EPA REGISTRATION DIVISION COMPANY NOTICE OF FILING FOR PESTICIDE PETITIONS PUBLISHED IN THE FEDERAL REGISTER (7/1/2007)

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INSTRUCTIONS: **Please utilize this outline in preparing the pesticide petition. In cases where the outline element does not apply, please insert "NA-Remove" and maintain the outline. Please do not change the margins, font, or format in your pesticide petition. Simply replace the instructions that appear in green, i.e., "[insert company name]," with the information specific to your action.**

TEMPLATE:

[Rhodia Inc.]

[8E7316]

EPA has received a pesticide petition **([8E7316])** from **[Rhodia Inc. c/o SciReg, Inc.], [12733 Director's Loop, Woodbridge, VA 22192]** proposing, pursuant to section 408(d) of the Federal Food, Drug, and Cosmetic Act (FFDCA), 21 U.S.C. 346a(d), to amend 40 CFR part 180.

(Options (pick one)

1. by establishing a tolerance for residues of – NA- remove

2. to establish an exemption from the requirement of a tolerance for

[alkyl (C10-C16) dimethylamine oxide (CAS No. 70592-80-2) in or on growing crops under 40 CFR 180.920 when used as a wetting-agent in pesticide formulations applied pre-harvest to all raw agricultural commodities] EPA has determined that the petition contains data or information regarding the elements set forth in section 408 (d)(2) of FDDCA; however, EPA has not fully evaluated the sufficiency of the submitted data at this time or whether the data supports granting of the petition. Additional data may be needed before EPA rules on the petition.

A. Residue Chemistry

1. *Plant metabolism.*

2. *Analytical method.* **[Rhodia Inc. is petitioning that alkyl (C10-C16) dimethylamine oxide be exempt from the requirement of a tolerance. Therefore, an**

analytical method to determine residues on treated crops is not relevant.]

3. *Magnitude of residues.* **[Rhodia Inc. is petitioning that alkyl (C10-C16) dimethylamine oxide be exempt from the requirement of a tolerance. Therefore, magnitude of residues on treated crops is not relevant.]**

B. Toxicological Profile

1. *Acute toxicity.* **[Acute Oral Toxicity: Reported LD50s in rats for alkyl (C10-C16) dimethylamine oxide range from greater than 600 to 1330 mg/kg of body weight (BW), placing this specific amine oxide in Toxicity Category III.**

Acute Dermal Toxicity: The acute dermal LD50s in rabbits for alkyl (C10-C16) dimethylamine oxide is >530 mg/kg BW placing this amine oxide in Toxicity Category II.

Acute Inhalation Toxicity: Commercial products containing amine oxides include hair spray and other aerosol products. In general, the following statement regarding inhalation toxicity from the overall Screening Information Data Summary applies to alkyl (C10-C16) dimethylamine oxide.

"There is potential for workers to be exposed during manufacturing, formulation and industrial end use of products. Exposure could occur as a result of inhalation and/or dermal contact with aqueous material. The potential for human exposure to amine oxides by inhalation is minimized by its low volatility and because the production, formulation and industrial end use of products are in aqueous solutions."

While acute inhalation toxicity data are not available for alkyl (C10-C16) dimethylamine oxide, data are available for the primary component, dodecyl dimethylamine oxide (CAS No. 1643-20-5). An acute inhalation study with rats was conducted using a 0.3% material as an aerosol. This rate is equivalent to 5.3 mg/L of product or 0.016 mg/L of amine oxide (AO). The LC50 for this inhalation study was found to be > 0.016 mg AO/L.

Acute Eye Irritation: Several acute eye irritation studies have been conducted with alkyl (C10-C16) dimethylamine oxide. In these studies, 0.1 ml of test material was instilled into one eye of each rabbit. Observations were taken for up to 21 days. Based on these studies, alkyl (C10-C16) dimethylamine oxide is considered to be irritating to severely irritating rabbit eyes.

Acute Dermal Irritation: Dermal irritation data are not available for alkyl (C10-C16) dimethylamine oxide. Data are, however, available for dodecyl dimethylamine oxide from several studies conducted with 0.5 mL of 5% or 30% amine oxide products. The 5% material was found to be non-irritating, while the 30% material was found to be irritating to severely irritating.

<u>Skin Sensitization:</u> A skin sensitization study conducted with alkyl (C10-C16) dimethylamine oxide on guinea pigs found 0.4 ml of neat (27.72%) test material to be non-sensitizing using a modified Buehler method.]

2. *Genotoxicty*. **[Genotoxicity studies conducted with dodecyl dimethylamine oxide are summarized below.**

<u>Ames reverse mutation assay (*Salmonella typhimurium* strains TA1535, TA1538, TA100 and TA98):</u> In a plate incorporation assay, a single dose level (250 µg/plate), with and without metabolic activation, was evaluated. This dose level was cytotoxic to TA1535 in the absence of S9. Dodecyl dimethylamine oxide was not mutagenic alone, either with or without rat liver S9. After nitrosation with nitrous acid, the N-nitroso derivative of dodecyl dimethylamine oxide was mutagenic with S9 activation to *Salmonella* strain TA1535. Overall, dodecyl dimethylamine oxide was not considered to be mutagenic.

<u>Syrian hamster embryo cells:</u> Dose levels evaluated in this *in vitro* assay were 0.1, 0.5, 1.0, 5.0, 10, and 20 µg/mL. The positive control was 3-methylcholanthrene. Pregnant hamsters were killed on days 13 and 14 of gestation for preparation of target cells and feeder layer cells, respectively.

The cytotoxic concentration was determined to be between 10 and 20 µg/mL. Overall, dodecyl dimethylamine oxide was not considered to be mutagenic.

<u>Ames reverse mutation assay (*Salmonella typhimurium* strains TA98 and TA100):</u> Dose levels evaluated in this assay were between 10 and 200 µg/plate, with and without rat live S9 activation. The positive controls were 4-nitroquinoline 1-oxide, N-methyl-N´-nitro-N-nitrosoguanidine, 2-acetoaminofluorene, and N-nitrosodimethylamine. Some cytotoxicity was observed at 100-200 µg/plate without metabolic activation. Overall, dodecyl dimethylamine oxide was not considered to be mutagenic.

<u>Dominant lethal assay:</u> Dose levels evaluated in this *in vivo* assay were 10, 100, and 1000 mg/kg BW. The test material, dodecyl dimethylamine oxide, was administered in the drinking water to male and female mice. After the last treatment, males were mated with untreated females for a period of seven days. After the last treatment, each male was housed with two untreated females for one week. Each male was then housed with two additional females for a period of seven weeks. Pregnant females were sacrificed on day 13 or 14 of pregnancy and the number of implantations, resorptions, and dead embryos were recorded. *Corpora lutea* were not counted. There were no treatment-related effects in any of the treatments. Overall, dodecyl dimethylamine oxide was not considered to be mutagenic.]

3. *Reproductive and developmental toxicity*. **[<u>Developmental toxicity/teratogenicity study:</u> Female rats were gavaged at dose levels of 0, 25, 100,**

or 200 mg AO/kg BW on days 6-19 of gestation, and were sacrificed on day 20. This study showed that alkyl (C10-C16) dimethylamine oxide at 200 mg AO/kg BW caused delayed ossification.

Clinical signs included local alopecia, excessive salivation, rales, urine-stained abdominal fur, brown or red peri-oral substance, labored breathing, gasping, brown peri-nasal substance, and soft liquid feces. Two animals died, one by dosing error and one spontaneously. The maternal and developmental NOAELs were determined to be 25 mg AO/kg BW.

Reproductive toxicity study: A two-generation feeding study in rats was conducted with dodecyl dimethylamine oxide. Males and females of the F0 generation were initially dosed at 0, 750 ppm (40 mg AO/kg BW/day), 1500 ppm (80 mg AO/kg BW/day), or 3000 ppm (160 mg AO/kg BW/day). However, following a marked inhibition of bodyweight gain at the two highest dose levels, doses were reduced to 0, 188 ppm (11 mg AO/kg BW/day), 375 ppm (20 mg AO/kg BW/day), and 750 ppm (40 mg AO/kg BW/day). The F1 generation received 0, 188, 375, and 750 ppm for 120 days prior to mating.

Administration of the test material at concentrations of 188, 375, and 750 ppm was associated with slight reductions in bodyweight gain of both parents and offspring, but was without adverse effect on their mating performance and fertility. The general condition of the animals throughout the study was unaffected by treatment. At all treatment levels, absolute bodyweights of both sexes remained slightly below that of controls. Mating performance, fertility, and conception rate were not affected by treatment in either generation. Gestation and parturition proceeded normally. There was a slight reduction in the number of F2 offspring born at the 750 ppm level; however, there were no adverse effects of treatment on litter size at birth, live birth index and birth weight in either generation. Therefore, this was not considered an adverse effect. Viability of offspring was unaffected in the first generation, but there were slight reductions in viability of the F2 offspring at the 188 and 750 ppm levels. Offspring viability in the 375 ppm group was similar to the control group. This reduction was within the range of historical controls and did not appear to be dose dependent. Therefore, this was not considered an adverse effect. At all treatment levels, the rate of bodyweight gain for the F1 and F2 offspring was reduced during the lactation period; however, this reduction was not greater than 10%.This was not considered to be an adverse effect since the bodyweight change only reached statistical significance when the rat pups were getting the majority of their calories from solid food and was not associated with any other effects. No macroscopic abnormalities or histopathological changes were attributable to treatment with the test substance.]

4. *Subchronic toxicity*. **[Several subchronic (28-day and 91-day) studies have been conducted with alkyl (C10-C16) dimethylamine oxide. These studies are summarized below.**

<u>91-day dietary toxicity study</u>: This study in rats revealed that alkyl (C10-C16) dimethylamine oxide did not cause compound-related ophthalmoscopic, hematological, clinical chemistry, urinalysis, gross pathology, histopathology, organ weights, or organ to body weight ratio effects. Statistically significant decreases in mean body weight were noted in males receiving 0.4% test material-treated feed and in females receiving 0.2% and 0.4% test material-treated feed.

Animals were assigned to treatment groups receiving feed containing 0%, 0.1%, 0.2% or 0.4% test material as follows.

0.1% = 63 mg AO/kg BW/day (males); 80 mg AO/kg BW/day (females)
0.2% = 112 mg AO/kg BW/day (males); 150 mg AO/kg BW/day (females)
0.4% = 236 mg AO/kg BW/day (males); 301 mg AO/kg BW/day (females)

The reported NOAEL was 80 mg AO/kg BW/day; the LOAEL was 150 mg AO/kg BW/day.

In addition, three subchronic dermal toxicity studies showed no long-term dermal effects. The results are presented below. See also the results of the two-year dermal reproduction study in the "Reproductive and Developmental Toxicity" section.

<u>28-day dermal toxicity study (abraded skin):</u> This study was conducted at 0.1%, 0.5%, and 1.0% alkyl (C10-C16) dimethylamine oxide. Results showed that when applied to the abraded skin of rats for 28 consecutive days, the systemic NOEL was determined to be 1% (1 mg AO/kg BW). Local slight to moderate erythema and edema were noted at the 1% level, but not at the lower dose levels.

<u>91-day dermal toxicity study (unabraded skin):</u> This study was conducted at 0.5%, 1.0%, and 2.5% alkyl (C10-C16) dimethylamine oxide. Results showed that when applied to the intact skin of rats for 91 consecutive days, the systemic NOEL was determined to be 2.5% (2.5 mg AO/kg BW). Slight to moderate erythema, edema, atonia, and desquamation were noted at the 2.5% level, and slight to moderate erythema was observed at the 2.5% level but not at the 0.5% and 1.0% dose levels.

<u>91-day dermal toxicity study (unabraded skin):</u> This study was conducted at 0.5% (0.3 mg AO/kg BW), 1.0% (0.6 mg AO/kg BW), and 2.5% (1.5 mg AO/kg BW) alkyl (C10-C16) dimethylamine oxide. Results showed that when applied to the intact skin of rabbits for 91 days, the systemic NOEL was determined to be greater than 2.5% (>1.5 mg AO/kg BW). Slight transient skin irritation was observed at the 2.5% level, but not at lower levels. There were no treatment-related deaths, signs of systemic toxicity or compound-related microscopic or macroscopic lesions in any dosage group. There were no statistically significant differences in mean body weights or organ weights. There was a slight, but statistically significant, increase in the mean corpuscular hemoglobin in male animals in the 0.5% group, and slight increases in platelet, eosinophil and basophil counts were noted in females in the 1% group. Since there were no dose-response relationships, these findings were considered

incidental. There were no other hematologic changes in treated animals. Males in the 1% group showed a slight increase in absolute and relative liver weights. However, since this was not dose dependent, and since there were no microscopic changes in the livers of these animals, this was not considered biologically significant.]

5. *Chronic toxicity.* **[Two long-term studies have been conducted with alkyl (C10-C16) dimethylamine oxide.**

Mouse: **A 2-year dermal carcinogenicity study in male and female mice was conducted at dose levels of 0, 0.05, 0.13, and 0.26% in distilled water. Applications were made three times per week. Males in the 0.26% dose group had decreased overall survival; females in the 0.13% dose group had increased survival rates compared to controls. These random values were within historical variability of controls and were not considered treatment related. There were no statistical differences in group average body weights, organ weights, and organ to body weight ratios among treated animals compared to controls. Compound-related skin irritation (diffuse acanthosis and hyperkeratosis) was observed microscopically in the 0.26% dose groups. No skin tumors were observed in any group. There were no compound-related skin or systemic neoplasms in the study, nor was there any evidence of a carcinogenic response.**

Rat: **A 2-year carcinogenicity feeding study in male and female rats was conducted at dose levels of 0, 0.01, 0.1, and 0.2% (0, 5, 50, and 100 mg/kg BW/day; calculated assuming a dietary conversion factor for rats of 0.0001% equating to 0.05 mg/kg BW/day). There were no significant differences in survival, no significant, compound-related differences in mean feed consumption, clinical chemistry or ophthalmology. Bodyweights were lower in treated males compared to controls at several time points during the study. Mean bodyweights were significantly lower at the 0.2% (100 mg/kg BW/day) dose level in both males and females. Increases in kidney, heart, ovary and brain weights (females) and brain weight (males) occurred in the 0.2% (100 mg/kg BW/day) dose groups due to decreases in mean body weight. Mean absolute liver weight was decreased statistically in males at 0.1% (50 mg/kg BW/day), but was within the range of normal biologic variability and, therefore, was not considered related to test substance administration. There were no compound-related effects upon histopathologic examination. There was no evidence of a carcinogenic response.]**

6. *Animal metabolism.* **[While no metabolism studies are available with alkyl (C10-C16) dimethylamine oxide, a number of metabolism studies in humans, rats, rabbits, and mice have been performed with dodecyl dimethylamine oxide.**

Rat (excretion study): **A single oral dose at 100 mg/kg BW (methyl-^{14}C) was administered to male and female rats, and at 100 mg/kg BW (1-dodecyl-^{14}C) to males only. Rapid and extensive absorption was observed. Excretion was mainly via urine and CO_2 (less in feces).**

<u>Rat (tissue distribution study):</u> A single oral dose at 100 mg/kg BW (methyl-^{14}C) was administered to male and female rats, and at 100 mg/kg BW (1-dodecyl-^{14}C) to males only. Rapid and extensive absorption was observed. Excretion was mainly via urine and CO_2 (less in feces).

<u>Rat (bile duct cannulation study):</u> A single oral dose at 40 or 100 mg/kg BW (methyl-^{14}C) was administered to male rats. Rapid and extensive absorption was observed. Excretion was mainly via urine and CO_2 (less in feces).

<u>Rat (dermal excretion study):</u> A single dermal dose of 20 mg/mL (methyl-^{14}C) was administered to male rats. Approximately 40% of the applied dose was excreted, mainly via the urine.

<u>Rat, mouse, rabbit (tissue distribution study):</u> A single dermal dose of 20 mg/mL (methyl-^{14}C) was administered to rats, 10 mg/mL (methyl-^{14}C) was administered to mice, and 20 mg/mL (methyl-^{14}C) was administered to rabbits. Approximately 40% of the applied dose in rats and mice, and approximately 60% of the applied dose in rabbits was excreted, mainly via the urine.

7. *Metabolite toxicology*. **[NA-Remove]**

8. *Endocrine disruption*. **[Extensive literature searches and review of numerous summaries of amine oxide data indicate there is no evidence that the amine oxides are endocrine disruptors or that they have any known effect on immune systems.]**

C. Aggregate Exposure

1. *Dietary exposure.* **[NA-Remove]**

i. *Food.* **[Dietary exposure to alkyl (C10-C16) dimethylamine oxide should not be of concern due to the low toxicity shown in acute, subchronic, carcinogenicity, reproduction, developmental, and metabolism studies. Further, alkyl (C10-C16) dimethylamine oxide is not mutagenic, as demonstrated by *in vitro* and *in vivo* studies. No adverse health effects to animals or the environment have been associated with this compound. Dietary exposure due to the proposed use patterns in post-emergent herbicides is anticipated to be very low to non-existent.]**

ii. *Drinking water.* **[Alkyl (C10-C16) dimethylamine oxide does not pose a risk to drinking water. It is rapidly degraded, both aerobically and anaerobically, and is considered inherently biodegradable. Agricultural practices minimize spray drift and typical end-use product labels prohibit direct application to water. Alkyl (C10-C16) dimethylamine oxide is not likely to be present at significant concentrations in aquatic environments.]**

2. *Non-dietary exposure*. **[Non-dietary exposure to alkyl (C10-C16) dimethylamine oxide will be much more likely through daily use of laundry**

detergents, dishwashing detergents, and personal care products, than through use as an inert ingredient in pesticide formulations. To the best of our knowledge, use of amine oxides in laundry detergents, dishwashing detergents, and personal care products by broad segments of the world's population has not resulted in any significant reported adverse effects.]

D. Cumulative Effects

[Section 408(b)(2) of the FFDCA requires that, when considering whether to establish an exemption from a tolerance, the Agency consider available information concerning the cumulative effects of the particular ingredient's residues and other substances that have a common mechanism of toxicity. These considerations include the possible cumulative effects of such residues on infants and children. Rhodia is unaware of other chemicals that share a common mechanism of toxicity with alkyl (C10-C16) dimethylamine oxide, nor is Rhodia aware of any adverse cumulative effects associated with the use of amine oxides.]

E. Safety Determination

1. *U.S. population.* **[Amine oxides have a long history of safe use in soaps and detergents, as well as in many personal care products. Amine oxides, as a class, and alkyl (C10-C16) dimethylamine oxide specifically, exhibit very low toxicity, as demonstrated by the acute, subchronic, carcinogenicity, reproductive, developmental, and metabolism studies summarized above. Further, alkyl (C10-C16) dimethylamine oxide was not mutagenic in *in vitro* and *in vivo* studies. When alkyl (C10-C16) dimethylamine oxide is used on raw agricultural commodities in accordance with good agricultural practice, it meets the reasonable certainty of no harm requirement.]**

2. *Infants and children.* **[It is believed that the potential exposure of infants and children to residues of alkyl (C10-C16) dimethylamine oxide through its use in pesticide formulations is significantly smaller than this subgroup's exposure via the numerous other uses for amine oxides (e.g., soaps, detergents, personal care products, etc.). There is no available information to suggest that infants and children are more susceptible to the effects of alkyl (C10-C16) dimethylamine oxide than are adults.]**

F. International Tolerances

[There are no known international tolerances for alkyl (C10-C16) dimethylamine oxide or any other amine oxide in food or feed.]