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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Review of The Proctor & Gamble Company New Chemical
Registration For Alkyl(C₁₀-C₁₆) Dimethyl Amine Oxide
in Support of the Product Registration for the
Product, CLEANING MAGIC I.

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ID No: 003573-LO Cleaning Magic I

DP Barcode: D253849

Submission: S538885

Case No: 062115

PC Code: 000439 Alkyl(C₁₀-C₁₆) Dimethyl Amine Oxide

MRID No: 444349-10

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Introduction:

The Proctor & Gamble Company has submitted an application for registration of the new active ingredient, Alkyl(C₁₀-C₁₆) Dimethyl Amine Oxide intended for use in four proposed concentrated antimicrobial dishwashing detergents to be registered under the names, CLEANING MAGIC I, CLEANING MAGIC II, CLEANING CARE I and CLEANING CARE II.

AD's Regulatory Management Branch I requests that AD/RASSB review the submitted data in support of the new product registration for CLEANING MAGIC I, EPA ID#: 003573-LO. The instructions for this Bean Sheet are to review the dietary exposure study, MRID No. 444349-10, Human Exposure Calculations for Dodecyl Dimethyl Amine Oxide(DDAO).

Background:

There are no EPA registrations for this chemical.

AD/RASSB review of Title 21 CFR did not reveal any Food & Drug Administration Regulations for this chemical.

The dietary exposure study that AD/RASSB is requested to review has been previously reviewed by RASSB in its 10/5/98 review by Doreen Aviado.

Conclusions:

1. OPPTS GLN 860.1200 Proposed Use.

There are two uses proposed on the label(s). The first use is for a general dishwashing use. The second use is to kill germs on dishes. The second use involves the direct application of the product to dishware.

2. OPPTS GLN 860.1300 Nature of the Residue.

There are no data submitted to elucidate the nature of the residue deposited on dishes and transferred from washed dishes to food. Part per billion trace amounts of nitrosamines are reported in the product CSF's. The primary residue that will occur in food contacting washed dishes will be alkyl dimethyl amine oxide. A biodegradation study is also being reviewed in RASSB for the related compound, dodecyl dimethyl amine oxide. That study reports the presence of dimethyl (4-hydroxybutyl)-amine-N-oxide at 10-16% of the total residue. However, in the absence of any additional data, RASSB will assume that the residue of toxicological concern for the proposed use in this registration action to be the parent compound, alkyl dimethyl amine oxide.

3. OPPTS GLN 860.1300 Enforcement Analytical Method.

- a. There is no analytical method submitted for the analysis of alkyl dimethyl amine oxide in food.
- b. The residue data generated in the dietary exposure study was generated using a radiometric method. This method is not an enforcement method.

4. OPPTS GLN 860.1500 Residue Chemistry.

- a. The dietary exposure study submitted by Proctor & Gamble has previously been reviewed in RASSB(Review of 10/5/98). This study reflects the general dishwashing use on the label. Several deficiencies were noted regarding the study which raise questions as to the acceptability of the study.
- b. Germ Killing use on dishes. AD/RASSB has calculated the dietary exposure from this use using very conservative assumptions. These calculations result in an alkyl dimethyl amine oxide level in food of 26 ppm and an estimated daily ingestion level of 1.1 mg/kg bwt/day. It should be emphasized that this is not expected to be the typical use of this product. This use involves direct application of the product to dishes for germ killing purposes. We would expect that this type of use would involve special circumstances where germ killing is important; eg in cases of illnesses.
- c. General dishwashing use. This would be the typical use of the product.

(i) The Proctor & Gamble submitted study for general dishwashing use has been previously reviewed by RASSB and found to have deficiencies. However, the study will be discussed here because of its interest. If RASSB were to accept the study as being valid and without deficiencies, the dietary exposure resulting from the general dishwashing use without rinsing dishware would be 26.8 micrograms/kg bwt/day of amine oxide.

(ii) If RASSB uses the Food & Drug Administration(FDA) worst case calculations described in the " Sanitizing Solutions: Chemistry Guidelines For Food Additive Petitions ", the dietary exposure resulting from the general dishwashing use without rinsing dishware would be 9.4 microgram/kg bwt/day. This would be a very conservative estimate. Dietary exposure would likely be much lower than this level after dishes and utensils are rinsed with water.

(iii) AD/RASSB has no definitive explanation as to the reason for this difference between actual data and the FDA calculations. Obviously, the P & G actual residue data resulted in an amine oxide level greater than the 1 milligram/cm² that the FDA uses in its worst case model. This may be attributable in part to the chemical/properties of the amine oxide ingredient or to the properties of the cleaning product and also to the fact that 6 year old melamine was used in the study. The 6 year old melamine may have many scratches on the surface in which the amine oxide would be deposited.

(iv) AD/RASSB believes that a conservative estimate of the

dietary exposure from the general dishwashing use would be 9.4 micrograms amine oxide/kg bwt/day.

5. The registrant has provided calculations to show that the dietary exposure to alkyl dimethyl amine oxide from the ingestion of drinking water would be 0.0029 micrograms/kg bwt/day. This appears to be reasonable.

Recommendations:

Provided that the dietary exposure estimates are acceptable to the AD/RASSB toxicologists, no additional residue/dietary exposure data are needed to support the proposed registration.

The use proposed on the label is for a household use. A tolerance Regulation is not needed for this use. If, in the future the registrant decides to broaden the use to include commercial usage, then a tolerance or tolerance exemption will be required.

Detailed Considerations

OPPTS GLN 860.1100 Chemical Identity.

There are four products submitted: Cleaning Magic I, containing 4.81% alkyl dimethyl amine oxide, Cleaning Magic II containing 5.2% alkyl dimethyl amine oxide, Cleaning Care I containing 3.61% alkyl dimethyl amine oxide and Cleaning Care II containing 3.9% alkyl dimethyl amine oxide. The inert ingredients and CSF have been reviewed by Anna Skapars (AD review of 6/5/98).

The active ingredient is: alkyl(C₁₀-C₁₆) dimethyl amine oxide; CAS 70592-80-2.

OPPTS GLN 860.1200 Proposed Use.

There are two uses proposed on the the label(s).

For General Dishwashing: Use as any dishwashing detergent. The product is not for use in dishwashers.

To Kill Germs on Dishes: Apply directly on dishes. Spread and allow to stand 5 minutes, then rinse.

The proposed use is for household usage.

OPPTS GLN 860.1300 Nature of the Residue.

No data are submitted which are intended to elucidate the nature of the residue in/on food contacting treated dishware/glass/utensil surfaces washed with the alkyl dimethyl

amine oxide dishwasher solution or the detergent product.

A biodegradation study using the related chemical, dodecyl dimethyl amine oxide, did show the presence of a dimethyl (4-hydroxybutyl)-amine-N-oxide biodegradate present at 10-16 % of the total residue.

Degradation of some kind may occur on washed surfaces or in food. In the absence of data, AD/RASSB will assume that the residue of concern is the parent compound. This is likely to be the worst case situation.

The CSF for the product(s) does report part per billion amounts of nitrosamines in the product.

OPPTS GLN 860.1300 Enforcement Analytical Method.

No analytical method is submitted for the analysis of alkyl dimethyl amine oxide in food.

The residue data generated in the dietary exposure study was from the use of a radiometric method. Standard procedures for radioassay were used. The ¹⁴C radioactivity measured in an aliquot of a given solvent extract solution was calculated as total dodecyl dimethyl amine oxide (DDAO), based on the 100 ml of extract solution added. Removal was calculated as micrograms/cm² based on the area of the dinnerware piece in contact with the extract solution. The percent DDAO was entered into the calculation.

OPPTS GLN 860.1500 Residue Chemistry.

*A dietary exposure study and calculation using the related chemical, radiolabeled dodecyl dimethyl amine oxide, was submitted by the registrant.

It is entitled:

" Human Exposure Calculation for Dodecyl Dimethylamine Oxide(DDAO)", MRID No. 444349-10.

This study was previously reviewed by AD/RASSB (review of 10/5/98 by Doreen Aviado). The following deficiencies relating to dietary exposure were noted:

a. The study measures residue dissipation after the dishware has been washed, rinsed and dried after twenty-four hours, which would be appropriate for general use. However, this study does not measure dissipation over time, define sampling intervals or provide enough data to establish a dissipation curve.

b. Duplicate samples were taken for food simulating solvents such as demineralized water, but not for 8 % v/v ethanol water or heptane.

c. Residue samples were not stored in a manner to minimize deterioration and loss.

d. Collection of residues were measured only after dinnerware was dried for twenty-four hours. Collection of residues directly after washing was not measured.

e. There were several Good Laboratory Practice(GLP) deficiencies in the study. However, this study was conducted prior to the implementation of GLP requirements.

The study submitted by the registrant reflects the washing of dinnerware, glasses and utensils with ¹⁴C DDAO detergent. Following the washing process, these items were either rinsed with water for 10 seconds, rinsed for 1 minute or were left unrinsed. After a 24 hour drying period, the items were extracted with food simulating solvents. The radioactivity levels on the washed and rinsed and on the washed and unrinsed items were determined. The residue levels extracted into the food simulating solvents was averaged for the 10 second and 1 minute rinses. The residues on the unrinsed items were extracted and determined and considered to be a worst case.

The adult daily exposure reported from the rinsed items was 4.7 micrograms /kg bwt/day. The worst case daily exposure reflecting the unrinsed items was reported to be 26.8 micrograms/kg bwt/day. These calculations are based on the assumption that a person weighs 70 kg. For small children, the calculations would be based on the assumption of a child weight of 10 kg.

Residue Levels Estimated Using the FDA Sanitizing Solutions Guidelines

Given:

A maximum of 5.2 % Alkyl dimethyl amine oxide in the detergent(from the P & G labels submitted).

Assume 0.29 % Alkyl dimethyl amine oxide in the dishwasher(the same level as was used in the P & G ¹⁴C DDAO study).

Assume an Alkyl dimethyl amine oxide deposit on all treated surfaces of 1 mg/cm²(from the FDA Sanitizing Solutions guidelines).

Assume 4384 cm²/person/day(This is the same dinnerware exposure used in the P & G study).

Then:

$0.052 \times 0.0029 \times 10^6 = 150.8$ ppm Alkyl dimethyl amine oxide in dishwater.

$EDI = 150.8 \text{ mcg}/1000\text{mg} \times 1 \text{ mg}/\text{cm}^2 \times 4384 \text{ cm}^2/\text{person}/\text{day} = 661.1$ micrograms/person/day.

For a 70 kg person, this is $661.1 \text{ micrograms}/\text{person}/\text{day} = 9.4$ micrograms/kg bwt/day.

Assuming a 3 kg diet, this is $661.1 \text{ micrograms}/\text{person}/\text{day}/3000 \text{ gm} = 0.22$ ppm contribution of alkyl dimethyl amine oxide to the daily diet.

Obviously the P & G residue study resulted in an amine oxide level greater than the 1 milligram/cm² that the FDA uses in what they consider to be generally a worst case model. This may be attributable in part to the chemical/physical properties of the amine oxide ingredient and to the fact 6 year old melamine was used in the P & G study. The 6 year old melamine would be expected to have many scratches on the surface to which the amine oxide would be deposited and adhere. AD/RASSB believes a very conservative estimate of dietary exposure from the general dishwashing use would be 9.4 micrograms amine oxide/kg bwt/day. Dietary exposure would likely be much lower than this level after rinsing dishware and utensils.

Residue Levels Estimated From the Germ Killing Use on the Label.

The label bears a use that is claimed to be a germ killing use. The product is to be applied directly to the dinnerware, spread and allowed to stand for five minutes. The dinnerware is then rinsed. AD/RASSB does not consider this to be the typical use for this product, but rather a use that would involve special circumstances wherein germ killing is important; eg in cases of illness.

AD/RASSB has attempted to calculate and provide some estimate of exposure for this use. We have made very conservative assumptions in our calculations.

Given: A maximum of 5.2 % alkyl dimethyl amine oxide on the product labels.

Squirt the product on a plate, spread, let sit and rinse. Use plate.

For a 10 inch diameter plate, the area of the plate is πr^2 and is 78.5 inch².

Add 2 ml of 5.2 % alkyl dimethyl amine oxide detergent to the 10

inch plate. Assume that 2 ml of the detergent product = 2 gm.
Therefore, 2 gm detergent x 0.052 alkyl dimethyl amine oxide =
0.104 gm alkyl dimethyl amine oxide(ADAO)/2ml.

Then, there is 104 mg ADAO/10 inch plate(78.5 inch²).
or

104 mg ADAO/78.5 inch² plate = 1.32 mg ADAO/inch² of plate.

Assume that water rinse of plate leaves 20 % of the applied ADAO
on the plate.

Then: 1.32 mg ADAO x 0.2 = 0.26 mg/ADAO/inch² on the rinsed
plate.

Assume: 10 grams food/inch² on plate(FDA assumption).
(There is 0.26 mg ADAO/inch² on the plate.)

Then: 0.26 mg ADAO/inch²/10 gm or 10000 mg = x/1000000
= 26 ppm ADAO in food

This is 26 mg/kg of ADAO in/on food.

Assume 3 kg food /person/day intake.

Then: 26 mg/kg ADAO x 3 kg food/person/day = 78 mg ADAO mg
ADAO/person/day.

Assume a 70 kg person:

Then: 78 mg ADAO/person/day/70 kg bwt/person = 1.1 mg ADAO/kg
bwt/day.

Obviously, this is a very conservative estimate.

Residue Levels of Alkyl Dimethyl Amine Oxide in Drinking Water

The registrant has provided calculations for the levels of the
related chemical, dodecyl dimethyl amine oxide, to be expected in
drinking water. AD/RASSB assumes that the registrant wants us to
translate these data to alkyl dimethyl amine oxide. The
registrant's calculation estimates exposure to dodecyl dimethyl
amine oxide to be 2.0×10^{-7} gram/person/day or 0.0029
micrograms/kg bwt/day. AD/RASSB concurs with this estimate and
will translate this estimate to Alkyl dimethyl amine oxide.