



Department of Pesticide Regulation



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MEMORANDUM

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TO: Kevin Solari, Registration Specialist
Pesticide Registration Branch **HSM-00007**

FROM: Michael H. Dong, Ph.D., CNS, DABT, Staff Toxicologist [Original signed by M. Dong]
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DATE: March 8, 2000

SUBJECT: REVIEW OF *IN VIVO* DERMAL PENETRATION STUDY OF NALED IN THE RAT

PRODUCT NAME: Dibrom-8® Emulsive
ACTIVE INGREDIENT: Naled
COMPANY NAME: AMVAC Chemical Corporation
I.D. NUMBER: SBRA-181561-E
DOCUMENT NUMBER: 215-173
EPA REGISTRATION NUMBER: 59639-15
TITLE: Naled: *In Vivo* Dermal Penetration Study in the Rat

The above study was reported to have been conducted in compliance with practice set forth in the U.S. Environmental Protection Agency 40 CFR Part 160, and with the UK Principles of Good Laboratory Practice (along with the OECD Principles of Good Laboratory Practice). No information was reported regarding the test substance's stability. In spite of this deficiency which is considered to be inconsequential due to the high recoveries (87 to 98%) observed, **this review recommends that a dermal absorption rate of 35% be used to estimate the daily absorbed dose in persons exposed to naled via the dermal route**, until and unless acceptable human or further animal dermal absorption data have become available. A summary of this *in vivo* rat study and the evaluation of its results are presented below.

Study Design and Dose Administration

The nominal doses used in the study were 4.2, 0.52, 0.19, and 0.045 mg per 10 cm² of shaved rat skin. These study doses were prepared by adding the appropriate amounts of [¹⁴C]-labeled Dibrom-8 (radiopurity > 98.3%) and unlabeled Dibrom-8 (purity 95.1%) to a blank formulation and suspended in water. Each dilution was applied to the skin of up to 28 rats, with application sites protected but not occluded. All rats were housed individually in metabolism cages for the collection of urine and feces, with exhaled volatile metabolites collected over 10 and 24 hours. After exposure intervals of 0.5, 1, 2, 4, 10, and 24 hours, four rats were anesthetized (with Halothane Ph Eur vapor) and the skin washed to remove the unabsorbed dose. The rats were then terminated by cardiac puncture under terminal anesthesia. The protective covers were then removed and the application site skin was tape-stripped to remove the stratum corneum.

Preparation of Animals

Adult male CrI:CD(SD)BR strain rats obtained from Charles River (UK) Ltd. were used. The body weights of these Sprague-Dawley rats ranged from 200 to 250 grams at the time of dosing. These animals were inspected for their health conditions before they were acclimatized in stock



rat cages for at least 4 days. Experimental rooms were air conditioned to provide a minimum of 15 air changes per hour, with the temperature maintained at 20 to 25° C and at a relative humidity of 30 to 70%. The light cycle was 12 hours of artificial light and 12 hours dark. On the day before dosing, the rats were taken randomly from the stock available. The fur from behind both shoulders of each of these rats was shaved and the exposed skin swabbed with acetone to remove sebum. A Viton rubber 'O' ring (25.5 mm internal diameter) was glued to the shaved skin behind each shoulder to define each application site (of 5 cm²). The prepared rats were then acclimatized to individual metabolism cages, using stainless steel cages for those rats terminated up to 4 hours and glass cages for those terminated at or after 10 hours of dosing.

Collection of Samples and Analysis

After each nominal dermal exposure period (0.5, 1, 2, 4, 10, and 24 hours), four rats were taken for skin washing (typically with 6 sponges of soap solution and 6 of water per shoulder site). Termination and sampling times were recorded accordingly to enable each exposure interval to be calculated precisely. Urine and feces were collected from each cage at the end of the exposure period, after each cage had been rinsed with approximately 5 ml of water. These cage washings, along with any urine collected from the bladder, were added to the corresponding excreted sample. The gastrointestinal tract and its contents were removed and, like the (residual) carcasses, homogenized for sample oxidation. Following removal of rats and the collection of excreta, the metabolism cages were washed with approximately 100 ml of ethanol:water (1:1 v/v). These washings were stored refrigerated prior to analysis.

Results and Recommendations

Distributions of radioactivity following the applications of the four test doses are summarized in Table 1. For the purpose of this review, the radioactivity present in both the stratum corneum and the skin beneath the application site is considered as absorbed. These skin residues are considered to be bioavailable because it can be argued that at least some of them could be absorbed beyond the duration of exposure. In this review, percent dose absorbed is thus defined as the sum of the individual percent recoveries in the treated skin, exhaled air (where applicable), carcass, blood, urine (plus cage wash), and feces, and *then* corrected for 100% recovery. The results in Table 1 do not seem to support much the general observation that the efficiency of dermal absorption is dose dependent. At all four dose levels, most of the absorbed dose was seen to have been metabolized to carbon dioxide, bound to the treated skin, or distributed to the carcass. Less than 5% of each dose was reported to have been eliminated in urine (< 4%) and feces (< 1%) combined.

This review concludes that a dermal absorption of 35% be used as an estimate of *human* dermal absorption, until and unless an acceptable human or further animal dermal absorption study has become available. This (rounded) dermal absorption rate was observed in the lowest (0.045 mg per 10 cm²) dose group following a 10- or 24-hour exposure. The basis for relying on this dosing is that the 10- or 24-hour exposure at this lowest test dose is considered to be closest to most human and worker exposures to naled via the dermal route.

Table 1. Percentage Distribution of Absorbed Radioactivity Following Single Applications of Test Doses of Naled on Rat Skin^a

Exposure	Skin ^b	Urine	Feces	Cage ^c	GI Tract ^d	Exh. Air ^e	Carcass ^f	Total Abs. ^g	µg Equiv. ^h
<i>4.2 mg/10cm²</i>									
0.5 hr	2.97	0.06	<i>0.01</i>	<i>0.01</i>	0.34		3.09	6.70	4,013.80
1.0 hr	5.36	0.08	<i>0.01</i>	<i>0.01</i>	0.39		3.52	9.73	3,999.70
2.0 hr	6.73	0.18	<i>0.01</i>	<i>0.01</i>	0.48		3.74	11.39	4,008.90
4.0 hr	6.30	0.38	0.01	<i>0.01</i>	0.75		5.32	13.51	3,926.20
10.0 hr	9.21	1.05	0.06	0.10	0.76	2.58	6.29	21.42	4,143.10
24.0 hr	6.69	2.55	0.47	0.18	1.13	6.48	10.86	32.18	3,905.70
<i>0.52 mg/10cm²</i>									
0.5 hr	5.36	<i>0.01</i>	<i>0.01</i>	<i>0.01</i>	1.01		7.28	14.54	486.20
1.0 hr	6.12	<i>0.01</i>	<i>0.01</i>	<i>0.01</i>	1.23		8.95	17.64	486.00
2.0 hr	7.49	<i>0.54</i>	<i>0.01</i>	<i>0.06</i>	1.10		7.14	17.54	490.30
4.0 hr	4.81	0.99	0.02	<i>0.12</i>	1.17		9.92	18.93	467.20
10.0 hr	8.44	1.49	0.21	0.37	0.86	4.12	8.13	25.32	483.00
24.0 hr	13.37	2.38	0.89	0.36	0.93	6.80	9.37	37.51	474.50
<i>0.19 mg/10cm²</i>									
0.5 hr	5.17	0.24	<i>0.07</i>	<i>0.02</i>	1.18		9.95	17.68	172.40
1.0 hr	6.09	<i>0.11</i>	0.01	<i>0.02</i>	1.50		12.14	21.57	168.80
2.0 hr	7.04	1.67	0.01	<i>0.12</i>	2.36		17.73	31.97	165.60
4.0 hr	6.01	1.30	0.04	0.04	1.23		9.68	20.01	167.60
10.0 hr	7.38	2.73	0.30	0.21	1.20	6.05	10.40	29.78	190.00
24.0 hr	12.95	2.10	0.38	0.15	0.64	5.12	7.07	31.57	181.10
<i>0.045 mg/10cm²</i>									
0.5 hr	5.44	<i>0.07</i>	0.01	<i>0.09</i>	1.71		11.85	20.92	39.41
1.0 hr	6.16	<i>0.45</i>	<i>0.01</i>	<i>0.10</i>	1.49		9.79	19.72	39.20
2.0 hr	9.18	<i>0.28</i>	<i>0.01</i>	<i>0.04</i>	0.70		5.88	17.53	39.92
4.0 hr	9.34	1.19	<i>0.01</i>	<i>0.07</i>	1.04		7.88	21.65	38.69
10.0 hr	7.76	3.12	0.33	0.25	1.47	5.61	11.82	33.75	44.73
24.0 hr	7.43	3.37	0.57	0.25	0.98	7.88	10.43	35.50	43.58

^a those individual recoveries in italics are soft percentages, meaning less than the amount shown.

^b residues that were bound to stratum corneum and skin beneath application site.

^c cage wash (to account for complete urine and fecal contents).

^d gastrointestinal (GI) tract including its contents.

^e exhaled air.

^f including recovery (0.2 - 2.0%) in blood (using the default 7% of the 225 g average body weight as blood volume).

^g total absorbed dose = sum of individual percent recoveries listed here, then corrected for 100% recovery.

^h µg equivalents of naled recovered from all (absorbed or unabsorbed) sources (from group mean of 4 rats).