trial data are adequate to satisfy data requirements. The use pattern of the field trials adequately reflects the maximum proposed use pattern for dodine on peanut. Generally, HED requires that 9 crop field trials be conducted for peanut to support a registration when residues are below the LOQ, in Zone 2 (5 trials), 3 (1 trial), 6 (2 trials), and 8 (1 trial). The petitioner previously requested approval of a reduced field trial data set for peanut, based on residues below the LOQ in/on four trials conducted in Zone 2 at 1x (3 trials) and 3x (1

trial) the proposed maximum seasonal rate. The request was addressed by the HED Chemistry Science Advisory Council (see minutes of 3/29/06 meeting), which concluded that a reduced field trial data set was acceptable provided that two additional trials be conducted in Zones 6 and 8 and that residues were below the LOQ in/on samples from these additional trials. The petitioner has conducted 6 trials for peanuts, in Zone 2 (4 trials), 6 (1 trial), and 8 (1 trial) and residues were below the LOQ in/on all samples. Therefore, the number and location of crop field trials are adequate for the purposes of this petition.

Because the petitioner has proposed a feeding restriction for peanut hay, neither residue data nor a tolerance is required for peanut hay.

The available field trial data will support a tolerance for residues of dodine in/on peanut at the LOQ, 0.013 ppm.

HED does not require residue data for any processed commodities of banana. Residue data are required for peanut processed commodities meal and refined oil. The submitted processing data are adequate to satisfy data requirements. The data indicate that residues of dodine are not likely to concentrate above the LOQ in peanut meal or refined oil. No tolerances for peanut processed commodities are needed.

5.1.11 International Residue Limits

No Codex, Canadian, or Mexican Maximum Residue Limits (MRLs) for dodine exist on bananas and peanuts; therefore, no tolerance harmonization issues are associated with these commodities.

5.2 Dietary Exposure and Risk

5.2.1 Acute Dietary Exposure/Risk

No acute dietary endpoint was identified for dodine; therefore, an acute dietary risk assessment was not conducted.

5.2.2 Chronic Dietary Exposure/Risk

A chronic aggregate dietary (food and drinking water) exposure and risk assessment was conducted using the Dietary Exposure Evaluation Model DEEM-FCID™, Version 2.03 which use food consumption data from the U.S. Department of Agriculture's Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998.

The chronic dietary risk estimate for the U.S. population is 3.4 % of the chronic population-adjusted dose (cPAD). The highest risk estimate is for children 1-2 years of age at 20% of the cPAD. Therefore, the risk estimates for all population subgroups are below HED's level of concern (i.e., < 100% of the cPAD). Given the use of percent crop treated estimates, the dietary risk estimates should be considered to be moderately refined.

Table 5.2.2. Summary of Dietary (Food and Drinking Watery) Exposure and Risk for Dodine						
Population Subgroup	Acute Dietary		Chronic Dietary		Cancer	
	Dietary Exposure (mg/kg/day)	% aPAD*	Dietary Exposure (mg/kg/day)	% cPAD*	Dietary Exposure (mg/kg/day)	Risk
General U.S. Population	N/A		0.000674	3	Not likely a human carcinogen	
All Infants (< 1 year old)			0.003504	18		
Children 1-2 years old			**0.004072**	**20**		
Children 3-5 years old			0.002365	12		
Children 6-12 years old			0.000886	4		
Youth 13-19 years old			0.000336	2		
Adults 20-49 years old			0.000325	2		
Adults 50+ years old			0.000441	2		
Females 13-49 years old			0.000351	2		

* %PADs are reported to 2 significant figures. The values for the highest exposed population for each type of risk assessment are bolded.

5.2.3 Cancer Dietary Risk

There was no evidence of carcinogenicity in studies in rats and mice. As a result, HED believes that there is no cancer risk associated with dodine.

5.3 Anticipated Residue and Percent Crop Treated (%CT) Information

The chronic assessment is based on tolerance-level residues and incorporates percent crop treated information for pome fruit, stone fruit, strawberry, pecan, and walnut, and assumes 100% crop treated for bananas and peanuts. Default processing factors from DEEM 7.78 were used for all processed commodities. An estimate of dodine residue in water was incorporated directly into the analysis.

6.0 Residential (Non-Occupational) Exposure/Risk Characterization

There are no residential and/or non-agricultural uses currently registered for dodine, and no new proposed uses at this time. However, a closely related chemical, dodecylguanidine hydrochloride (DGH, PC Code 044303) is used as an antimicrobial in household, industrial, and commercial products having residential and non-occupational exposure potential. Dodine (n-dodecylguanidine acetate; Chemical Code No. 044301; Case No. 0161) and DGH (dodecylguanidine hydrochloride; Chemical Code No. 044303; Case No. 0161) are in the same case number based on their similar chemical compositions and properties. In the 1987 Registration Standard for Dodine, dodine and DGH were reviewed as bio-equivalents. Because both dodine and DGH are expected to be almost completely dissociated under most environmental conditions, and certainly under physiological conditions, the two anions are expected to have negligible effect on the dodecylguanidinium moiety, so data for dodine can also be considered representative of DGH data, and vice versa. This should be especially true for toxicological data (D323607, J. Morales). The Antimicrobials Division (AD) previously assessed the potential for non-dietary residential exposures and risks for the antimicrobial uses of DGH in paints and impregnated disposable diapers (DGH, Dietary and Non-dietary Exposures and Risks from Antimicrobial Uses, C.Walls, D313682, 5/26/2005) which was included in the

dodine RED (Morales, J. J., D323607,11/15/2005). HED has incorporated this assessment into the residential exposure assessment.

6.1 Handler Exposure

6.1.1 Paints

AD assessed the exposures and risks to the residential painters using the dermal and inhalation exposures from the PHED. Since residential painters typically paint on an intermittent basis, only the short-term exposure duration (1 -30 days) was necessary to assess.

All of the assumptions used for calculating the exposures in this assessment are based on the Agency's standard values. The assumptions used to calculate the MOEs are presented in Table 6.1.1.

All inhalation, dermal, and total MOEs of painters were greater than 100 and therefore represent risk estimates that do not exceed the Agency's level of concern for residential uses.

Table 6.1.1. Short-term Residential Exposures and Risks from Handling DGH Treated Paint (From Morales, J. J., D323607, 11/15/2005).									
Exposure Scenari	Unit Exposure (mg/lb ai)[a]		Amount Handled (gal/day)	Application Rate (lb ai/gal)[b]	Daily Dose (mg/kg/day)[c]		MOEs[d]		Total MOE[e]
	Dermal	Inhalation			Dermal	Inhalation	Dermal	Inhalation	
Applying paint with a paint brush	180	0.28	2	0.0035	0.018	0.000028	11,000	360,000	11,000
Applying paint with an airless sprayer	38	0.83	15	0.0035	0.029	0.00062	7,000	16,000	4,900
Applying paint with an aerosol can	190	1.3	0.28	0.0035	0.0027	0.000018	75,000	550,000	66,000

[a] UE = unit exposures for residential painters were derived from PHED Version 1.1, May 1997 "Best Available Grades" (PHED, 1977) wearing single layer of clothing and no gloves, body weight = 70 kg.

[b] Use rate was derived from maximum concentration listed on product labels. Labels 67869-43 and 67869-30 are 35% ai and list 0.1% product added to coating systems (paints and coatings as finished products). 0.0035 lb ai/gal = 0.1% product x 35% ai x 10 lb paint/gal (assumed paint density).

[c] Daily Dose (mg/kg/day) = UE (mg/lb ai) x Amt handled (gal/day) x Application Rate (lb ai/gal)/Body weight (kg).

[d] Short-term Dermal and Inhalation MOE = NOAEL (mg/kg/day)/Short-term dose (mg/kg/day). Dermal NOAEL = 200 mg/kg/day; Inhalation NOAEL = 10 mg/kg/day; Target dermal and inhalation MOE = 100.

[e] Total MOE = $1/[(1/MOE_{dermal} + 1/MOE_{inhalation})]$

6.2 Post-application Exposure

6.2.1 Dermal and Inhalation Postapplication Exposure to Paint

Post-application dermal contact with wet paint was not assessed because the paint is expected to dry within a day, so any potential exposure is expected to be negligible. Furthermore, DGH has a low vapor pressure (i.e., $<1x10^{-7}$ mmHg @25°C), therefore it is not likely to generate sufficient vapor to cause an inhalation concern to residential populations performing post-application tasks or occupying recently treated areas. Thus, there are no risk concerns and inhalation post-application exposures were not quantitatively evaluated.

6.2.2 Incidental Ingestion of Paint Chips

The incidental ingestion of paint chips from uses of DGH was assessed using the HED's Residential Standard Operating Procedures (SOP). Exposure is anticipated to be short-term in duration.

The HED level of concern is equal to a MOE of 100 for all residential uses. The short- term oral MOE is greater than 100 and therefore not of concern. This estimate may be somewhat underestimating the exposure since it is assumed that the percent of active ingredient in the wet paint is unchanged when it dries. Dry paint has a higher percent of active ingredient. Table 6.2.2 summarizes the short- term oral MOE for ingestion of paint chips containing pesticide residues by children.

Table 6.2.2: Postapplication Exposure and Risk Ingestion of Paint Chips

Scenario	IgR (G/day)	P [a]	F	CF1 (mg/g)	BW (kg)	PDR [b] (mg/kg/day)	MOE [c]
Paints and Coatings EPA Reg No.67896-43 and 678969-30	0.04	0.035	0.2	1,000	10	0.00028	93,000

a. % of ai in product is 35%; however, the % of ai in paint is 0.035% (35% x 0.1% product added to paint or coating = 0.035%)
b. PDR = potential dose rate = IgR x (P/100) x F x CF1 ÷BW (10 kg)
c. MOE = NOAEL (26 mg/kg/day)/PDR

6.2.3 Impregnated Disposable Diapers

DGH is also incorporated as a bacteriostat in the manufacturing of the absorbent material used in disposable diapers. AD assessed the residential dermal exposures and risks to infants (< 1 year old) who wear DGH-impregnated diapers. Since infants typically wear diapers on a continuous basis, short-, intermediate- and long-term exposure durations were assessed.

No data on leaching or migration data of DGH to skin of infants were provided to support this use, therefore all of the assumptions used for calculating the exposures in this assessment are based on the Agency's standard values. The application rate of 0.007 g ai/diaper is based on assuming that there is 10 g of absorbent fiber in each diaper which is treated with 0.2% product containing 35% ai (0.007 g ai/diaper = 10 g/diaper x 0.2% product x 35 % ai). It was also assumed that an infant (< 1 year old) wears 8 diapers per day.

For estimating the exposure of infants to DGH when used in diapers, AD used two transfer factors, 100 and 5%. A 100% transfer factor resulted in MOEs of concern for all exposure durations (MOE = 36). However, using a transfer factor of 5%, which is based on the default percent transfer factor for pesticide residues migrating from carpets to skin surfaces (Revisions to the Standard Operating Procedures (SOPs) for Residential Exposure Assessments; Policy 12; US EPA, 2001), the MOEs for all durations were greater than 100 and were not of concern (MOE = 714). In order to refine dermal exposure resulting from use of DGH-impregnated diapers and to fully answer the rate of migration of DGH to the skin of infants, AD indicated the need for an impregnated diaper migration study as confirmatory data to support the lower transfer factor assumption.

For purposes of refining the dermal exposure resulting from use of diapers impregnated with DGH and incorporating this use into an aggregate risk estimate (ie., dietary + drinking water + residential exposure) for the Dodine Human Health Risk Assessment, HED back calculated to determine what transfer factor would be required to reach an acceptable MOE of 120 (for purposes of aggregate risk since a MOE of 100 for diaper exposure alone will not be sufficient). The calculations determined that a 30% transfer factor would be required to result in an MOE of 120. The assumptions, resulting exposures, and MOEs are presented in Table 6.2.3.

HED believes that a transfer factor of 100% is an overestimate of exposure in determining the amount of DGH transferred to infants from diapers. Although using either 30 or 5 % transfer factors result in MOEs that are not of concern, HED has no means to confirm these estimates of exposure. Therefore, **HED concurs with AD's request for submission of an impregnated diaper migration study as confirmatory data.**

Table 6.2.3 Short-, Intermediate-, and Long-Term Residential Exposures and Risks from Infants Wearing DGH-impregnated Diapers

Details	Acronyms Used	No Confirmatory data needed	Confirmatory data needed	Confirmatory data needed
Application Rate (g ai/diaper) [a]	AR	0.007	0.007	0.007
Exposure Frequency (diapers/day)[b]	EF	8	8	8
Percent Transfer (%)[b]	TF	**100%**	**30%**	**5%**
Conversion factor (1000 mg/g)	CF	1000	1000	1000
Body Weight (kg) [b]	BW	10	10	10
Dermal Dose (ST/IT/LT) (mg/kg/day)[c]	ST/IT/LT PDD	5.6	1.68	0.28
ST, IT and LT MOE[d]		**36**	120	714

[a] The application rate of 0.007 g ai/diaper is based on assuming that there is 10 g of absorbent fiber in each diaper which is treated with 0.2% product containing 35% ai, 0.007 g ai/diaper = 10 g/diaper x 0.2% product x 35 % ai
[b] AD standard exposure assumption
[c] PDD (mg/kg/day) = AR (g ai/diaper) x EF (diapers/day) x TF (%) x CF (1000mg/g) / BW (10kg for child < 1 year old)
[d] MOE = NOAEL (mg/kg/day) / PDD (mg/kg/day) where ST/IT/LT dermal NOAEL = 200 mg/kg/day. ST/IT/LT Target MOEs = 100.

6.3 Residential Aggregate Risk

Because of the similarity between dodine and DGH, HED has considered the contribution of DGH residential uses to the overall aggregate assessment for dodine.

In evaluating residential uses, HED combines risk estimates resulting from separate exposure scenarios (i.e., oral, dermal, and inhalation) when it is likely they can occur simultaneously based on the use pattern and the behavior associated with exposed population. In an effort to facilitate an aggregate risk estimate for the Human Health Risk Assessment for dodine (dietary + drinking water + residential exposure) the residential exposure components (exposure to DGH from application of paint and impregnated diapers) have been identified and summarized in the following sections.

6.3.1 Short-term Aggregate Residential Exposure Risk

The short-term aggregate exposure for adults consists of combining adult dietary (food + drinking water) and both dermal and inhalation exposure as a result of handling paint. Of the three handler paint scenarios provided in Table 6.1.1, applying paint with an airless sprayer was the most conservative assessment, and therefore, it is used to represent adult residential exposure estimates for the overall human health aggregate risk assessment. Aggregate exposure for children consists of children's dietary (food + drinking water) and dermal exposure resulting from use of diapers since inhalation exposure is expected to be negligible. Although there is a potential for oral exposure to children from incidental ingestion of paint chips, HED does not believe that this would occur on a regular basis. Therefore, based on this professional judgment, HED did not include oral exposure due to ingestion of paint chips into the aggregate assessment for short-term exposure. The short-term residential MOEs to be used for the human health aggregate assessment are summarized in the Table 6.3.1.

Table 6.3.1: Short-term Residential Aggregate Risk

Scenario	MOE_{Dermal}	$MOE_{Inhalation}$	MOE_{Total} [c]
Adults			
Paint Products (Short-Term, Adults)	7,000 [a]	16,000 [a]	4,900
Children			
Disposable Diapers (Short-, Intermediate-, Long-Term, Infants) at **5%** Transfer factor	714 [b]	n/a	714
Disposable Diapers (Short-, Intermediate-, Long-Term, Infants) at **30%** Transfer factor	120 [b]	n/a	120
Disposable Diapers (Short-, Intermediate-, Long-Term, Infants) at **100%** Transfer factor	36 [b]	n/a	**36**

a. Paint dermal and Inhalation MOE are based on calculations for applying paint with sprayer scenario shown in Table 6.1.1. This scenario assumes worst case of all paint scenarios

b. Diaper dermal MOEs are based on calculations from Table 6.2.3.

c. $MOE_{TOTAL} = \frac{1}{\frac{1}{MOE_{DERMAL}} + \frac{1}{MOE_{INHAL}}}$

6.3.2 Intermediate- and Long-Term Aggregate Residential Exposure Risk

Intermediate- and long-term residential aggregate exposures (food + drinking water + intermediate- and long-term residential exposure) result only from infants wearing DGH-

impregnated diapers. Intermediate- and long-term exposures to DGH in paints are not anticipated for adult handlers. Since the intermediate- and long-term dermal exposures and endpoints are the same as the short-term dermal values the MOEs will be the same as those provided in Table 6.3.1. No additional calculations are required. Risk resulting from short-term aggregate exposure to wearing DGH-impregnated diapers is equivalent to the risk from intermediate- and long-term aggregate exposures.

7.0 Aggregate Risk Assessments and 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 exposure. 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 risk from various sources, HED considers both the route and duration of exposure.

7.1 Acute Aggregate Risk

No acute dietary endpoint was identified for dodine; therefore, an acute aggregate risk assessment was not conducted.

7.2 Short- and Intermediate Term Aggregate Risk

In determining short- and intermediate-term aggregate risks, HED examined the oral (i.e. dietary) and non-oral routes (i.e., dermal and inhalation) of exposure. Dietary (food + drinking water) exposure estimates are found in Table 5.2.2. Incidental oral exposure (ingestion of paint chips) was not aggregated as it is considered a non-routine event and not likely to occur on a regular basis. Residential handler exposure (i.e., non-oral routes of exposure) is expected to be short-term only and consisted of combined dermal and inhalation exposure as a result of handling paint. Short- and intermediate-term dermal exposure to children resulted from use of diapers impregnated with DGH. Inhalation exposure is expected to be negligible for the diaper scenario. The margins of exposures for residential exposure to adults and infants are provided in Table 6.3.1.

Table 7.2 provides a summary of the aggregate margins of exposure for adult and children subpopulations to dodine. Since the endpoints for all routes of exposure were based on the same toxicological effects, the following method was used to estimate exposure

$$MOE_{tot} = \frac{1}{\frac{1}{MOE_{ORAL}} + \frac{1}{MOE_{DERMAL}} + \frac{1}{MOE_{INHAL}}}$$

$$\text{Where, } MOE_X = \frac{NOAEL_X}{Exposure_X}$$

The aggregate risk for adult subpopulations resulted in MOEs > 100 and; therefore, are not of concern to HED. The aggregate risk for infants wearing impregnated diapers resulted in MOEs

ranging from 34 to 300. HED has no means to confirm these estimates of exposure for infant use of impregnated diapers. In order to refine dermal exposure resulting from use of DGH-impregnated diapers and to fully answer the rate of migration of DGH to the skin of infants, **HED recommends a conditional registration based on submission of an impregnated diaper migration study as confirmatory data.**

Table 7.2. Short-Term and Intermediate-Term Aggregate Risk Calculations *(intermediate-term for children only)*

Population	Short- and Intermediate-Term Scenarios					
	LOC for Aggregate Risk[1]	MOE food & water[2]	MOE oral[3]	MOE dermal[4]	MOE inhalation[5]	Aggregate MOE (food and residential)[6]
Adult Male, Handling Paint	100	59,000	N/A	7000	16,000	4500
Adult Female, Handling Paint	100	74,000	N/A	7000	16,000	4600
Child-DGH-impregnated diapers	100	6400	N/A	714	N/A	640
				120		120
				36		36

[1] Level of concern for all scenarios is 100 based on standard UF=100
[2] MOE food = [(short- or intermediate-term oral NOAEL)/(dietary exposure)] NOAEL= 26 mg/kg/day; Adult males (50+years)= 0.000441; Adult females (13-49)=0.000351; Children (1-2 years)= 0.004072 (Table 5.2.2).
[3] MOE oral =N/A=Not applicable
[4] MOE dermal =[(short- or intermediate-term dermal NOAEL)/(high-end dermal residential exposure)] Dermal NOAEL = 200 mg/kg/day; Dermal MOE = Adult males (50+years)/ females (13-49) =7000, Children; 714, 100, and 36 (Tables 6.1.1 and 6.2.3).
[5] MOE inhalation = [(inhalation NOAEL)/(high-end inhalation residential exposure)] Inhalation NOAEL (based on oral study) = 10 mg/kg/day; Inhalation MOEs: Adult males (50+years)/ females (13-49)=16000 (Table 6.1.1).
[6] Aggregate MOE (food and residential) = 1/[[(1/MOE food) + (1/MOE dermal) + (1/MOE inhalation)]

7.3 Long-Term Aggregate Risk

Long-term residential aggregate exposure results only from infants wearing DGH-impregnated diapers. Risk resulting from long-term aggregate exposure is shown in Table 7.3. As with short- and intermediate-term durations, MOE's are shown for three transfer factors used to assess exposure from diapers.

Table 7.3. Long-Term Aggregate Risk Calculations

Population	Long-Term Scenario					
	LOC for Aggregate Risk[1]	MOE food & water[2]	MOE oral[3]	MOE dermal[4]	MOE inhalation[5]	Aggregate MOE (food and residential)[6]
Child-DGH-impregnated diapers	100	500	N/A	714	N/A	300
				120		100

Table 7.3. Long-Term Aggregate Risk Calculations						
Population	Long-Term Scenario					
	LOC for Aggregate Risk[1]	MOE food & water[2]	MOE oral[3]	MOE dermal[4]	MOE inhalation[5]	Aggregate MOE (food and residential)[6]
				36		34

[1] Level of concern for all scenarios is 100 based on standard UF=100
[2] MOE food = [chronic dietary NOAEL)/(dietary exposure)] NOAEL= 2 mg/kg/day; Children (1-2 years)= 0.004072 (Table 5.2.2).
[3] MOE oral =N/A=Not applicable
[4] MOE dermal =[long-term dermal NOAEL)/(high-end dermal residential exposure)] Dermal NOAEL = 200mg/kg/day; Dermal MOE = Children; 714, 100, and 36 (Table 6.2.3).
[5] MOE inhalation =N/A=Not applicable
[6] Aggregate MOE (food and residential) = 1/[[(1/MOE food) + (1/MOE dermal)]

7.4 Cancer Risk

Exposure to dodine did not result in a treatment-related increase in tumor formation in rats and mice; therefore, a cancer risk assessment was not conducted.

8.0 Cumulative Risk Characterization/Assessment

Section 408(b)(2)(D)(v) of the FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information concerning the cumulative effects" of a particular pesticide's residues and "other substances that have a common mechanism of toxicity."

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 dodine and any other substances, and dodine does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, EPA has not assumed that dodine has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

9.0 Occupational Exposure/Risk Pathway

Dodine (n-dodecylguanidine acetate) is a fungicide registered for the control of certain fungal diseases on apples, cherries, peaches, pears, pecans, walnuts, strawberries, and ornamental trees. The petitioner is proposing a Section 3 registration for the use of dodine on bananas and peanuts. The proposed product, Syllit® FL Fungicide (EPA Reg. No. 55260-6), is formulated as a flowable concentrate (FlC), which contains 39.6 % dodine as the sole active ingredient (ai). Based on the proposed use pattern of Syllit® FL Fungicide on banana and peanut, handlers and post-application exposure is expected to be short- and intermediate-term in duration.

9.1 Short-and intermediate-Term Handler Risk

Based on the proposed use patterns of dodine on banana and peanut, the handlers would be subjected to short- and intermediate-term exposures. The intermediate-term exposures may result from multiple applications of dodine at intervals of 7-15 days on banana and at 10-14 days on peanut.

The label specifies a basic PPE for handlers (long sleeved shirt and long pants, socks, and shoes) plus chemical-resistant gloves made of waterproof material, protective eyewear, chemical-resistant headgear for overhead exposure, and a chemical-resistant apron when mixing or loading.

The petitioner has not submitted any product specific occupational exposure data; therefore, HED default values and PHED were used to estimate the exposures to pesticide handlers

Short-term Non-cancer Risks

HED's level of concern is equal to greater than a MOE of 100. Therefore, all MOEs greater than 100 are not of concern. Since the dermal and inhalation endpoints are based on the same effects, the dermal and inhalation exposures were added together to result in a Total MOE.

The exposure estimates indicate that the risks from all handler scenarios are not of concern (MOEs $\geq$ 100) at baseline (long-sleeve shirt, long pants, shoes, and socks), with two exceptions. The mixer/loader scenarios at baseline resulted in risks of concern (Dermal MOE=11 and 94). However, the addition of gloves resulted in MOEs that are not of concern (MOE > 100). Furthermore, since the label mandates use of rubber gloves for handlers under PPE; no additional mitigation language is required. Table 9.1 summarizes the short-term dermal and inhalation exposures and risks to handlers.

Table 9.1: Short and Intermediate-term Handler Exposure and Risk for Dodine									
Crop and Max. Rate/Appl.	Exposure Scenario	PPE [1]	Dermal Unit Exp. (mg/kg/day)	Inhalation Unit Exp. (µg/kg/day)	Dermal		Inhalation		Total MOE
					Dose (mg/kg/day) [2]	MOE [3]	Dose (mg/kg/day) [2]	MOE [3]	
Banana 1.3 lb ai/A. (350 A/day)	Mixer/loader, liquid, open mixing/loading for aerial application	Baseline	2.9	1.2	18.85	11	0.008	1,300	11
		Baseline + gloves	0.023	1.2	0.154	1,300	0.0078	1,300	650
	Applicator, liquid, aerial, fixed wing, enclosed cockpit	Baseline	0.005	0.068	0.0325	6,200	0.000442	23,000	5,000
	Flagger, liquid	Baseline	0.011	0.35	0.0715	2,800	0.00228	4,400	1,700
Peanut 0.64 lb ai/A. (80 A/day)	Mixer/loader, liquid, open mixing/loading for ground boom Appl.	Baseline	2.9	1.2	2.12	94	0.000878	11,000	93
		Baseline + gloves	0.023	1.2	0.0168	12,000	0.00878	11,000	5,700
	Applicator, liquid, ground boom, open cab	Baseline	0.014	0.74	0.01	20,000	0.00054	19,000	10,000

1. Baseline PPE consists of long-sleeved shirt, long pants, shoes with socks.
2. Dermal doses (mg/kg/day): [max. single appl. rate * acres treated/day * dermal unit exp.*] / body weight.
Inhalation dose (mg/kg/day): [max. single appl. rate * acres treated/day * inhal. unit exp.] / body weight.
3. Dermal MOE (short- and intermediate-term) = Dermal NOAEL (200 mg/kg/day) / Dermal dose (mg/kg/day),
4. Inhalation MOE (short- and intermediate-term) = Inhalation NOAEL (10 mg/kg/day) / Inhalation dose (mg/kg/day

9.2 Short-and Intermediate-Term Postapplication Risk

Based on the proposed use patterns of dodine on banana and peanut, the post-application workers would be subjected to short- and intermediate-term exposures. The intermediate-term exposures result from multiple applications of dodine at intervals of 7-15 days on banana and at 10-14 days on peanut.

The petitioner has not submitted a product specific post-application exposure study for calculating the risks to workers who may enter the treated field for weeding, scouting, harvesting, etc. Therefore, post-application worker exposures were estimated using default dermal transfer coefficients from the HED's ExpoSAC Policy No. 3.1.

It should be noted that there was no transfer coefficient data in Policy 3.1 for banana. Therefore, surrogate transfer coefficient values for bunch/bundle crop groups (i.e., hops and tobacco) were used to assess postapplication exposure and risk for bananas.

All postapplication MOE were greater than 100 and therefore are not of concern to HED.

Table 9.2: Short- and Intermediate-term Postapplication Risks to Workers Entering Fields Treated With Syllit® FL Fungicide.

Crops	Appl. Rate (lb ai/A)	Work Activity	Transfer Coefficients (cm2/hr) [1]	Dislodgeable foliar residue (µg/cm2) [2]	Dermal Dose/Day (mg/kg/day) [3]	MOE [4]
Banana (Bunch/ Bundle)	1.3	hand harvesting, weeding, scouting	100	2.92	0.033	6,000
		Hand harvesting, stripping, training	2000		.666	300
Peanut	0.64	irrigation, scouting	100	1.44	0.016	12,000
			1500		0.246	800

1. ExpoSAC SOP No. 3.1 (2000).
2. DFR = AR * F * $(1\text{-}D)^t$ * 4.54 E+8 * 2.47E-8
3. DD = (DFR * 0.001 mg/µg * TC * ET) / BW (70 kg)
4. Dermal MOE = Dermal NOAEL (200 mg/kg/day) / Dermal Dose.

Restricted Entry Interval

Dodine has moderate acute toxicity by oral, dermal, and inhalation routes (Categories III) and is not a skin sensitizer. However, it is a severe dermal and eye irritant (Toxicity Categories I). Chemicals classified as toxicity category 1 require a 48-hour REI in accordance with Worker Protection Standards (WPS). Therefore, HED concurs with the 48-hour REI on the proposed product label.

10.0 Data Needs and Label Requirements

10.1 Toxicology

None

10.2 Residue Chemistry

Directions for Use

- The proposed use on banana does not include a maximum seasonal rate. In addition, the crop field trial data from Hawaii do not reflect the proposed use pattern. The petitioner should modify the proposed label such that the use pattern on banana corresponds to the use pattern of the banana crop field trials: five applications at 0.71 lb ai/A/application, for a maximum seasonal rate of 3.6 lb ai/A, with a minimum retreatment interval of 6 days and a PHI of 0 days.

- The petitioner has indicated that the proposed tolerance for bananas is intended to apply to domestic bananas as well as imported bananas, but that the use directions for foreign countries have not yet been finalized. To allow HED to determine that the submitted crop field trial data adequately reflect the use of dodine on bananas in countries outside the U.S., when the use directions have been finalized, the petitioner should submit copies of product labels (with English translations, if needed) with use directions on bananas from all countries in which dodine is to be applied to bananas destined for import into the U.S. If the finalized use directions differ significantly from the use patterns of the submitted crop field trial data, additional data may be required.

Residue Analytical Methods

- Method METH1595.02 should be modified to remove the conversion of residue results to "dodine free base" (this calculation is made at the step in which standard solutions are prepared). Residue results must be calculated in terms of dodine, as N-dodecylguanidine acetate. In addition, the typographical error in step 9.3.7 of the method should be corrected ["Repeat steps 9.2.3 to 9.2.6 two more times" should be changed to "Repeat steps 9.3.3 to 9.3.6 two more times"].

Proposed Tolerances

- The proposed tolerance for peanut should be revised from 0.03 ppm to 0.013 ppm.

Confined Accumulation in Rotational Crops

- Confined rotational crop data are required to support the proposed use on peanuts. A confined rotational crop study was required in the Revised RED Chapter (DP# 320758, 9/14/05, D. Soderberg). These data remain outstanding. HED recommends the registration of the uses on peanuts be made conditional on the future submission of these data.

Field Accumulation in Rotational Crops

- The need for field rotational crop studies and/or rotational crop restrictions/tolerances will be determined when an adequate confined rotational crop study has been submitted.

10.3 Occupational and Residential Exposure

- HED recommends a conditional registration based on submission of an impregnated diaper migration study as confirmatory data.

References:

Corrections to Phase III –Revised as per 30-day Error Only Registrant Comments. Dodine: HED Chapter of the Reregistration Eligibility Decision (RED). D323607. 11/15/2005. J. Morales.

Dodine and Salts. Reregistration Eligibility Decision (RED). Summary of Analytical Chemistry and Residue Data. D314320. 9/14/05. D. Soderberg.

Dodine. Petition for Establishment of Permanent Tolerances for Residues of Dodine in/on Bananas and Peanuts. Summary of Analytical Chemistry and Residue Data. D338572, D342401. M. Doherty.

Dodine. Chronic Aggregate Dietary (Food and Drinking Water) Exposure and Risk Assessment for the Section 3 Registration on Banana and Peanut. D346911. M. Doherty.

Dodine: Occupational Exposure Assessment for the New Uses on Banana and Peanut. D338783. S. Oonnithan

Appendix A: Toxicology Assessment

A.1 Toxicology Data Requirements

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

Test	Technical	
	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 Oral Subchronic (rodent)	yes	yes*
870.3150 Oral Subchronic (nonrodent)	yes	yes**
870.3200 21-Day Dermal	yes	yes
870.3250 90-Day Dermal	no	-
870.3465 90-Day Inhalation	no	-
870.3700a Developmental Toxicity (rodent)	yes	yes
870.3700b Developmental Toxicity (nonrodent)	yes	yes
870.3800 Reproduction	yes	yes
870.4100a Chronic Toxicity (rodent)	yes	yes***
870.4100b Chronic Toxicity (nonrodent)	yes	yes
870.4200a Oncogenicity (rat)	yes	yes
870.4200b Oncogenicity (mouse)	yes	yes
870.4300 Chronic/Oncogenicity	yes	yes
870.5100 Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300 Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5375 Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5385 Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a Acute Delayed Neurotox. (hen)	no	-
870.6100b 90-Day Neurotoxicity (hen)	no	-
870.6200a Acute Neurotox. Screening Battery (rat)	no	-
870.6200b 90 Day Neuro. Screening Battery (rat)	no	-
870.6300 Develop. Neuro	no	-
870.7485 General Metabolism	yes	yes
870.7600 Dermal Penetration	no	-
Special Studies for Ocular Effects		
Acute Oral (rat)	no	-
Subchronic Oral (rat)	no	-
Six-month Oral (dog)	no	-

*Satisfied by the chronic (rodent) toxicity study-guideline 870.4100a
**Satisfied by the chronic (nonrodent) toxicity study-guideline 870.4100b
***Satisfied by the chronic/oncogenicity study-guideline 870.4300

A.2 Toxicity Profiles

Table A.2.1 Acute Toxicity Profile - Dodine				
Guideline No.	**Study Type**	**MRID(s)**	**Results**	**Toxicity Category**
870.1100	Acute oral [rat]	00124280	LC_{50} males =1931 mg/kg LC_{50} females =1171 mg/kg LC_{50} combined =1456 mg/kg	III
870.1200	Acute dermal [rabbit]	00124280	LD_{50} >2000 mg/kg	III
870.1300	Acute inhalation [rat]	00157300	LC_{50} = 1.05 mg/kg	III
870.2400	Acute eye irritation [rabbit]	00124280	Severe	I
870.2500	Primary dermal irritation [rabbit]	00124280	Primary Dermal Irritation Index, PDII - 7.5	I
870.2600	Skin sensitization [human]	00157386	Negative	Neg

Table A.2.2. Subchronic, Chronic and Other Toxicity Profile for Dodine		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.3100 90-Day oral toxicity (rat)		Satisfied by chronic toxicity study in rats- MRID 44704401
870.3100 90-Day oral toxicity (mouse)		NOAEL = 350/305 mg/kg/day (M/F) LOAEL = 181/223 mg/kg/day (M/F) Based on increased mortality and clinical signs of toxicity (stiffening of the tail) in females, and decreased body weights, body weight gains, and food consumption in both sexes.
870.3200 21/28- Day dermal toxicity (rat)	46420701(1998) Acceptable/guideline M&F: 0, 50, 125, 200 mg/kg/day	**Systemic** NOAEL = ≥200 mg/kg/day LOAEL = not identified* **Dermal** NOAEL = not identified LOAEL = 50 mg/kg/day based on dermal irritation. Based on the weight of evidence, the risk assessment team anticipates that increasing dermal doses above 200 mg/kg/day would result in minimal systemic toxicity (i.e. body weight effects; see section 4.4.6).
870.3700a Prenatal developmental (rat)	41900304 (1989) Acceptable/guideline F: 0, 10, 45 or 90 mg/kg/day (GD 6-16)	**Maternal** NOAEL = 10 mg/kg/day LOAEL = 45 mg/kg/day based on decreased body weight gain and food consumption. **Developmental** NOAEL = ≥90 mg/kg/day LOAEL = not identified
870.3700b Prenatal developmental in (rabbit)	41900303 (1989) Acceptable/Non-guideline 0, 10, 40 or 80 mg/kg/day (GD 6-18)	**Maternal** NOAEL = 80 mg/kg/day LOAEL = not identified. **Developmental** NOAEL = ≥80 mg/kg/day LOAEL = not identified.
870.3800 Reproduction and fertility effects (rat)	44246001(1996) Acceptable/guideline 0, 200, 400 or 800 ppm 0, 13, 26 or 53 mg/kg/day	**Parental/Systemic** NOAEL = 26 mg/kg/day LOAEL = 53 mg/kg/day based on decreased body weight, body weight gain and food consumption. **Reproductive** NOAEL = ≥53 mg/kg/day LOAEL = not identified. **Offspring:** NOAEL = 26 mg/kg/day LOAEL = 53 mg/kg/day based on decreased pup body weights.
870.4100b Chronic toxicity (dog)	44246101 (1996) Acceptable/guideline M&F: 0, 2, 10, or 20 mg/kg/day	NOAEL = 10/2 mg/kg/day (M/F) LOAEL = 20/10 mg/kg/day based on decreased food consumption/decreased weight gain. (M/F)

Table A.2.2. Subchronic, Chronic and Other Toxicity Profile for Dodine		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.4200 Carcinogenicity (mouse)	44703201(1998) Acceptable/guideline 0, 200, 750 or 1500 ppm M: 0, 29, 110, 225 mg/kg/day F: 0, 38, 136, 277 mg/kg/day	NOAEL = 110/38 mg/kg/day (M/F) LOAEL = 225/136 mg/kg/day based on decreased body weight, body weight gain and food consumption. (M/F) **No evidence of carcinogenicity.**
870.4300 Chronic/ Carcinogenicity (rat)	44704401 (1998) Acceptable/guideline 0, 200, 400 or 800 ppm M: 0, 10, 20, 42 mg/kg/day F: 0, 13, 27, 54 mg/kg/day	NOAEL = 20 mg/kg/day LOAEL = M: 42 mg/kg/day based on decreased body weight gain; F: 54 mg/kg/day based on decreased body weight and food consumption. **No evidence of carcinogenicity.**
870.5100 Bacterial reverse mutation test	40315504 Acceptable/Guideline	No evidence of an increase in revertants in any strain, with or without activation up to a dose of 50 µg/mL.
870.5300 Gene Mutation (CHO)	41711002 (1985) Acceptable/guideline	No biologically significant increase in the number of mutant colonies over background. Dosed up to 35.0 µg/mL with S9-mix and 20.0 µg/mL without.
870.5375 Cytogenetics- Human Lymphocytes chromosome aberration test	41711001 (1985) Acceptable/guideline	No evidence of chromosomal aberrations induced when dosed with up to 15.0 µg/mL with and 10.0 µg/mL without metabolic activation.
870.5385 Mammalian bone marrow chromosomal aberration test (mouse)	42311601 (1992) Acceptable/guideline	Negative in genotoxic effects in male and female mice treated with a single oral dose of up to 400 mg/kg.
870.6200a Acute neurotoxicity screening battery	Not available	N/A
870.6200b Subchronic neurotoxicity screening battery	Not available	N/A

Table A.2.2. Subchronic, Chronic and Other Toxicity Profile for Dodine		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.7485 Metabolism and pharmacokinetics (rat)	42479001 (1992) Acceptable/guideline Single dose of 40 or 400 mg/kg ^{14}C-labeled dodine 40 mg/kg/day non-labeled dodine x 14 days with single dose of 40 mg/kg ^{14}C-labeled	Rapid absorption, metabolism, distribution, and excretion; major excretion routes are urine and feces. Major metabolite found in urine was a dodine alcohol, hydroxydodecylguanidine; parent compound found in feces. Proposed metabolic pathway was ß-oxidation pathway.

A.3a Executive Summaries

A.3.1 Subchronic Toxicity

870.3100 Subchronic Oral Toxicity Study-Mouse

EXECUTIVE SUMMARY: In a subchronic oral toxicity study (MRIDs 46585001 and 46544401), dodecylguanidine acetate (Dodine; 94.07% a.i.; Batch # APA batch 303/90) was administered to 10 Swiss
CR1:CD$_R$-1 (ICR)BR mice/sex/dose in the diet at dose levels of 0, 150, 300, 600, 1250 or 2500 ppm (equivalent
to 0/0, 24/31, 48/60, 94/116, 181/223, and 350/305 mg/kg/day in males/females) for 13 weeks.

No treatment-related effects were observed on food consumption ratios, ophthalmoscopy, hematology, clinical
chemistry, organ weights, gross pathology, or histopathology. At 2500 ppm, treatment-related deaths were observed in 4/10 of the females. During the first two weeks of treatment, three females were sacrificed *in extremis* on Days 7, 8, and 14 and one female was found dead on Day 6. Stiffening of the tail was noted in 4/10 females (including the 3 females that were sacrificed) beginning on day 7 of treatment and lasting until week 3 or until death. This observation was considered to be treatment related and was not present in the remaining groups. Decreased (p#0.05) body weights were observed in the males (917-24%, Weeks 1-13) and females (910-15%, Weeks 1-2 and 6-10) resulting in decreased (p#0.01) body weight gains in both (males968% and females944%) sexes. Decreases (not statistically significant [NS]) of 30% - 46% in mean food consumption for the 13-week treatment period were also observed in both sexes. Decreases (NS) of 11% -12% in food consumption was the only finding observed in the 1200 ppm group.

The LOAEL is 2500 ppm (equivalent to 350/305 mg/kg/day M/F), based on increased mortality and clinical signs of toxicity (stiffening of the tail) in females, and decreased body weights, body weight gains, and food consumption in both sexes. The NOAEL is 1250 ppm (equivalent to 181/223 mg/kg/day M/F).

This study is classified as **acceptable/guideline.** It satisfies the guideline requirement for a subchronic oral toxicity study (OPPTS 870.3100; OECD 410) in mice.

870.3200.1 28-Day Dermal Toxicity Study-Rat

EXECUTIVE SUMMARY: In a 28-day dermal toxicity study (MRID 46420701), dodine (98%, a.i., Lot No. OP750142) was applied to the shaved skin of ten Crl:CD IGS (SD)BR rats/sex/dose at concentrations of 0 (deionized water), 50, 125, or 200 mg/kg/day, 6 hours/day, 5 days/week for 4 consecutive weeks. A non-GLP pilot study was conducted for dose determination.

There were no treatment-related deaths or clinical signs of systemic toxicity in the rats. No effects on body weight, food consumption, hematology, clinical chemistry, urinalysis, ophthalmological examination, or organ weight were observed in either treated or control animals. Gross and histopathological lesions observed were related only to dermal irritation.

Based on the results of this study, the systemic LOAEL for dodine in male and female rats can not be identified, and the systemic NOAEL is 200 mg/kg/day.

Evidence of dermal irritation was observed in all of the treated animals, but not in controls. The females were more affected than males. The Draize scoring criteria used for erythema and edema in the rats ranged from none to severe for erythema and none to slight for edema. Only one male and female had a severe erythemic lesion in the low-dose group and a slight dose related increase in severity of lesions in mid- and high-dose groups was observed. For the entire study, erythema in males was observed in 0/10, 5/10, 10/10 and 9/10 males in the control, 50, 125 and 200 mg/kg/day groups, respectively; edema was observed in 0/10, 2/10, 9/10 and 8/10 males in the control, 50, 125, and 200 mg/kg/day groups, respectively. Erythema in females was observed in all treated groups, and edema throughout the study was observed in 0/10, 3/10, 10/10, and 10/10 females in the controls, 50, 125 and 200 mg/kg/day groups, respectively.

Gross pathology and histopathology were limited to the dermal lesions. Scabbing was the predominant gross lesion and was identified in all dose groups. Histopathology in the mid- and high-dose groups included ulcers, suppurative inflammation, hyperkeratosis, epidermal hyperplasia, subacute inflammation and parakeratosis. Minimal exudate and parakeratosis was the only histopathological lesion identified in one low-dose female.

Based on the results of this study, the dermal LOAEL for dodine in male and female rats is 50 mg/kg/day, and the dermal NOAEL is not identified.

This 28-day dermal toxicity study in rats is **Acceptable/Guideline.** It satisfies the guideline requirements for a 28-day dermal toxicity study (OPPTS 870.3200; OECD 410) in rats.

A.3.2 Prenatal Developmental Toxicity

870.7600870.3700 Developmental Toxicity Study- Rat

EXECUTIVE SUMMARY: In a prenatal developmental toxicity study (MRID 41900304), dodine (Lot No. 92/88/2) was administered to 25 pregnant Sprague-Dawley rats per dose by oral intubation at doses of 0, 10, 45, or 90 mg/kg/day on gestation days 6 through 16. Animals were dosed with 10 mL of suspension (dodine and distilled water) per kg body weight. Day 0 of gestation was based on the presence of a copulatory plug or the presence of sperm in a vaginal lavage. On gestation day 20, cesarean sections were performed on all pregnant rats. The uteruses were weighed, and the following reproductive parameters examined: number of corpora lutea, implantation sites, live/dead fetuses, early/late resorptions and fetal weights. One-half of the fetuses were further examined for visceral and skeletal abnormalities and the other-half examined for soft-tissue abnormalities.

No mortality occurred in any group. The clinical sign of excessive salivation was noted in 3/25 rats in the 90 mg/kg/day group on two treatment days. Rats in the 90 mg/kg/day group exhibited a non-significant decrease in mean body weight gain on gestation days 6-9. In the 45 mg/kg/day group, weight gain was 57% of the control level on gestation days 6-9. By gestation day 9, weight gain was similar in all groups. Food consumption decreased during gestation days 6-10 in the 90 mg/kg/day group (70 % of controls) and slightly less in the 45 mg/kg/day group (86% of controls) but again was similar among all groups after day 10. During gestation days 6-10, the number of rats consuming less than 20 grams of food was 1/22 (4.5%) of controls, 2/21 (9.5%) low-, 9/23 (39%) mid- and 16/24 (67%) high-dose. Upon necropsy, visual examination of the dams' abdominal and thoracic cavity showed no abnormalities. No statistically significant abnormalities were recorded in any of the reproductive parameters.

The lowest-observed-adverse-effect-level (LOAEL) for maternal toxicity for dodine in rats is 45 mg/kg/day based on decreased body weight gain and food consumption. The no-observed-adverse-effect-level (NOAEL) for maternal toxicity is 10 mg/kg/day.

No treatment-related external, visceral or skeletal malformations/variations were observed in any fetus. Fetal body weights were similar among control and treated groups.

The NOAEL for developmental toxicity of dodine in rat is 90 mg/kg/day and the LOAEL can not be determined from this study.

This study is **Acceptable/Guideline** and does satisfy the requirements for a developmental study in rats. [OPPTS 870.3700(§83-3A)].

870.3700 Developmental Toxicity Study-Rabbit

EXECUTIVE SUMMARY: In a prenatal developmental toxicity study (MRID 41900303), dodine (Lot No. 92/88/2) was administered to pregnant New Zealand White rabbits by oral intubation at doses of 0, 10, 40, or 80 mg/kg/day on gestation days 6 through 18. Sixteen animals were in the 0, 10 and 40 mg/kg/day groups; twenty were in the 80 mg/kg/day group. Animals were dosed with a volume of 4 mL/kg of suspension (dodine and distilled water). Animals arrived to the study facility pregnant. Doses were based on a previous study (Project No. 437724) but no details were provided. On day 29 of gestation, cesarean sections were performed on all pregnant rabbits. The uteruses were weighed and the following reproductive parameters examined: number of corpora lutea, implantation sites, live/dead fetuses, early/late resorptions and fetal weights. Two-thirds of the fetuses were further examined for visceral and skeletal abnormalities and one-third prepared for whole-body dissection.

Some mortalities and abortions did occur. During dosing, three does died or were sacrificed due to dosing errors. Another doe in the high-dose group was sacrificed due to poor condition. One doe each aborted in the control and low-dose group and two aborted in the high dose group. Neither the deaths nor abortions can be definitively seen as treatment-related. No definitive treatment-related body weight or body weight gain was recorded in the does. Food consumption was decreased during gestation days 6-18 in the 80 mg/kg group. The amount consumed was 77% of the control level. This trend reversed post-dosing. Visual examination of the does' abdominal and thoracic cavity showed no abnormalities and no statistically significant abnormalities were recorded in any of the reproductive parameters.

The lowest-observed-adverse-effect-level (LOAEL) for maternal toxicity in rabbits for dodine cannot be determined. A decrease in food consumption with no effect on body weight does not make this dose level conclusive enough to set a LOAEL. The no-observed adverse-effect-level (NOAEL) for maternal toxicity is 80 mg/kg/day.

No treatment-related malformations/variations were recorded in the external, visceral or gross soft-tissue observations in any fetus. Fetal body weights were comparable between controls and treated animals.

The LOAEL can not be determined from this study. The NOAEL for developmental toxicity of dodine in rabbits is 80 mg/kg/day.

This study is **Acceptable/Non-Guideline** and does satisfy the requirements for a developmental study in rabbits. [OPPTS 870.3700b (§83-3B)]. Although a definitive LOAEL for maternal toxicity was not established, the rat (most sensitive species) prenatal developmental study will be protective for all effects (MRID 41900304). Data

870.7601870.3800 Multi-generation Reproduction Study - Rat

EXECUTIVE SUMMARY: In a two-generation reproduction toxicity study, dodine was administered to male and female rats at nominal dietary concentrations of 0, 200, 400 or 800 ppm. This corresponded to 0, 13, 26 or 53 mg/kg/day. The P animals began exposures at 7 weeks and F_1 animals began exposures at post-natal day (PND) 21; all parental animals were exposed for approximately 10 weeks prior to mating. Reproductive performance was not affected in any generation. Parental toxicity was exhibited by a decrease in body weight, body weight gain or food consumption for the high-dose P and F_1 males and females. High-dose P males and females exhibited decreased body weight gain during premating/mating that was statistically significant. Mean body weight in P animals was lower than controls throughout the study but was not of toxicological concern. Food consumption in high-dose P animals, while slightly decreased at first, was similar to controls by week 5 during pre-mating. Food consumption decreased in P females during lactation; however, mean body weight gain was increased in P females when compared to controls at lactation days14-21.

The parental systemic LOAEL is 800 ppm (53 mg/kg/day) based on decreased body weight, body weight gain, and food consumption. The parental systemic NOAEL is 400 ppm (26 mg/kg/day).

In high-dose F_1 males, decreased body weight, body weight gain and food consumption occurred starting on week one and was consistently lower than controls. In high-dose F_1 females, body weight was consistently lower than controls throughout the study. Body weight gain in high-dose F_1 females decreased when compared to controls during premating, mating and gestation periods, stabilized at lactation days 0-14 and then increased during lactation days 14-21. Food consumption was consistently lower than controls during the study in high-dose F_1 females.

The reproductive toxicity NOAEL is 800 ppm (53 mg/kg/day) and the reproductive toxicity LOAEL was not identified.

Offspring body weight was decreased at the highest dose beginning as early as PND 4. F_1 males and females in the high-dose group showed decreased body weight ($p < 0.05$ or 0.01) during PND 4-21

and were decreased by 7-17% in males and 9-17% in females. F_2 pup body weight was also decreased ($p < 0.01$) by 8-17% in high-dose males at PND 4-21 and high-dose females by 9-18% at PND 7-21. Total body weight gain was also decreased for all F_1 and F_2 pups during PND 0-21. The lower body weight, decreased body weight gain and decreased food consumption for adults at the beginning of premating is a continuation of the preweaning effects.

The offspring toxicity LOAEL is 800 ppm (53 mg/kg/day) based on decreased pup body weights. The offspring toxicity NOAEL is 400 ppm (26 mg/kg/day).

This study is **Acceptable/Guideline** and does satisfy the requirements for a developmental study in rats. [OPPTS 870.3800(§83-4)].

A.3.4 Chronic Toxicity

870.4100 ChronicToxicity-Dog

EXECUTIVE SUMMARY: In a chronic toxicity study (MRID 44246101), Dodine (98.6% a.i., Batch No. 1174) was administered to 4 beagle dogs/sex/group in a gelatin capsule at doses of 0, 2, 10, and 20 mg/kg/day. The capsules were administered orally once a day, 7 days/week, for at least 52 weeks. All animals survived to terminal sacrifice. There were no dose- or treatment-related differences in hematology, clinical chemistry, urinalyses, ophthalmoscopic examinations, organ weights, or gross- or histopathology in either sex.

Slight to severe salivation was observed in all mid- and high-dose males and females but not in the low-dose or control animals. Salivation was seen most often prior to dosing, was a persistent finding during the study, and was first noted in mid-dose males during week 10, in mid-dose females and high-dose males during week 3, and in high-dose females during week 2. The frequency and severity were greater in females than in males.

No statistically significant differences were observed for group mean values in absolute body weights, overall weight changes, food consumption, or food efficiency between the treated and control groups of either sex. However, one mid-dose female, one high-dose female, and one high-dose male dog exhibited marked weight losses due to reduced food consumption during the first few weeks of the study. Supplemental feeding of basal diet mixed with water and/or canned dog food was initiated during weeks 2 or 3 to promote eating by these animals and to prevent further weight loss. The mid-dose female and the high-dose male were returned to the basal diet starting at weeks 15 and 8, respectively. The high-dose female required supplemental feeding throughout most of the study to prevent continued weight loss.

Therefore, the LOAEL for female beagle dogs is 10 mg/kg/day based on body weight loss by individual animals and the NOAEL for female beagle dogs is 2 mg/kg/day. The LOAEL for male beagle dogs is 20 mg/kg/day based on body weight loss by an individual animal and the NOAEL for male beagle dogs is 10 mg/kg/day.

This study is classified as **Acceptable /Guideline** and satisfies the requirements for a chronic toxicity study in dogs [870.4100b(§83-1)].

A.3.5 Carcinogenicity

870.4200a Combined Chronic/Carcinogenicity Study – Rat

EXECUTIVE SUMMARY: In a combined chronic toxicity/carcinogenicity study (MRID 44704401), dodine (98.6% a.i., Lot No. 1174) was administered continuously in the diet to 60 Sprague-Dawley rats/sex/dose at concentrations levels of 0, 200, 400 or 800 ppm for up to 106 weeks. Concentrations were equivalent to 0, 10.17, 20.34 or 41.93 mg/kg/day in males and 0, 13.19, 26.46 or 53.50 mg/kg/day in females, respectively. In addition, 10 animals/sex/dose were terminated at 53 weeks for interim evaluation. Doses were based on a previous toxicity studies (28-day dietary toxicity and 28-day oral gavage toxicity study) and consultation with the U.S. EPA.

No treatment-related differences in mortality were noted between control and treated groups during the study. Male rats exhibited some clinical signs in controls, low-, mid- and high-dose including: no righting reflex in 0, 1, 2, 3 and 4, respectively; hunched posture in 1, 2, 4 and 7, respectively and absence of grasping reflex in 2, 4, 4 and 8, respectively. No dose-related trends were seen in females.

High-dose male rats had a decrease in body weight ($p \leq 0.01$) when compared to controls during weeks 1-25 but these decreases were ≤ 8%. High-dose males showed decreases in body weight gain in week 1 of 20%, weeks 1-8 of 7% and weeks 8-25 of 18% compared to controls. High-dose males gained more weight than controls during weeks 25-53 but decreased again during the first six months of the second year (-18%). Food consumption was decreased slightly (-3 to 7%) in high-dose males compared to controls during the first year but was comparable during year two. No difference in food efficiency at any dose level was observed.

High-dose female rats consistently had lower body weight throughout the study compared to controls. Decreases ranged from 4% at week 1 to16% by week 101. Body weight gain in high-dose females decreased compared to controls 25% in week 1, 13% in weeks 1-25, 15% in weeks 25-53 and 34% in weeks 53-77. Total body weight gain in high-dose females decreased 22% over the 101 weeks. Females in the high-dose group had decreases in food consumption at the following time points compared to controls ($p \leq 0.05$ or 0.01): 4% at week 10, 8% at week 49, 13% at week 77 and 16% at week 97. Feed efficiency for the 101 weeks in females compared to controls decreased by 24% in the mid-dose and 18% in the high-dose group indicating a lack of a dose-related trend.

No treatment-related differences between treated and control groups were observed for ophthalmic or urinalysis parameters. Differences in hematological and clinical chemistry values were noted but were not dose-dependent, were transient or were due to high control values thus making them not of toxicological concern.

At the interim necropsy, no differences in organ weights of toxicological concern were in treatment groups compared to controls. At termination, relative liver (to brain) weight was lower (-10%, $p \leq 0.05$) in high-dose males than in controls, but no corresponding histopathological lesions were reported. An increase in absolute and relative (to body) epididymis weights (6-12%, $p \leq 0.05$ or 0.01) in mid- and high-dose males, and an increase in relative (to body) brain weight (12-14%) in mid- and high-dose females, were observed, but they were not dose-dependent.

No treatment-related gross pathological abnormalities were found in either the control or treated groups at the interim necropsy. The only finding at the termination necropsy was a non-dose dependent increase in the number of high-dose females with enlarged adrenal glands (13/36 high-dose vs 8/37 control) and/or white mottled (12/36 high-dose vs. 3/37 controls) adrenal glands. No corresponding histopathological lesions were identified.

The lowest-observed-adverse-effect-level (LOAEL) for chronic toxicity in male and female rats for dodine is 800 ppm (41.93/53.50 mg/kg/day, M/F) based on treatment-related decreased body weights and food consumption in females and a decreased body weight gain in males. The no-observed-adverse-effect-level (NOAEL) in males and females is 400 ppm (20.34/26.46 mg/kg/day, M/F).

Treatment-related neoplastic lesions were not observed in any dose groups in males or female rats at the interim or final sacrifice. Evidence of carcinogenicity is not observed in rats.

This study is **Acceptable/Guideline** and does satisfy the requirements for a chronic toxicity/carcinogenicity study in rats [OPPTS 870.4300 (§83.5)].

870.4200b Carcinogenicity (feeding) – Mouse

EXECUTIVE SUMMARY: In a mouse oncogenicity study (MRID 44703201), dodine (98.6% a.i., Lot No. 1174) was administered in the diet to 60 Crl:CD-1 (ICR) BR mice/sex/dose at concentrations of 0, 200, 750 or 1500 ppm for up to 78 weeks. Concentrations were equivalent to 0, 29, 110 or 225 mg/kg/day in male mice and 0, 38, 136 or 277 mg/kg/day in female mice, respectively. An additional 10 animals/sex/group were terminated at 53 weeks for interim evaluation. Doses were based on a previous 90-Day range-finding study and U.S. EPA consultation; details about the previous study were included in the rat chronic toxicity/carcinogenicity study, MRID 44704401.

No increases in mortality were observed in either sex of any group, treated or control. An increased incidence in clinical signs of body tremors and excessive salivation were observed in both mid- and high-dose male and female mice but the increases were not dose-related.

Body weight of high-dose males was consistently decreased ($p \leq 0.05$) compared to controls throughout the study, 3% by week 2, 8% by week 13, 10% by week 54 and 9% at week 78. Sporadic statistical decreases observed in low-and mid-dose males were not toxicologically significant ($p \leq 0.05$). Mid- and high-dose female body weight was also decreased ($p \leq 0.05$). Mid-dose weight decreased 4, 9 and 10% compared to controls at week 13, 58 and 78, respectively. High-dose female body weight was decreased compared to controls by 4% at week 9 and progressed up to a 14% decrease by the end of the study.

High-dose males mean weight gain decreased ($p \leq 0.05$) by 32 % compared to controls in weeks 1-7, 25% in weeks 1-14 and 26% in weeks 14-54 but did become comparable to controls during weeks 54-78. Overall, the high-dose males had a decrease in weight gain of 26% from weeks 1-78 compared to controls. Mid-dose females had a progressive decrease in weight gain compared to controls. These decreases were 10% at week 14, 23% for week 14-54 and 37% for week 54-78 with total weight gain in mid-dose females decreasing by 20% compared to controls. Weight gain in the high-dose females was consistently lower than controls throughout the study. These decreases were 26% from week 1-14, 36% from week 14-54, and 63% from week 54-78. Overall high-dose females' weight gain decreased 35% compared to controls.

Food consumption in high-dose males decreased ($p \leq 0.05$) by 16%, compared to controls, during week 1 and although was always lower than controls improved to a decrease of 5% by week 49. Mid-dose and high-dose females had consistent decreases of food consumption compared to controls during the entire study. During the first two weeks, mid-dose female food consumption decreased from 10 to 16% and high-dose was 13%. For the rest of the first year, the decreases remained between

6-7% for mid-dose females and 5-11% for high-dose compared to controls. During the second year, mid-dose females' food consumption remained decreased between 6-10%; high-dose female food consumption progressively decreased from 11 to 19% between weeks 53 and 77. Overall food efficiencies (% body weight gain/food consumption) were 2.00, 1.97, 1.97 and 1.58 for controls, low-, mid- and high-dose males and 1.96, 1.89, 1.64 and 1.19 for control, low-, mid- and high-dose females. This resulted in a food efficiency decrease of 21% in high-dose males and 39% in high-dose females compared to controls.

In this study, ophthalmic exam, urinalysis, clinical chemistries or differential leukocyte counts were not performed. Differential counts were not performed based on the lack of evidence of hematopoietic neoplasia in the histopathological exam and the other parameters were not required under the guidelines accepted at the time the study was conducted.

At the interim sacrifice (53 weeks), high-dose females had an non-toxicologically significant increase ($p \leq 0.05$) in relative (to body and brain) kidney weight compared to controls, but no corresponding histopathological lesions were identified. At the terminal necropsy, high-dose females had an increase in right and left absolute kidney weight. Mid- and high-dose females also had an increase in relative (to body) kidney weight and a decrease in relative (to brain) adrenal weight but again no corresponding histopathological lesions were identified. Females showed a decrease in mid- and high-dose groups in absolute brain weight, and both high-dose males and females exhibited increased ($p \leq 0.05$) liver/gallbladder relative (to body) weight by 12-13 % compared to controls.

The lowest-observed-adverse-effect-level (LOAEL) for chronic toxicity for dodine in mice is 750 ppm (136 mg/kg/day) for females and 1500 ppm (225 mg/kg/day) for males based on treatment-related decreased body weight, body weight gain and food consumption. The no-observed-adverse-effect-level (NOAEL) is 200 ppm (38 mg/kg/day) for females and 750 ppm (110 mg/kg/day) for males.

At the doses tested, there was no statistical increase in the incidence of neoplastic lesions in male mice at any site. There is some evidence of potential carcinogenicity in high-dose female mice based on the increase incidence ($p \leq 0.05$) of hepatocellular adenoma and combined hepatocellular adenoma/carcinoma. The incidence of adenomas in high dose females were 0/60, 1/58, 1/59 and 4/60 and rates for carcinomas were 0/60, 1/58, 0/59 and 1/60 in control, low-, mid- and high-dose groups, respectively. Incidence rates for the combined adenoma/carcinomas in this group were 0/60 in controls, 2/58 in low-, 1/59 in mid- and 5/60 high-dose females. The incidence of combined adenoma/carcinoma for the high-dose females is statistically significant ($p \leq 0.05$) but only marginally higher than the upper range for historical control (8.3% vs 1-8% in the historical controls for Charles River).

This study is **Acceptable/Guideline** and does satisfy the requirements for a carcinogenicity study in mice [OPPTS 870.4300 (§83-2(b)]. No evidence of carcinogenicity.

A.3.6 Mutagenicity

870.5300 *In Vitro* Mammalian Cell Gene Mutation Test

EXECUTIVE SUMMARY: In a mammalian cell gene mutation assay at the HGPRT locus (MRID 41711002), Chinese hamster ovary CHO-K1 cells cultured *in vitro* were exposed to Dodine (Batch No. KG 8507, 98% a.i.) in ethanol for five hours at concentrations of 0.0, 2.5, 5.0, 10.0, 15.0 or 20.0

μg/mL in the absence of metabolic activation (S9-mix) and at concentrations of 0.0, 5.0, 10.0, 15.0, 20.0, 25.0, 30.0 or 35.0 μg/mL in the presence of S9-mix. Cell survival was determined 22 hours post-treatment. Following the expression period, the frequency of 6-thioguanine mutants, expressed as mutant/10^6 clonable cells, was determined. The S9-fraction was obtained from rat liver; however, the strain, sex and inducer were not specified.

Dodine was tested up to cytotoxic concentrations. Cell survival was too low to evaluate mutagenicity at the upper concentration both with and without S9-mix. There were no statistically significant increases in the average mutation frequency (mutants per 10^6 surviving cells) over the solvent control values at any test material concentration without S9-mix in either assay. In the presence of S9-mix, a statistically significant increase in mutant frequency was seen at 125 μg/mL in the initial assay, but not at higher concentrations and not at any concentration in the repeat assay. Although statistically significant, the increase in mutant frequency was within the solvent control range and lower than the solvent control value in the repeat assay; therefore, it was not considered biologically significant. The solvent control and the positive controls (Ethyl methanesulfonate without S9-mix and dimethylnitrosamine with S9-mix) induced the appropriate responses. There was no biologically significant increase in the number of mutant colonies over background with or without S9-mix.

This study is classified as **Acceptable/Guideline** and does satisfy the requirement for *in vitro* mutagenicity (mammalian forward gene mutation) data [OPPTS 870.5300, OECD 476].

COMPLIANCE: Signed and dated GLP and Quality Assurance statements were provided but the DER used to prepare this executive summary did not report the presence of a Data Confidentiality statement.

870.5375 *In Vitro* Mammalian Chromosome Aberration Test

EXECUTIVE SUMMARY: In a mammalian cell cytogenetics assay (Chromosome aberrations) (MRID 41711001), human lymphocytes in culture were exposed to Dodine (Lot No. KG 8507, 98% a.i.) in ethanol for 24 hours at concentrations of 0, 0.37, 1.11, 3.33 or 10.0 μg/mL without metabolic activation (S9-mix) or for 2 hours at concentrations of 0, 0.56, 1.67, 5.0 or 15.0 μg/mL with S9-mix. Cells were treated with Colcemid at 0.1 μg/mL immediately following exposure without S9-mix or after a 22-hour incubation after exposure with S9-mix. The length of the Colcemid treatment was not provided in the DER from which this Executive Summary was prepared. Cells were harvested following Colcemid treatment. Lymphocytes were obtained from a healthy male non-smoker. The S9-fraction was obtained from Aroclor 1254 induced male Wistar rat liver.

This executive summary was prepared from the Data Evaluation Record (DER) written in 1992 and not from the original 1985 study. Dodine was tested up to levels reducing the mitotic index to values approaching 50% of the solvent control values. Cells were collected and slides prepared by conventional cytological techniques. One-hundred well-spread metaphases (25 per slide) were scored for chromatid and chromosome aberrations. Numerical aberrations were not reported. No statistically significant (Fisher's exact probability test, two-sided) increases in the number of structural aberrations per cell over the solvent control values were seen at any test material concentration with or without S9-mix. The solvent and positive controls (Methyl methanesulfonate without S9-mix and Cyclophosphamide with S9-mix) induced the appropriate responses. There was no evidence of structural chromosomal aberrations induced over background in this study.

This study is classified as **Acceptable/Non-Guideline** and does satisfy the requirement for *in vitro* cytogenetic mutagenicity data [OPPTS 870.5375; OECD 473]. No information was provided on the pH or osmolality of the treatment medium and no historical control data were provided. GLP and Quality Assurance statements were said to be provided.

Mammalian Erythrocyte Micronucleus - Mouse

EXECUTIVE SUMMARY: A single acute dose selection study (MRID 41418901) was conducted prior to the main study in order to determine appropriate doses. The main study, a mammalian erythrocyte micronucleus assay (MRID 41418902), was designed to evaluate the mutagenicity of CT-334-87 (DGH, 35% a.i.) on ICR mice.

In the dose selection study, a single dose of 1500 mg/kg body weight CT-334-87 was administered to six ICR mice (3 males, 3 females) by oral gavage. All animals appeared normal immediately post-dosing. After about two hours, one female was found dead and all males were "languid with squinting eyes". The remaining two females appeared normal and healthy during the 3-day observation period. Within 26 hours of dosing, all males developed rough haircuts. About 44.5 hours post-dosing, the males had rough hair coats and squinted eyes with 2 showing hunched backs. About 67.5 post-dosing, all 3 had rough hair coats and the same 2 had hunched backs. Based on these observations, the doses selected for the mouse bone marrow micronucleus assay are 140, 467, and 1400 mg/kg body weight.

In the *in vivo* mouse micronucleus assay, 10 ICR (5 male, 5 female) mice/dose/harvest time group were administered CT-334-87 via oral gavage at concentrations of 140, 467, or 1400 mg/kg body weight. Animals administered the test article were euthanized 24, 48, and 72 hours post-dosing. The positive control, Cyclophosphamide (CP), was administered at 80 mg/kg. The vehicle control, sterile deionized water, was administered concurrently with the test article at a volume of 10mL/kg. Positive and vehicle controls were euthanized 24 hours after the administration of the control articles.

Within 45 minutes of dosing, two animals in the 467 mg/kg dose group had dies. All other animals were normal after dosing and appeared healthy 4.5 hours after dosing.

About 24 hours after dosing, three males in the 1400 mg/kg dose group and one male in the 467 mg/kg dose group, were found dead. One female in the 467 mg/kg dose group had a distended abdomen and this condition was unchanged 48-hours post dosing (harvest time). All males in the 467 and 1400 mg/kg dose group had rough hair coats. Several high-dose males had squinted eyes and/or were languid. One high-dose male was languid with a distended abdomen; he expired within 30 hours of dosing.

About 46 hours post-dosing, three animals in the 1400 mg/kg dose group (2 males, 1 female) and one male in the 467 mg/kg dose group were found dead. The other males had rough hair coats, but this condition subsided prior to the 72 hour harvest. All males in the 1400 mg/kg dose groups had rough hair coats and were languid; a few high dose males had squinted eyes. These conditions persisted until the harvest time.

The test article, CT-334-87, induced no significant increases in micronucleated polychromatic erythrocytes over the levels observed in the vehicle controls in either sex or at any of the harvest times. The positive control, CP, induced significant increases in micronucleated PCEs in both sexes.

The test material, CT-334-87, is considered NEGATIVE in the mouse bone marrow

micronucleus test.

This mammalian erythrocyte micronucleus assay is classified as **Acceptable-Guideline** and satisfies the guideline requirements for a mammalian erythrocyte micronucleus assay [870.5395 (§84-2)] in the mouse.

Mammalian Bone Marrow Chromosomal Aberration

EXECUTIVE SUMMARY: Acute dose range-finding and micronucleus assay studies (MRID 42311601) were conducted on male and female ICR mice with dodine (94%, a.i., Lot No. 303/90). Corn oil was the vehicle utilized. In the acute dose range-finding study, three males and three females per dose group received a single oral gavage dose of 50.0, 162.5, 275.0, 387.5 or 500 mg/kg with the volume of test substance administered being 10 mL/kg. A prior study indicated the LD_{50} for mice was 266 mg/kg and was used to establish these dose selections. For the micronucleus assay study, 15 males and 15 females were used in the treatment groups and were administered a single dose of 100, 200 or 400 mg/kg by oral gavage with bone marrow sampling at 24, 48 and 72 hours post-dosing. A secondary group of 5 males and 5 females were dosed at the high-dose to ensure availability of replacements in the case of mortality in the original group. One high-dose male was used from this secondary group. In this same study, positive and negative controls were utilized. Five males and five females were dosed once with vehicle only for the negative control with sampling 24 hours post-dosing. The positive control dosed five males and five females with cyclophosphamide (CP) dissolved in distilled water and delivered at a single dose of 80 mg/kg by oral gavage with sampling 24 hours post-dosing.

Treated animals in the range finding study were examined for clinical signs and/or mortality immediately after dosing and for three days post-dosing. One male each from the 387.5 and 500 mg/kg groups was found dead at 41 hours. All other mice in these dose groups exhibited rough haircoats at 41 hours and were languid with rough haircoat at the study's termination. No clinical signs were observed in the animals dosed with ≤ 275 mg/kg. Doses for the micronucleus assay were set at 100, 200 and 400 mg/kg with 400 mg/kg being 80% of the estimated maximum tolerated dose.

In the micronucleus assay study, one high-dose male died at 6 hours and one male in the secondary group died at 24 hours post-dosing. The only clinical sign reported was distended abdomens in two high-dose males, 48 and 72 hours post-dosing, respectively, and in one mid-dose male at 48 hours post-dosing. Bone marrow cell ratios of polychromatic erythrocytes (PCEs) to normochromatic erythrocytes (NCEs) for males in all treatment groups and harvest times were as much as or higher than the vehicle control males. Bone marrow cells from the mid- and high-dose females at 72 hours were approximately 50% lower than the controls. However, a statistically significant increase in the number of micronuclei in polychromatic erythrocytes (MPEs) was not reported at any dose level or harvest time in either males or females thus making it a negative test for genotoxic effects. The positive control did induce a significant ($p< 0.05$) increase in the frequency of MPEs in the bone marrow cells in both males and females.

This study is **Acceptable/Guideline** and does satisfy the requirements for a micronucleus test. [OPPTS 870.5385 (§84-2)].

A.3.7 Neurotoxicity

Not available

A.3.8 Metabolism

870.7485 Metabolism – Rat

EXECUTIVE SUMMARY: In a metabolism and pharmacokinetic study (MRID 42479001), male and female Sprague-Dawley (Crl: CL BR) rats were administered by gavage either a single dose of 40 or 400 mg/kg ^{14}C-labeled dodine (> 99% a.i., Lot No. 910225) or 40 mg/kg/day of non-labeled dodine (99.8% a.i., Lot No. FF1/88) for 14 days, followed by a single dose of radio-labeled dodine (40 mg/kg) on day 15. Five males and five females were dosed in the single low- and high-dose radio-labeled study; five males and six females were used in the multiple low-dose study. All studies used corn oil as a vehicle. A preliminary test using the 40 and 400 mg/kg radio-labeled dodine was performed to help determine the amount of ^{14}C-labeled dodine excreted in expired air.

In the preliminary study, most radioactivity was eliminated in the urine and feces within 72 hours post-dosing in the low-dose group but continued past 72 hours in the high-dose group. Expired air had <1% of the administered dose and the amount recovered was either $^{14}CO_2$ or radio-labeled volatiles. Based on results, sampling to 120 hours post-dosing was initiated in the definitive study.

In the definitive study, dodine was rapidly absorbed, distributed, metabolized and excreted at all dosing levels with no significant gender differences. Urine and feces were found to be major routes of excretion for the dodine. At 120 hours (5 days) post-exposure, 40.55 to 45.35 % of the dose was excreted in the urine and 47.63 to 59.69 % was excreted in the feces in all dose groups. Total recovery at 120 hours ranged from 93.61 to 102.22 % of the administered dose. Tissues were collected and analyzed for radioactivity. Upon analysis, ≤ 3.35% of the administered dose was recovered in tissues. The highest amounts recovered were in the gastrointestinal tract (0.16-1.14% of the dose), muscle (0.02-0.61% of the dose) and skin (0.06-0.21%). Urine and fecal samples from one animal/sex in each dose group were utilized in metabolite analysis. In urine, the unmetabolized parent compound was not identified; however, four metabolites were identified. The major metabolite found was an alcohol of dodine, hydroxydodecylguanidine, and accounted for 10.98 to 23.52% of the administered dose. Females did have a slight increase in this metabolite when compared to males. Fecal samples identified the parent compound as the major metabolite, 0.17 to 4.17% of the dose.

The proposed metabolic pathway for dodine in rats was a ß-oxidation pathway similar to medium- and long-chain fatty acids. Oxidation takes place by forming intermediate products with shorter chain lengths and these are eliminated in the urine. Urea is also formed in the liver from action on dodine or one of its metabolites.

Dosing of dodine appears adequate for the pharmacokinetics and metabolism to be identified based on the presence of radioactivity in samples taken.

This study is **Acceptable/Guideline** and does satisfy the requirements for a metabolism and pharmacokinetic study in rats [OPPTS 870.7485 (§85-1)].

870.7602 Dermal Penetration-Rat

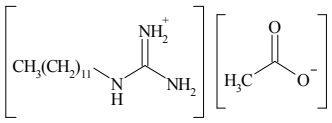
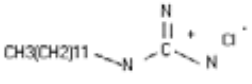
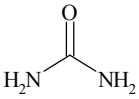
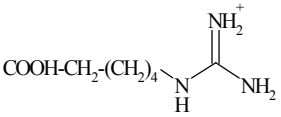
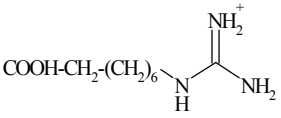
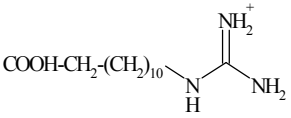
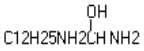
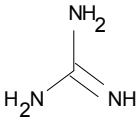
EXECUTIVE SUMMARY: In a dermal absorption study (MRID 46621303) [$_{14}$-C]- Dodine (n-dodecyl-$_{14}$C-guanidine acetate) was administered to three groups of four male Sprague Dawley CD rats/dose to a 12 cm^2 dorsal area in a formulation and water dilution thereof at dose levels of 4.0 and 0.004 mg/ cm^2. Exposure durations and percent of mean radioactivity absorbed, mean radioactivity

(percent of applied dose) remaining in the treated skin and mean radioactivity (percent of applied dose) removed by skin swab/guaze wash following a single topical application of a formulation of [^{14}-C]- Dodine are presented in the table below. The formulation was applied for 8 hours and then the application site washed with 1% Tween 80 in distilled water to remove unabsorbed material.

In the rats treated with 4.0 mg/ cm^2 [^{14}-C]- Dodine, the mean total recoveries were 98.7 ± 2.81%, 99.5 ± 1.30%, 97.5 ± 3.54% and 98.9 ± 1.44% at 8, 24, 48 and 72 hours, respectively, following application. In the rats treated with 0.004 mg/cm^2 [^{14}-C]- Dodine, the mean recoveries were 110 ± 6.55%, 106 ± 10.8%, 108 ± 15.1% and 99.6 ± 6.85% at 8, 24, 48, 72 hours, respectively following application. No radioactivity was detected in the blood, nor in the trapping fluids for expired carbon dioxide and volatile organic material for any group at either dose level. The mean percent radioactivity remaining in the treated skin in the 0.004 mg/cm^2 treatment groups were 36.6%, 49.5%, 45.2% and 40.3% at 8, 24, 48, 72 hours, respectively. Presumably, the [^{14}-C]- Dodine remaining in the treated skin has the potential to be absorbed by the skin over time; however, this is not demonstrated by the study. In fact the radioactivity remaining at the application site increases slightly over time indicating that the maximum absorption is likely to happen after 72 hours. Therefore, approximately 1% (0.77%) of the dose applied to male rats was demonstrated to be absorbed in skin with the resulting radioactivity being found in the urine, feces, cagewash, carcass and untreated skin. Although eight to ten hours is considered most applicable to the typical worker and the doses used are the typical worker doses, it is appropriate to utilize the 72 hour/low dose dermal absorption value to be conservative in risk assessment. These values are considered conservative because a portion of the active ingredient was retained at the skin site and it is unlikely that all of the skin residues will become systemically available.

The reviewers believe that the study provides useful information, however, since the purity of the test material was not reported, only two doses were used, information about the vehicles were not reported, and the exposure durations were non-guideline, the study does not satisfy the guideline requirements for a dermal penetration study in rats (OPPTS 870.7600 [§85-2]). Therefore, this study in the rat is considered **acceptable/ non-guideline**.

Appendix B: Metabolism Assessment

Table B.1. Chemical name and structure of Dodine metabolites	
Chemical name	**Chemical structure**
Dodine-dodecylguanidine monoacetate	
Guanidinium hydrochloride	
Urea	
Hexylguanidine carboxylic acid	
Octylguanidine carboxylic acid	
Dodecylguanidine carboxylic acid	
dodecylaminohydroxy- methylamine	
Guanidine	

Appendix C. Tolerance Reassessment Summary; Codex/International Harmonization

Table C1. Tolerance Summary for Dodine.			
Commodity	Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	Comments; *Correct Commodity Definition*
Banana	0.5	0.50	
Peanut	0.03	0.013	