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Office of Prevention, Pesticides and Toxic Substances

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MEMORANDUM

SUBJECT: Naled; Chemical No. 034401. Revised Assessment of Risk from Use of Naled in Pet Collars

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This provides HED's revised assessment of risk from use of naled in pet collars. The existing naled pet collar assessment was based entirely on assumptions on how much naled in a pet collar would be available for transfer to a child hugging or petting a dog. HED has received information from the MSU pet collar study on transferability of residues from chlorprifos-treated dogs that was not available for the original naled pet collar assessment.

The existing naled assessment assumed 20% of the residues are available for transfer. We now have new transferability estimates for assessing dog collars. We have also modified the hand-to-mouth scenario for pet collars by using the 5-minute petting routine in the study to represent the amount of residue a child would obtain over the day (i.e., the old 2 hour estimate x 20 hand-to-

mouth activities/events per hour). Tables 1 and 2 contain summaries of the MSU pet collar residues.

Because the collars can be replaced, exposures are assumed to be potentially chronic in nature. The new estimates for naled using the chronic oral NOAEL of 0.2 mg/kg/day and 21 percent dermal absorption (Short- and Intermediate-term dermal NOAEL of 10 mg/kg/day) are as follows:

Hand-to-Mouth (HTM):

The traditional estimates of hand-to-mouth exposure are based on estimates of residues on a child's hand, the frequency of which the hand goes in the mouth, and the duration the child is in contact with the treated surface. While duration estimates are available for a child playing outside (e.g., on lawn), no estimates of contact time are available for pets. Therefore, it is recommended for the pet collar scenario that the oral hand-to-mouth route be based on the amount of residue transferred from the neck with the collar (highest of the three areas monitored). The residues available from the 5 minute vigorous petting routine is believed to be a conservative estimate of the amount of residue available for ingestion for a day. It is believed to be a conservative estimate because it represents 7.5 seconds of petting *prior to each of 40 hand-to-mouth events* (i.e., (5 minutes sampling x 60 seconds/minute) / (2 hours per day x 20 hand-to-mouth events per hour)). The two hour duration is arbitrary, only presented as a point of reference. Furthermore, the biological monitoring data, even though inconclusive for regulatory decisions, do not indicate any dose levels higher than that estimated by the residue method. However, more research is needed in this area of pet collar exposure.

Chronic HTM dose (mg/kg/day) = (Neck with collar of 1.5 $\mu\text{g}/\text{cm}^2/\text{gram ai}$ x 3.8 gram ai naled collar x 0.001 mg/ μg x 0.5 saliva extraction efficiency x 20 cm^2 palmar surface area of fingers into mouth) / 15 kg body weight

Where: Neck with collar of 1.5 $\mu\text{g}/\text{cm}^2/\text{gram ai}$ = (TWA 340 μg neck with collar/88 cm^2 child's palm) / 2.54 gram ai in chlorpyrifos test collar. [child's hand surface area is 350 cm^2 for both hands; therefore, 175 cm^2 represents one hand and 88 cm^2 represents the palm of one hand]. The most conservative approach assumes that equilibrium is not attained, i.e. petting the dog in the sampling area (258 cm^2) would yield the same amount of transferable residue regardless if the hand used to pet the dog was an adult's hand (as monitored in the study) or a smaller hand of a child. If equilibrium were attained in the study, the *concentration* in $\mu\text{g}/\text{cm}^2$ would be the same on the child's hand vs. the adult hand and the total amount on the child's hand would be less by a factor of 2.6 reflecting the difference in areas of the hand.

Chronic Dose_(HTM) = 0.0038 mg/kg/day (0.0015 mg/kg/day if equilibrium was attained)

Chronic MOE_(HTM) = NOAEL 0.2 mg/kg/day / Dose 0.0038 mg/kg/day = 53 (140 if equilibrium was attained)

Dermal Contact:

The dermal contact scenario is based on the use of the transferable residue data normalized by the sampling area and by the amount of active ingredient in the collar (in units of $\mu\text{g}/\text{cm}^2/\text{gram ai}$). A linear relationship between the active ingredient and the residues is assumed.

The transferable residues are then extrapolated to the surface area of a "hug" (i.e., 1875 cm²). [The "hug" concept is based on HED's interaction with the SAP.] No data are available to determine the frequency of "hugs". However, the transferability of the residues from the 5 minute vigorous petting routine in the study is a reasonable surrogate for the transferability of a days worth of "hugs" of a dog by a child.

No defensible rationale is available to determine an "area" weighted mean of the residues from the neck with collar, neck without collar, and back. Therefore, to avoid unnecessary postulating on percentage of each area of the dog hugged, a simplistic use of proportions (i.e., thirds) of the three monitored areas of the dog has been selected. Table 2 illustrates the TWA values monitored from 1 to 168 DAT (excluding the 4 hour measurement). The surrogate value to be used as the dermal TWA transferable residue is 0.29 µg/cm²/gram ai (or 0.29 µg/cm²/gram ai x 1875 cm² hug = 540 µg/gram ai). This represents a daily exposure for a chronic duration.

Estimated Absorbed Dermal Dose (mg/kg/day) = (0.29 µg/cm²/gram ai x 0.001 mg/ug x 1875 cm² x 3.8 gr ai naled pet collar x 21 % dermal absorption) / 15 kg

ST & IT Potential Dose = 0.14 mg/kg/day

ST & IT MOE = NOAEL 10 mg/kg/day / dose 0.14 mg/kg/day = 71

Chronic Dose _(abs dermal) = 0.032 mg/kg/day

Chronic MOE = NOAEL 0.2 mg/kg/day / dose 0.029 mg/kg/day = 7

Discussion:

In support of the naled pet collars the registrant has used the biological monitoring portion of the chlorpyrifos study. This is of concern because:

- The biological monitoring in the pet collar study represents chlorpyrifos which has a low dermal absorption (3 percent) compared with naled (21 percent). Other pharmacokinetic differences need to be explored. A biological monitoring study with naled should be performed.
- A total of 24 households were selected for the study which ran for 168 days from the time the collars were placed on the dogs (biological monitoring was conducted using one adult and one child from each of the 24 households). The children were unaware of the study so as not to bias their playing with the dog. Time in room with the dog was recorded but no information was recorded on actual contact with the dog. Although the researchers concluded that the analysis of the urinary metabolites did not support the increased exposures as estimated using the transferable residues, the biological monitoring may have underestimated the absorbed dose of the population that plays routinely with their dog (e.g., the children that participated in the study were unaware they were being "observed" to reduce bias, contacts with the dog were not recorded, the urine samples were incomplete, and the creatinine levels have not been determined yet, etc.). The pet

collar study is a good start into researching the potential exposures children may receive from treated pet collars, but the design of the biological monitoring portion of the study was insufficient for regulatory purposes.

- Uncertainties arise in the biological monitoring (and transferable residues) based on the physical/chemical properties – will chlorpyrifos and naled both leach from the collars at the same rate?

Table 1. Mississippi State University Chlorpyrifos Pet Collar Transferable Residue Data.

DAT	Neck with Collar		Neck with Collar Removed		Back	
	(ug)	(ug/cm ²)	(ug/cm ²)	(ug/cm ²)	(ug/cm ²)	(ug/cm ²)
		(ai)	(ai)	(ug)		
4 hours	168 ± 132	0.7	0.26	49 ± 39	0.07	3 ± 4
1	190 ± 140	0.7	0.29	128 ± 170	0.20	5 ± 9
3	219 ± 120	0.8	0.33	124 ± 95	0.19	6 ± 5
7	186 ± 101	0.7	0.28	119 ± 74	0.46	4 ± 3
14	393 ± 365	1.5	0.60	242 ± 168	0.94	6 ± 7
28	318 ± 129	1.2	0.49	241 ± 180	0.93	13 ± 18
56	350 ± 196	1.4	0.53	238 ± 194	0.92	8 ± 9
84	310 ± 182	1.2	0.47	216 ± 124	0.84	14 ± 17
112	387 ± 236	1.5	0.59	252 ± 184	0.98	10 ± 9
140	377 ± 278	1.5	0.58	220 ± 122	0.85	10 ± 9
168	313 ± 158	1.2	0.48	194 ± 102	0.75	9 ± 11
TWA (1 to 168 days)	340	1.3	0.52	225	0.87	10
Average (1 to 168 days)	304	1.2	0.46	197.4	0.76	8.5
std (average of average)	79	0.3	0.12	53.5	0.20	3.3
Median (1 to 168 days)	316	1.2	0.48	218	0.84	8.5
Geo mean (1 to 168 days)	294	1.14	0.45	189.87	0.74	7.90

The 4-hour sample is not included in the summary statistics because insufficient time elapsed to spread the residues and the fact that 1 DAT samples are available.

TWA is the time weighted average from day 1 to 168. Std (average of average) represents the standard deviation of the sampling interval averages, not individual measurements. The results reported in "µg" are based on 5 minutes of petting an area of 4 x 10 inches. To convert the µg in the 40 in² area to cm² the equation is µg / (40 in² x 6.452 unit conversion). Collars (2.54 grams chlorpyrifos) were worn by all dogs (n = 24 for each sampling interval and each location on the dog, except at the 4-hr interval where back is represented by 17, at 14 day interval back n = 23, at 28 day interval all sample locations n = 23, at 56 day interval n = 21 for collar and n = 23 for neck and n = 23 for back; at 84 day interval n = 22 for collar; at 140 day interval n = 22 for collar and n = 23 for neck and n = 23 for back; and finally n = 22 for all sample locations).

Table 2. Surrogate Transferable Residues from Pet Collars.

Summary Statistics	Transferable Residues ($\mu\text{g}/\text{cm}^2/\text{gram ai in collar}$) ^a		
	Neck with Collar	Neck without Collar	Back
Time weighted average (TWA) ^b	0.52	0.34	0.015
Dermal exposure (Arith. mean) ^c	$0.29 \mu\text{g}/\text{cm}^2/\text{gram ai in collar} \times 1875 \text{ cm}^2 \text{ hug} = 0.54 \text{ mg}/\text{gram ai}$		

a The 4-hour sample is not included in the summary statistics because insufficient time elapsed to spread the residues and the fact that 1 DAT samples are available. The results reported in " μg " are based on 5 minutes of petting an area of 4 x 10 inches. To convert the μg in the 40 in² area to cm² the equation is $\mu\text{g} / (40 \text{ in}^2 \times 6.452 \text{ unit conversion})$. Collars (2.54 grams chlorpyrifos) were worn by all dogs (n = 24 for each sampling interval and each location on the dog).

b $\text{TWA} = ((\text{neck day } 1 \times 2) + (\text{neck day } 3 \times 4) + \dots + (\text{neck day } 168 \times 1)) / 168 \text{ days}$.

c Surrogate value = (neck with collar + neck without collar + back) / 3