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

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Follow-up to AD/RASSB Human Exposure Review of October 5, 1998:
Non-Dietary Residential Exposure/Risk Assessment and Re-Determination
of Human Exposure Data Requirements for **CLEANING MAGIC I**
Containing a New Active Ingredient Chemical: **Alkyl (C₁₀₋₁₆) Dimethyl
Amine Oxide (Amine Oxide).**

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DP Barcodes: D253878 (S538885). See also D244309 (S538885).

**Pesticide
Chemical No.:** 000439

**A.I. Chemical
Name:** Alkyl (C₁₀₋₁₆) Dimethyl Amine Oxide

Registrant: The Procter & Gamble Company

**EPA File
Symbol No.:** 3573-LO

MRID No.: 444349-10

BACKGROUND:

In an October 5, 1998 review, AD/RASSB evaluated an exposure study designated MRID# 444349-10 and titled "*Human Exposure Calculations for Dodecyl Dimethylamine Oxide (DDAO)*" by R.L.Campbell, dated June 30, 1982. The study was submitted by the Procter & Gamble Company in support of the registration of a new active ingredient (a.i.): Alkyl (C₁₀₋₁₆) Dimethyl Amine Oxide (Amine Oxide), intended for use in four proposed antibacterial dishwashing detergents to be registered under the product names: CLEANING CARE I & II, and CLEANING MAGIC I & II.

The data was reviewed specifically in support of new product registration for CLEANING MAGIC I, EPA File Symbol No. 3573-LO, and was evaluated for acceptability and adherence to current EPA guidelines for conduct of an Indoor Surface Residue Dissipation Study (FIFRA data guideline 875.2300, *Series 875-Occupational and Residential Exposure Test Guidelines*). The exposure study included calculated estimates of residential exposures from the oral and dermal routes based on the intended dishwashing use patterns and foreseeable product misuses.

The registrant made the argument that the DDAO active ingredient is substantially similar to Amine Oxide based on chemical structure, toxicity, and use pattern. Therefore this data was assumed to be valid for presenting a "realistic" estimation of chronic consumer exposure" that occurs from use of light duty liquid (LDL) detergent.

The AD/RASSB assessment of October 5, 1998 concluded that the "study" (both the exposure assessment and residue data portions) was found to be unacceptable since it did not meet certain requirements under EPA's Series 875.2000 Guidelines for conducting post application exposure studies, including not meeting requirements for conducting an Indoor Surface Residue Dissipation Study (guideline 875.2300). Also, the data was not acceptable for evaluating potential risks to children under FQPA.

The 1998 AD/RASSB review also indicated that due to the lack of sufficient toxicological data on file with the Agency, the toxicity profile for Amine Oxide could not be verified by RASSB toxicologists. Without a clear understanding of the toxicity of Amine Oxide, the RASSB review provided an overview of all pertinent Human Exposure Data Requirements which might be imposed by the regulatory management for the registration of the proposed product, CLEANING MAGIC I.

PURPOSE OF CURRENT ASSESSMENT:

Since the 1998 assessment, the registrant has not submitted any additional human exposure data. However, additional toxicology studies have been reviewed by RASSB enabling selection of certain toxicological endpoints for conducting a more complete human exposure review. Currently, AD's Regulatory Management Branch I, Product Management Team 31, has requested that RASSB utilize the previously submitted 1982 exposure study to conduct the following:

- A re-assessment of the residential exposure potential from the intended product use patterns (and foreseeable misuses) by conducting a non-dietary human exposure and risk assessment (adults and children) based on recent toxicological endpoint selection for Amine Oxide, and certain dermal dose estimates presented previously in the 1998 exposure review;
- Calculate the Margins of Exposure (MOEs) for the handler scenarios using the selected NOAELs, and;
- A re-determination of the Human Exposure Data Requirements for CLEANING MAGIC I.

PRODUCT USE PROFILE:

The proposed product, CLEANING MAGIC I concentrated dishwashing detergent, contains 4.81% Amine Oxide as the antibacterial active ingredient. The draft product labeling indicates that the product is intended for handwashing of dishes, dishware, cutlery, utensils, and cutting boards, and provides directions for both general dishwashing use and to kill germs on dishware (dishes/utensils). To kill germs, the product is to be applied manually as a concentrate directly onto dishware, spread over the surface and allowed to stand 5 minutes before rinsing.

Based on the dishwashing detergent use pattern, CLEANING MAGIC I is intended for use in household, institutional, and commercial settings for terrestrial, indoor, "non-food" sites. The product uses are considered "non-food" since the labeling use directions require that all treated surfaces (e.g., dishes/utensils, and cutting boards) must be rinsed with potable water prior to any contact with food. The draft labeling also indicates a proposed optional use as a hand soap to remove germs from hands.

HUMAN EXPOSURE CONSIDERATIONS:

Summary of Human Exposure Assessment Calculations based on October 5, 1998 Review Data for DDAO in Detergents:

The Procter & Gamble (P & G) study (i.e., an exposure assessment and indoor surface residue data) previously submitted to AD as "*Human Exposure Calculations for Dodecyl Dimethylamine Oxide (DDAO)*" by R.L.Campbell, dated June 30, 1982 (designated MRID# 444349-10) presented calculated dermal (e.g. percutaneous) exposure doses through incidental contact with the pesticide resulting from product use. For the dermal exposure route, assumptions were used to estimate available concentrations of DDAO during dishwashing, hand laundering, handwashing, bathing and shampooing. Table 1. details the dermal dose calculations presented in the AD/RASSB October 5, 1998 exposure assessment which were derived using a revised permeability constant (K_p).

Table 1.: Dose Calculations: Adult Percutaneous Exposure to DDAO Using a More Conservative K_p .

Product Use	Exposure Conc. of DDAO ^a (µg/ml)	Permeability Constant ^b (K_p) (cm/hr)	Steady State Flux ^c (µg/cm ² /hr)	Duration of Exposure ^d (hrs/day)	Area of Contact ^e (cm ²)	Total Daily Exposure ^f (µg/day)	Total Dose (µg/kg/day)
Intended Uses							
Dishwashing	145	1.3E-04	1.9E-02	0.45	1,800	15	0.21
Hand Laundering *	145	1.3E-04	1.9E-02	0.07	1,800	2	0.029
						Total	0.24
Foreseeable Misuses							
Bath	13	1.3E-04	1.7E-03	0.18	16,000	4.9	0.07
Shampoo	5,000	1.3E-04	0.65	0.004	1,900	4.9	0.07
Handwashing **	50,000	1.3E-04	6.5	0.006	900	35.1	0.5
						Total	0.64
						Total (Both Pathways)	0.88

Table 1. Legend:

- ^a **Exposure Concentration of DDAO:** (As per Registrant's 1982 study data.) The level of a.i. in the light duty liquid (LDL) detergent product is 5% v/v DDAO. Product use concentrations were derived as follows: dishwashing (0.29% a.i. use solution), hand laundering (0.29% a.i. use solution), bath (0.026% a.i. use solution), shampoo (10% a.i. use solution), and hand washing (100% a.i. concentration). Density was not given in study. The product use concentration for "dishwashing" was derived from data in a DDAO residue study which characterized the amount of DDAO residues available on dinnerware after use of an LDL detergent. The registrant did not provide references or clarification for the selection of the other product use concentrations (% a.i.) cited above. Exposure concentrations were calculated as follows:

Assuming the a.i. concentration in a 5% v/v DDAO product = 50,000 ppm (or 50,000 mg/L, or 50,000 µg/ml)
then 0.29% a.i. in dishwashing and hand laundering solution = $0.29/100 \times 50,000 = 145 \mu\text{g/ml}$;
and 0.026% a.i. for bathing = $0.026/100 \times 50,000 = 13 \mu\text{g/ml}$;
and 10% a.i. for shampooing = $10/100 \times 50,000 = 5,000 \mu\text{g/ml}$;
and 100% a.i. for handwashing = $100/100 \times 50,000 = 50,000 \mu\text{g/ml}$.
- ^b **Permeability Constant (K_p):** The original K_p derived from Rice, 1977 was 2.3E-06 and considered by the Agency to be too low since it only used the % absorption from the total excretion products (18%). Calculated from the equation $K_p = \text{flux}/\text{concentration}$. Where flux across human skin is $<0.046 \mu\text{g/hr}/\text{cm}^2$ and concentration is 20 mg/ml (e.g. $2E+4 \mu\text{g/ml}$). The K_p value was recalculated in Table 4. above based on animal study data on recovery of DDAO in excretion products and tissue samples (% absorption of 35%) to yield a more conservative permeability constant K_p of 1.3E-04.
- ^c **Steady State Flux** = $K_p \times \text{conc.}$
- ^d **Duration of Exposure:** (As per Registrant's 1982 study data.) The assumptions are as follows: dishwashing [based on 12.7 dishwashing per week (1.8 per day) at 15 min. per washing = 27 min. per day]; hand laundry [10 min/use and 3.1 times/week = 31 min. per week (4.4 min. per day)]; bath [17 min and 4.4 times/week = 74.8 min. per week (10.7 min. per day)]; shampoo [1 min and 1.7 times/week = 1.7 min. per week (0.24 min. per day)]; and handwashing [20 seconds once a day = 0.333 min per day].
- ^e **Area of Contact:** (As per Registrant's 1982 study data.) It was assumed that hands and arms are 10% of total adult body surface area of 18,000 cm² for dishwashing and hand laundering. Reference for assumptions used for bath, shampoo, and handwashing is not given.
- ^f **Total Daily Exposure** = steady state flux (µg/cm²/hr) x use time (hr/day) x surface area of contact (cm²).
- ^g **Total Dose** = daily exposure (µg/day)/ body weight (kg). (Adult body weight = 70 kg.)
- * As per the P & G Study, "Hand Laundering" was designated an "Intended Use" although the draft labeling for the CLEANING MAGIC I product (EPA File Symbol 3573-LO) includes no reference to this use pattern.
- ** As per the P & G Study, "Handwashing" was designated as a "Foreseeable Misuse" although the draft labeling for the CLEANING MAGIC I product (EPA File Symbol 3573-LO) includes a reference to this as an optional "hand soap" use pattern.

Critical Data Gaps Noted in the October 5, 1998 Review Concerning the DDAO Human Exposure Assessment:

- The study assessed only exposures to adults not children. With the passage of the Food Quality Protection Act of 1996 (FQPA), the Agency is required to examine potential exposure risks to children. Since the body weights of infants (10 kg) and children through the age of 12 years (15 kg - 39.1 kg) are much smaller than adults (70 kg), it is critical to assess risks among children separately from adults. Children also have a higher surface area to body weight ratio, resulting in a potentially higher dermal exposure per unit body mass.
- Included among the exposure factors in question is the surface area of contact. Guidance from the *Exposure Factors Handbook* (EPA, 1997) indicates that total body area can vary from 17,000 cm² to 23,000 cm² and the mean is reported as 20,000 cm². The DDAO exposure assessment reports the entire body surface area as 18,000 cm². In addition, the mean surface area of hands and forearms are reported in the *Exposure Factors Handbook* as 0.198 m² (1,980 cm²) and the DDAO exposure assessment reports a value of 1,800 cm². The DDAO exposure assessment also reports the surface area of skin available for contact in the bathing, shampooing, and handwash as 16,000, 1,900, and 900 cm², respectively. It does not include a reference or an explanation of the body parts available for contact. Using the *Exposure Factors Handbook*, it would seem reasonable that for bathing a total body surface area of 20,000 cm² should be used. For shampooing, the body contact would include at the least hands, forearms, and head exposure, which would equate to a body surface area of 3,160 cm². Finally, for handwashing the original scenario of hands and forearm exposure of 1,980 cm² might be a more conservative estimate of the body surface area.
- The permeability constant (K_p) listed is also of question. The study reports a K_p of 2.3E-06 cm/hr, and provides a reference to a human study examining flux of the chemical across the human skin (Rice, 1977). The value listed as the K_p is very low compared to other measured K_p's listed in EPA guidance. In addition, this guidance also provides an equation for estimation of the permeability coefficient:

$$\log K_p = -2.72 + 0.71 \log K_{ow} - 0.0061 MW \text{ (EPA 1992)}$$

Where:

$$MW = 229.41$$

$$\log K_{ow} = 6.273 \text{ estimated from EPIWIN database (Syracuse Research Corp., 1996)}$$

Using values from the EPIWIN database, an estimated K_p of 2.14 cm/hr was obtained for DDAO. This value was considered too high to use as an estimate of dose. Instead the Rice, 1977 study was reevaluated. The partition coefficients for rats in the Rice, 1977 study appeared to be the most conservative. Since the initial K_p was calculated only using the % absorption after total excretion (18%), the partition coefficient was recalculated using the % absorption after total excretion and tissue sampling analysis (35%). The calculated K_p was 1.3E-04 cm/hr.

- Some questions also exist over the duration of exposure listed. For example, the average shampoo times per week is listed as 1.7 times in the DDAO exposure assessment. It would seem reasonable to adjust this assumption to at least 3-5 times per week. Another questionable assumption listed in the DDAO exposure includes a 20 second handwashing duration per day. It would seem that a more conservative estimate would be a 20 second handwashing duration including at least 3 events per day before meal times.

NON-DIETARY RESIDENTIAL EXPOSURE RE-ASSESSMENT:

For the purposes of conducting a follow-up to the human exposure and risk assessment presented in the AD/RASSB review of October 5, 1998, the following apply:

- Applicable data and assumptions (derived from the 1982 exposure study), along with the recommended revised input values presented in the previous AD/RASSB review will be utilized for this assessment for consistency. (Please see the 1998 review generated under D244309 as background reference.)
- Exposure estimates for Adults and Children (representative ages of 3, 6, and 10-12 yrs.) will be calculated only for the dermal route (i.e., percutaneous absorption) in keeping with conducting a non-dietary exposure and risk assessment. Routes of exposure not covered in this assessment include incidental ingestion of Amine Oxide residues on dinnerware, direct ingestion of drinking water containing Amine Oxide residues, and inhalation exposure during CLEANING MAGIC I product use. Dietary exposures/risks will be assessed in a separate FQPA review to be prepared for this submission under data barcode D253848 by Tim McMahon, RASSB Senior Toxicologist.
- Calculated Margins of Exposure (MOEs) for short-term, intermediate, and chronic exposures will be derived using recently selected toxicological endpoints not available for the 1998 exposure assessment.

Acute Toxicity Profile of Amine Oxide:

Toxicology reviews on file with the Agency for both the Amine Oxide technical grade active ingredient (TGAI, 27.72% a.i.) and the formulated CLEANING MAGIC I end-use product (4.81% a.i.) reveal the following acute toxicity as presented in Tables 2. and 3..

Table 2.
Acute Toxicity of Amine Oxide:
TGAI (27.72% a.i.)

Guideline No.	Study Type	MRIDs #	Results	Toxicity Category
81-1	Acute Oral	44475201	LD ₅₀ = 4800 mg/kg	III
81-2	Acute Dermal	44475202	LD ₅₀ > 1880 mg/kg	II
81-3	Acute Inhalation	no study	data waiver accepted	
81-4	Primary Eye Irritation	44434904	corrosive, primary eye irritation	I
81-5	Primary Skin Irritation	44434905	severe dermal irritant	unassigned (data limited)
81-6	Dermal Sensitization	44434906	dermal sensitizer	
81-8	Acute Neurotoxicity	no study		

Table 3.
Acute Toxicity of Amine Oxide:
CLEANING MAGIC I (4.81% a.i.)

Guideline No.	Study Type	MRIDs #	Results	Toxicity Category
81-1	Acute Oral	44434706	LD ₅₀ > 5000 mg/kg	IV
81-2	Acute Dermal	no study	data waiver submitted and denied	
81-3	Acute Inhalation	no study	data waiver accepted	IV
81-4	Primary Eye Irritation	no study	data waiver submitted and denied	
81-5	Primary Skin Irritation	44434707	dermal irritant	II
81-6	Dermal Sensitization	44434711	nonsensitizer	

Selection of Toxicological Endpoints for the Residential Exposure Re-Assessment:

The toxicological endpoints selected for the residential exposure re-assessment are presented below in Table 4. and were derived from the Agency's current database on Amine Oxide. There are no available studies on the potential neurotoxicity of Amine Oxide, and limited data on developmental toxicity. The selection of percentage (%) dermal absorption to be used in the exposure calculations is 35% as derived from the revised permeability constant (K_p) selected by the Agency, based on the registrant's 1982 data on DDAO.

TABLE 4.: TOXICOLOGICAL ENDPOINTS SELECTED FOR NON-DIETARY RESIDENTIAL EXPOSURE RE-ASSESSMENT OF AMINE OXIDE		
EXPOSURE SCENARIOS	TOXICITY ENDPOINT (mg/kg/day)	DATA SOURCE
Short -Term Dermal/ Intermediate -Term Dermal	Oral NOAEL = 25 This dermal endpoint was derived from a dietary study therefore an Uncertainty Factor (UF) of 100 will be applied, along with an FQPA Uncertainty Factor of 3. (100 UF x 3 FQPA UF = Acceptable MOE of 300)	Developmental Toxicity - Rat (MRID 44762401)
Long -Term Dermal	Oral NOAEL = 42.3 This dermal endpoint was derived from a chronic dietary study therefore an Uncertainty Factor (UF) of 100 will be applied. No FQPA UF is applied for this exposure. (100 UF = Acceptable MOE of 100)	Chronic Toxicity/ Carcinogenicity - Rat (MRID 44586201)

Using the revised inputs recommended in the October 5, 1998 review (i.e., revised K_p , body surface areas, and exposure durations) combined with the recent selection of toxicological endpoints for Amine Oxide, facilitated a re-assessment of residential exposures which included both Adults and Children (representative ages of 3, 6, and 10-12 yrs.). Table 5. details the new dose determinations and Table 6. the calculated MOEs for each non-dietary exposure scenario.

Table 5.

Dose Calculations: Adult and Child Percutaneous Exposure to DDAO Using Revised Inputs

Product Use Scenarios	Exposure Conc. of DDAO* (µg/ml)	Permeability Constant ^b (K _p) (cm/hr)	Steady State Flux ^c (µg/cm ² /hr)	Duration of Exposure ^d (hrs/day)	ADULT EXPOSURE/DOSE			CHILD EXPOSURE/DOSE		
					Area of Contact ^e (cm ²)	Total Daily Exposure ^f (µg/day)	Total Daily Dose ^g (µg/kg/day)	Area of Contact ^e (cm ²)	Total Daily Exposure ^f (µg/day)	Total Daily Dose ^g (µg/kg/day)
INTENDED USES										
Dishwashing (Adult and Youth)	145	1.3E-04	1.9E-02	0.45	1,980	17	0.24	Toddler (Age 3 yrs.) BW = 15 kg		
Mock Dishwashing (as pretend play activity for "Toddler" and "Child" age groups)								1,343	11.5	0.77
								Child (Age 6 yrs.) BW = 22 kg		
								1,521	13.0	0.6
Hand Laundering* (Adult and Youth)								Youth (Age 10-12 yrs.) BW = 39.1 kg		
								2,329	19.9	0.5
								Toddler (Age 3 yrs.) BW = 15 kg		
Mock Hand Laundering (as pretend play activity for "Toddler" and "Child" age groups)								1,343	1.8	0.1
								Child (Age 6 yrs.) BW = 22 kg		
								1,521	2.0	0.09
								Youth (Age 10-12 yrs.) BW = 39.1 kg		
								2,329	3.1	0.08
								Toddler (Age 3 yrs.) BW = 15 kg		

FORESEEABLE MISUSES:

Bath	13	1.3E-04	1.7E-03	0.18	20,000	6.1	0.09	Toddler (Age 3 yrs.) BW = 15 kg		
								6,565	2.0	0.13
								Child (Age 6 yrs.) BW = 22 kg		
								8,545	2.6	0.12
		Youth (Age 10-12 yrs.) BW = 39.1 kg		12,700	3.9	0.1				
Shampoo	5,000	1.3E-04	0.65	0.01	3,160	20.5	0.3	Toddler (Age 3 yrs.) BW = 15 kg		
								2,236	14.5	0.97
								Child (Age 6 yrs.) BW = 22 kg		
								2,640	17.2	0.78
		Youth (Age 10-12 yrs.) BW = 39.1 kg		3,439	22.4	0.57				
Handwashing**	50,000	1.3E-04	6.5	0.02	1,980	257	3.67	Toddler (Age 3 yrs.) BW = 15 kg		
								1,343	174.6	11.6
								Child (Age 6 yrs.) BW = 22 kg		
								1,521	197.7	9.0
		Youth (Age 10-12 yrs.) BW = 39.1 kg		2,329	302.8	7.7				

Table 5. Legend.

- * Exposure Concentration of DDAO: (As per Registrant's 1982 study data.) The level of a.i. in the light duty liquid (LDL) detergent product is 5% v/v DDAO. Product use concentrations were derived as follows: dishwashing (0.29% a.i. use solution), hand laundering (0.29% a.i. use solution), bath (0.026% a.i. use solution), shampoo (10% a.i. use solution), and hand washing (100% a.i. concentration). Density was not given in study. The product use concentration for "dishwashing" was derived from data in a DDAO residue study which characterized the amount of DDAO residues available on dinnerware after use of an LDL detergent. The registrant did not provide references or clarification for the selection of the other product use concentrations (% a.i.) cited above. Exposure concentrations were calculated as follows:

Assuming the a.i. concentration in a 5% v/v DDAO product = 50,000 ppm (or 50,000 mg/L, or 50,000 µg/ml)
then 0.29% a.i. in dishwashing and hand laundering solution = $0.29/100 \times 50,000 = 145 \mu\text{g/ml}$,
and 0.026% a.i. for bathing = $0.026/100 \times 50,000 = 13 \mu\text{g/ml}$,
and 10% a.i. for shampooing = $10/100 \times 50,000 = 5,000 \mu\text{g/ml}$,
and 100% a.i. for handwashing = $100/100 \times 50,000 = 50,000 \mu\text{g/ml}$.
- b Permeability Constant (K_p): The original K_p derived from Rice, 1977 was 2.3E-06 and considered by the Agency to be too low since it only used the % absorption from the total excretion products (18%). Calculated from the equation $K_p = \text{flux/concentration}$. Where flux across human skin is $<0.046 \mu\text{g/hr/cm}^2$ and concentration is 20 mg/ml (e.g. 2E+4 µg/ml). The K_p value was recalculated in Table 5. above based on animal study data on recovery of DDAO in excretion products and tissue samples (% absorption of 35%) to yield a more conservative permeability constant K_p of 1.3E-04.
- c Steady State Flux = $K_p \times \text{conc.}$
- d Duration of Exposure: (As per Registrant's 1982 study data and certain Agency revisions for shampoo and handwashing.) The assumptions are as follows: dishwashing [based on 12.7 dishwashing per week (1.8 per day) at 15 min. per washing = 27 min. per day]; hand laundry [10 min/use and 3.1 times/week = 31 min. per week (4.4 min. per day)]; bath [17 min and 4.4 times/week = 74.8 min. per week (10.7 min. per day)]; shampoo [1 min and 5 times/week = 5 min. per week (0.71 min. per day)]; and handwashing [20 seconds 3 times a day = 1 min per day].
- e Area of Contact: The values selected for Adult and Child exposures are as follows:

ADULT: Area of contact (hands and forearms) was estimated at 1,980 cm² for dishwashing, hand laundering, and handwashing. It was assumed that the whole body is exposed during bathing, so the total adult body surface area of 20,000 cm² was used. For shampooing, the area of contact (hands, forearms, and head) was estimated at 3,160 cm². All values selected were taken from the *Exposure Factors Handbook* (EPA, 1997).

CHILD: Area of contact (hands and arms) was estimated at 1,343 cm² (Toddler), 1,521 cm² (Child), and 2,329 cm² (Youth) for dishwashing, hand laundering, and handwashing. It was assumed that the whole body is exposed during bathing, so the total body surface area of 6,565 cm² was used for Toddler, 8,545 cm² for Child, and 12,700 cm² for Youth (as the average of the median M & F values for 10-12 year-olds). For shampooing, the area of contact (hands, arms, and head) was estimated at 2,236 cm² (Toddler), 2,640 cm² (Child), and 3,439 cm² (Youth). All values selected were taken from the *Exposure Factors Handbook* (EPA, 1997).
- f Total Daily Exposure = steady state flux (µg/cm²/hr) x use time (hr/day) x surface area of contact (cm²).
- * Total Daily Dose = daily exposure (µg/day)/body weight (kg). (Adult body weight = 70 kg; Toddler body weight = 15 kg; Child body weight = 22 kg; and Youth body weight = 39.1 kg.)
- * As per the P & G Study, "Hand Laundering" was designated an "Intended Use" although the draft labeling for the CLEANING MAGIC I product (EPA File Symbol 3573-LO) includes no reference to this use pattern.
- ** As per the P & G Study, "Handwashing" was designated as a "Foreseeable Misuse" although the draft labeling for the CLEANING MAGIC I product (EPA File Symbol 3573-LO) includes a reference to this as an optional "hand soap" use pattern.

Table 6.

MOE Calculations: Adult and Child Percutaneous Exposure Assessment

Product Use Scenarios	Short-Term & Intermediate-Term Exposures						Long-Term Exposures					
	ADULT DAILY DOSE		CHILD DAILY DOSE		MOES		ADULT/CHILD DAILY DOSE		MOES		MOES	
	Total Daily Dose ^a (µg/kg/day)	Adjusted Total Daily Dose ^b (mg/kg/day)	Total Daily Dose ^a (µg/kg/day)	Adjusted Total Daily Dose ^b (mg/kg/day)	Adult ^c	Child ^c	Adult ^d (mg/kg/day)	Child ^d (mg/kg/day)	Adult ^c	Child ^c	Adult ^e	Child ^e
Dishwashing/ Mock Dishwashing	0.24	2.4E-4	Toddler = 0.77	7.7E-4	104,167	32,467	2.4E-4	7.7E-4	176,250	54,935	176,250	54,935
			Child = 0.6	6.0E-4		41,667		6.0E-4		70,500		70,500
			Youth = 0.5	5.0E-4		50,000		5.0E-4		84,600		84,600
Hand Laundering*/ Mock Hand Laundering	0.04	4.0E-5	Toddler = 0.1	1.0E-4	625,000	250,000	N/A	N/A	N/A	N/A	N/A	N/A
			Child = 0.09	9.0E-5		277,778		N/A		N/A		N/A
			Youth = 0.08	8.0E-5		312,500		N/A		N/A		N/A
Bath	0.09	9.0E-5	Toddler = 0.13	1.3E-4	277,778	192,308	9.0E-5	1.3E-4	470,000	325,385	470,000	325,385
			Child = 0.12	1.2E-4		208,333		1.2E-4		325,500		325,500
			Youth = 0.1	1.0E-4		250,000		1.0E-4		423,000		423,000
Shampoo	0.3	3.0E-4	Toddler = 0.97	9.7E-4	83,333	25,773	3.0E-4	9.7E-4	141,000	43,608	141,000	43,608
			Child = 0.78	7.8E-4		32,051		7.8E-4		54,231		54,231
			Youth = 0.57	5.7E-4		43,860		5.7E-4		74,210		74,210
Handwashing**	3.67	3.67E-3	Toddler = 11.6	1.16E-2	6,812	2,155	3.67E-3	1.16E-2	11,526	3,646	11,526	3,646
			Child = 9.0	9.0E-3		2,778		9.0E-3		4,700		4,700
			Youth = 7.7	7.7E-3		3,247		7.7E-3		5,493		5,493

Table 6. Legend:

- Total Daily Dose:** The total daily doses ($\mu\text{g}/\text{kg}/\text{day}$) for Adult and Child groups are taken from Table 5. Daily exposure ($\mu\text{g}/\text{day}$) / body weight (kg) = total daily dose. (Adult body weight = 70 kg; Toddler body weight = 15 kg; Child body weight = 22 kg; and Youth body weight = 39.1 kg.)
- Adjusted Total Daily Dose:** ($\text{mg}/\text{kg}/\text{day}$) = Total daily dose ($\mu\text{g}/\text{kg}/\text{day}$) x .001 conversion factor of micrograms (μg) to milligrams (mg).
- Short-Term & Intermediate-Term MOEs:** (Adult and Child) The Margins of Exposure (MOEs) were derived from the selected Oral NOAEL (No-observed-adverse-effect-level) of 25 $\text{mg}/\text{kg}/\text{day}$ for both Short-Term & Intermediate-Term dermal exposure (Developmental Toxicity - Rat, MRID 44762401). $\text{MOE} = \text{Oral NOAEL} (\text{mg}/\text{kg}/\text{day}) / \text{Adjusted total daily dose} (\text{mg}/\text{kg}/\text{day})$. Acceptable Short-Term/Intermediate-Term MOE = 300 or greater (100 UF x 3 FQPA UF).
- Adult/Child Long-Term Dose = Adjusted Total Daily Dose** ($\text{mg}/\text{kg}/\text{day}$) (See footnote ^b above.) Note that the "hand laundering/mock hand laundering" scenario was < 180 days/year (i.e., 161 days/year) and therefore was not assumed to be a long-term (chronic) exposure scenario (hence, "N/A" designation).
- Long-Term MOEs:** (Adult and Child) were calculated for scenarios in which exposures > 180 days/year. The Margins of Exposure (MOEs) were derived from the selected Oral NOAEL (No-observed-adverse-effect-level) of 42.3 $\text{mg}/\text{kg}/\text{day}$ for Long-Term dermal exposure (Chronic Toxicity/ Carcinogenicity - Rat, MRID 44586201). $\text{MOE} = \text{Oral NOAEL} (\text{mg}/\text{kg}/\text{day}) / \text{Adjusted total daily dose} (\text{mg}/\text{kg}/\text{day})$. Acceptable Long-Term MOE = 100 or greater (100 UF).
- * As per the P & G Study, "Hand Laundering" was designated an "Intended Use" although the draft labeling for the CLEANING MAGIC I product (EPA File Symbol 3573-LO) includes no reference to this use pattern.
- ** As per the P & G Study, "Handwashing" was designated as a "Foreseeable Misuse" although the draft labeling for the CLEANING MAGIC I product (EPA File Symbol 3573-LO) includes a reference to this as an optional "hand soap" use pattern.

Discussion of Exposure Re-Assessment Findings:

Based on this limited exposure re-assessment (i.e., the dose and MOE calculations presented in Tables 5. and 6.), there appears to be minimal potential for adverse dermal exposures and risks to adults and children from both intended product use patterns and foreseeable misuses. All the derived MOEs exceeded the minimum criteria for acceptable exposures (i.e., ≥ 300 for short-term and intermediate exposures, and ≥ 100 for long-term exposures).

However, these findings are considered preliminary until the Agency compiles a more complete toxicology database for Amine Oxide, and the registrant submits acceptable indoor surface residue dissipation data (post-application exposure guideline 875.2300) and indoor dermal exposure data (application exposure guideline 875.1200). This reviewer cautions basing regulatory decisions on the findings of this exposure re-assessment, since the data from which most of the exposure assumptions were based have not been verified, namely data from the 1982 DDAO exposure study.

Re-Assessment Data Gaps/Limitations:

The most critical data gaps and limitations to this residential exposure re-assessment are noted below:

- Calculations of dermal doses for the Adult and Child groups were derived primarily from the 1982 DDAO exposure study inputs which included unverifiable assumptions for exposure concentrations, and exposure durations.
- The reliance on a permeability constant (K_p) from the Rice, 1977 study (i.e., *Rice, B.D. 1977. The Absorption, Tissue Distribution, and Excretion of Dodecyl Dimethylamine Oxide DDAO in Selected Animal Species and the Absorption and Excretion of DDAO in Man. Toxicol. Appl. Pharmacol. 39:377-389.*) in order to estimate dermal absorption as 35%, might not be appropriate for characterizing the actual percentage (%) dermal absorption during product use scenarios.

HUMAN EXPOSURE DATA REQUIREMENTS:

Human exposure data are required under FIFRA (40CFR 158, Subdivisions K, and U) when based on the antimicrobial pesticide's toxicity, certain toxicological criteria trigger the need for such data, (e.g., the Acute Toxicity Studies indicate Category I or II Toxicity) and the human activities associated with the use patterns can lead to potential adverse exposures to handlers and bystanders. The AD Regulatory Management Branch I, Product Management Team 31, requested a re-determination of applicable human exposure data requirements based on the outcome of this residential exposure re-assessment.

RASSB recommends that the registrant address the Application and Post Application Human Exposure Data Requirements (FIFRA, Series 875) outlined in Table 7, based on the following:

- No additional human exposure studies have been submitted since the October 5, 1998 review was conducted and the only data available to RASSB (i.e., the 1982 DDAO exposure study) was considered unacceptable since the data was not generated according to Series 875 Test Guidelines for conducting an Indoor Surface Residue Dissipation Study (post-application exposure guideline 875.2300), nor did it address potential exposures to children as per FQPA considerations. Therefore, the Agency is still in need of data which realistically characterizes the exposure potential for residential handlers (adults/children) of formulated Amine Oxide liquid detergent products..
- The toxicological database is still considered limited (both product toxicology, and mammalian toxicology for the TGAI) and the toxicity category for CLEANING MAGIC I (from which the precautionary labeling statements are based) remains unconfirmed until further product toxicology studies are submitted, specifically an Acute Dermal Study and Primary Eye Irritation Study. Also, data from the Primary Skin Irritation Study indicates that the formulated end-product (4.81% a.i.) is a toxicity category II dermal irritant, triggering the need for the Indoor Dermal Exposure Study (application exposure guideline 875.1200). Also, the proposed optional antibacterial "hand soap" use pattern reinforces the need for such data.
- Due to the lack of an acceptable Indoor Surface Residue Dissipation Study (post-application exposure guideline 875.2300), the Agency can not confirm what the actual available concentration of Amine Oxide residues would be for post-application dermal contact, even though it is assumed to be negligible after rinsing of dishware with potable water (and/or rinsing of hands after "hand soap" use.) However, until the additional product toxicology data is submitted to gauge acute dermal toxicity, and pending the results of the Indoor Dermal Exposure Study (application exposure guideline 875.1200) requested of the registrant, RASSB reserves the data requirements at this time for both the Indoor Surface Residue Dissipation Study (post-application exposure guideline 875.2300) and the Indoor Dermal Exposure Study (post-application exposure guideline 875.2400).
- Human exposure data requirements for all "Inhalation" exposure studies (application exposure guidelines 875.1300, 875.1400 and post-application exposure guideline 875.2500) will be waived since no breathable aerosol is anticipated to be formed during and after product use.
- Human exposure data requirements for all "Outdoor" exposure studies (application exposure guidelines 875.1100, and 875.1300) will be waived since the product use patterns are restricted to indoor settings.

TABLE 7.
Human Exposure Data Requirements - (Application/Post Application):

CLEANING MAGIC I End-Use Product Containing Amine Oxide (4.81% a.i.)

Data Requirement	Use Categories II, III & IV	Notes, Conditions	Test Substance	Guideline Reference OLD	Guideline Reference NEW
Application					
Product Use Information	R	Complete product labeling with use site and use rate application information Detailed description of use pattern activities associated with product application	TEP	none	875 1700
Dermal Exposure Indoor	R	Data required if toxicity criteria and human activities associated with product use trigger potential adverse exposure concerns. The product is a Toxicity Category II dermal irritant. Therefore this data requirement must be addressed.	TEP	233	875 1200 875 1600
Biological Monitoring	CR	Biological Monitoring Data may be submitted in addition to or instead of dermal exposure data provided adequate pharmacokinetics data are available to interpret the biological monitoring data	TEP	235	875 1500 875 1600
Post Application					
Product Use Information	R	Complete product labeling with use site and use rate application information Detailed description of use pattern activities associated with reentry into treated areas	TEP	none	875 2700
Description of Human Activity	R	Complete information on the types of human activities associated with product use and post application activities in treated areas Define the exposed populations in the commercial/residential/institutional settings	TEP	133-1	875 2800
Indoor Surface Residue Dissipation	R	Data required if the use pattern and formulation types involve significant potential exposure to humans by evaporation of residues from surfaces or contact with residues on treated surfaces. The 1982 P & G exposure study on DDAO (MRID 444349-10) did not meet EPA Series 875 Guidelines for conducting such studies and was found to be unacceptable. This data requirement is reserved pending the results of additional product toxicology data and application exposure data for 875.1200.	TEP	none	875 2300 875 2900
Dermal Exposure Indoor	R	Testing for post application exposure would be needed <u>unless</u> the product use information, description of human activity, or chemical characteristics of the product, indicates <u>exposure</u> in or near areas where pesticide was applied is <u>not likely to be significant</u> . This data requirement is reserved pending the results of additional product toxicology data and application exposure data for 875.1200.	TEP	133-3	875 2400 875 2900
Biological Monitoring	CR	Biological Monitoring Data may be submitted in addition to or instead of dermal exposure data provided adequate pharmacokinetics data are available to interpret the biological monitoring data	TEP	235	875 2600 875 2900

Note: CR=Conditionally Required, R= Required, TEP=Typical End-Use Product.

cc: Doreen Aviado/RASSB/AD (7510C)
Chemical File
Circulation