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Date: **September 8, 1999**

MEMORANDUM

SUBJECT: ***DICOFOL*** - **REVISED** Report of the Hazard Identification Assessment Review Committee.

FROM: Jess Rowland, Co-Chair 9/8/99
and
Pauline Wagner, Co-Chair Pauline Wagner 9/8/99
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Robert Travaglini, Risk Assessor
Reregistration Branch 3
Health Effects Division (7509C)

PC Code: 010501

On December 12, 1997, the Health Effects Division's Hazard Identification Review Committee (HIARC) evaluated the toxicology data base, the doses and endpoints for acute dietary, chronic dietary (RfD) as well as occupational and residential exposure risk assessments for dicofol. Additionally, the HIARC addressed the sensitivity of infants and children from exposure to dicofol as required by the Food Quality Protection Act (FQPA) of 1996.

At that meeting, the Committee thoroughly evaluated all the relevant data for establishing a dermal absorption factor. An acceptable dermal absorption study was not available. The Committee set the dermal absorption factor as 60% of the oral equivalent dose. The registrant disagreed with this value and explored ways to obtain "a more reasonable value". After several meetings with the Agency, HED suggested to the registrant that a specialized dermal toxicity study in the dogs be conducted to examine the most sensitive effect (inhibition of ACTH stimulated cortisol release) of dicofol. The Agency would compare the results from the existing 90-day oral toxicity study (MRID 40042043) to those of the special 90-day dermal toxicity to derive a dermal absorption factor.

On March 25, April 22, and August 12, 1999, the HIARC evaluated the 90-day dermal toxicity study in dogs (MRID No. 44720501) submitted by the registrant for consideration in endpoint selection for dermal risk assessments. The Committee's conclusions are presented in this report. This report supercedes the previous HIARC report for dicofol.

Committee Members in Attendance

At the March 25, 1999 meeting, members in attendance were: P. Wagner, J. Rowland, B. Burnam, P. Hurley, K. Raffaele, S. Makris, P. Shah, T. Levine, D. Anderson, N. Paquette, and Brenda Tarplee (Executive Secretary). Also in attendance:: Philip Budig and Robert Travaglini. Data were presented by Whang Phang, RRB2.

At the April 22, 1999 meeting, members in attendance were: D. Anderson, V. Dobozy, K. Hamernik, P. Hurley, M. Ioannou, T. Levine, N. Paquette, K. Raffaele, J. Rowland, and P. Wagner.

At the August 12, 1999 meeting, members in attendance were: D. Anderson, W. Burnam, V. Dobozy, P. Hurley, M. Ioannou, S. Makris, N. Paquette, K. Raffaele, J. Rowland, PV Shah, P. Wagner, and Brenda Tarplee (Executive Secretary). Also in attendance: P. Budig, SRRD.

I. HAZARD IDENTIFICATION

A. Acute Reference Dose (RfD)

Study Selected: Acute Neurotoxicity - Rat §81-8

MRID Nos. 42633303

Executive Summary: In an acute neurotoxicity study, groups of Crl:CD BR VAF/Plus rats (10/sex/dose) received a single oral administration of Dicofol(95.5%) in corn oil at doses of 0, 15, 75, or 300 mg/kg. Treatment-related effects observed included: urine or feces stained fur (both sexes at 350 mg/kg); change in air righting response as indicated by increased incidence of uncoordinated landing (females at 75 and 350 mg/kg); increased incidence of sleeping (females at 350 mg/kg) decrease in motor activity (both sexes at 350 mg/kg); increased incidence of ataxia (both sexes at 350 mg/kg) and decreases in body weights as well as food consumption (both sexes at 75 and 350 mg/kg). The NOAEL was 15 mg/kg/day and the LOAEL was 75 mg/kg/day based on decreased body weights and reduced food consumption.

Dose and Endpoint for Risk Assessment: NOAEL of 15 mg/kg/day based on decreases in body weights and food consumption at 75 mg/kg (LOAEL).

Comments about Study and Endpoint: This dose and endpoint is appropriate for the general population including infants and children. No effects attributable to a single exposure (dose) was seen in the oral developmental toxicity studies in rats and rabbits.

This risk assessment is required.

B. Chronic Reference Dose (RfD)

RfD Established in 1994

Study Selected: Chronic Toxicity - Dog §83 1

MRID No. 40997101

Executive Summary: In a chronic toxicity study , groups of beagle dogs (6/sex/dose) were fed diets containing Dicofol (93.3%) at dose levels of 0, 5,30 or 180 ppm for 52 weeks. These doses corresponded to (0, 0.12, 0.82, and 5.71 mg/kg/day in males; 0, 0.13, 0.85 or 5.42 mg/kg/day in females. The NOAEL was 5 ppm (0.12 mg/kg/day) and the LOAEL was 30 ppm (0.82 mg/kg/day) based on inhibition of adrenal cortical trophic hormone (ACTH) stimulated release of cortisol in both sexes of dogs (MRID No. 40997101).

Dose/Endpoint for establishing the RfD: NOAEL = 0.12 mg/kg/day based on inhibition of ACTH stimulated release of cortisol in both sexes of dogs at 0.82 mg/kg/day (LOAEL).

Re-Assessment of the RfD : The above RfD established in 1994 was re-assessed by this Committee pursuant to the FQPA. The Committee concurred with the dose and the endpoint selected previously.

C. Occupational/Residential Exposure

1. Dermal Absorption

Since an acceptable dermal absorption study is not available, the HIARC calculated a dermal absorption factor of 30% based on the comparison of LOAELs from the 90-day oral toxicity study in dogs (3.3 mg/kg/day), and the 90-day dermal toxicity study in dogs (10.0 mg/kg/day). The endpoint in both of these studies was inhibition of ACTH stimulated release of cortisol.

Dermal Absorption Factor: 30%.

2. Short-Term Dermal - (1-7 days)

Study Selected: 90-day Dermal Toxicity Study - Dog §82-3

MRID No. 44720501

Executive Summary: This special 90-day dermal toxicity study in beagle dogs was designed and conducted to obtain results which could be used along with those from the 90-day oral toxicity (MRID 40042043) to estimate a dermal absorption factor for occupational exposure risk assessment. For this study, groups of 6 male beagle dogs/dose were dosed dermally with Kelthane® 50 wettable powder (49.8% a.i.) at levels of 3, 10, 20, and 75 mg a.i./kg/day. The dogs were exposed to the test chemical for 6 hrs/day, 5 days/week for 3 months. A control group of 6 dogs received water dermally in a similar manner as the treatment groups. The ACTH stimulated serum cortisol levels were examined 30 and 90 minutes after ACTH administration (IM) during the two week of the pretest period and at weeks 1, 2, 4, 9, 11, and 13 during the treatment period.

Clinical signs of toxicity, mortality, food consumption, body weights were not affected in any dose groups. At any examination weeks of the pre-ACTH injection interval, serum cortisol levels of the treated dogs were comparable to those of the controls. However, after ACTH administration, at the 30 minute measurement interval, treatment-related decreases in serum cortisol levels were seen at week 13 in 10 and 20 mg/kg groups and at weeks 9, 11, and 13 in the 75 mg/kg group. At 90-minutes post- ACTH administration, the treatment-related reduction in serum cortisol levels was even more apparent. For 10, 20, and 75 mg/kg groups, marked decrease began on weeks 4 through the end of the study. However, from weeks 4 through 9, the reduction seen in 10 mg/kg group was not statistically significant after adjusting for the base-line serum cortisol levels while the reduction in the other groups were statistically significant.

A dose-related and statistically significant decrease in ACTH-stimulated serum cortisol level was absent at weeks 1 and 2 examination periods in both 30 and 90 minutes collections, and statistically significant reduction in cortisol levels was not seen in any examination periods or collection times in 3 mg/kg group although a dose-related trend was reported from weeks 4 through 13. In general, the data indicated a dose-related response with respect to the time for reduction in serum cortisol level (i.e., as the dose level increased, the time for statistically significant reduction in serum cortisol level occurred earlier). This may indicate that as dosing continued, a slow accumulation of dicofol in the body occurred, and at the higher dose levels the effective dose was approached earlier. This is also supported by the finding that dicofol possesses an estimated $t_{1/2}$ for elimination from various tissues of ≈30 hrs (MRID 43070103).

Based on the lack of statistically significant reduction in cortisol levels during the week 1 and 2 measurements, the NOAEL is 75 mg a.i./kg/day (HDT).

Based of the results of the entire study, the LOAEL was 10 mg a.i./kg based on statistically significant reduction in serum cortisol levels at weeks 11 and 13 and at 30- and 90-minutes post-ACTH administration. The NOAEL was 3 mg a.i./kg.

Dose and Endpoint for Risk Assessment: NOAEL = 75 mg a.i./kg/day.

Comments about Study and Endpoint: This dose is based on the lack of statistically significant reduction in cortisol levels during the week 1 and 2 measurements and is appropriate only for this exposure scenario and duration since bioaccumulation is not a concern within this time period.

This risk assessment is required.

3. Intermediate-Term Dermal (7 Days to Several Months)

Study Selected: 90-day Dermal Toxicity Study - Dog §82-3

MRID No. 44720501

Executive Summary: See Short-term Dermal above.

Dose and Endpoint for Risk Assessment: NOAEL = 3.0 mg a.i./kg/day based on statistically significant reduction in serum cortisol levels at weeks 11 and 13 and at 30- and 90-minutes post-ACTH administration at the LOAEL of 10 mg a.i./kg/day.

Comments about Study and Endpoint: This dose and endpoint are more appropriate than those from the 90-day dog oral toxicity study because the route of exposure is the same as the human exposure conditions.

This risk assessment is required.

4. Long-Term Dermal (Several Months to Life-Time)

Study Selected: Chronic Toxicity - Dog §83 1

MRID No. 40997101

Executive Summary: See Chronic Dietary

Dose/Endpoint for Risk Assessment: NOAEL = 0.12 mg/kg/day based on inhibition of ACTH stimulated release of cortisol in both sexes of dogs at 0.82 mg/kg/day (LOAEL).

Comments about Study and Endpoint: This dose and endpoint was used in establishing the RfD. Since an oral dose was selected, a dermal absorption rate of 30% should be used in dermal risk assessments.

This risk assessment is required.

5. Inhalation Exposure (Any-Time period)

Except for an acute inhalation toxicity study, for which Dicofol is placed in Toxicity Category IV (LC_{50} = >5.0 mg/L), no other studies are available via this route. Therefore, the HIARC selected the following oral NOAELs for inhalation exposure risk assessments:

Short-term - 15 mg/kg/day (Acute Neurotoxicity Study - Rat)
Intermediate-term - 0.29 mg/kg/day (90-day Oral Toxicity Study - Dog)
Long-Term - 0.12 mg/kg/day (Chronic Oral Toxicity Study - Dog)

Since the doses identified for inhalation risk assessments are from oral studies the risk assessment should be as follows:

The inhalation exposure component (i.e., mg a.i./lb) using a 100% absorption rate (default value) should be converted to an equivalent oral dose (mg/kg/day) and compare to the doses above to obtain the Margin of Exposure (MOE).

This risk assessment is required.

D. Margin of Exposure for Occupational/Residential Exposures:

A Margin of Exposure (MOE) of 100 is adequate for occupational exposure assessments. The FQPA Safety Factor Committee recommended that an additional safety factor of 3x is required for dicofol, therefore, a MOE of 300 is required for residential exposure assessment (HED Doc. No. 012575).

E. Recommendation for Aggregate Exposure Risk Assessments

For **Acute** aggregate exposure risk assessment, combine the high end exposure values from food + water and compare it to the acute Population Adjusted Dose (aPAD).

For **Short-, and Intermediate-Term** aggregate risk assessments, the dermal and inhalation MOEs can be combined since a common toxicological endpoint was observed:

$$\frac{1}{\frac{1}{MOE_{Dermal}} + \frac{1}{MOE_{Inhalation\ (oral\ equivalent)}}}$$

For **Long-Term** aggregate risk assessment, the oral, dermal, and inhalation MOEs can be combined since a common toxicological endpoint was observed:

$$\frac{1}{\frac{1}{MOE_{Oral}} + \frac{1}{MOE_{Dermal\ (oral\ equivalent)}} + \frac{1}{MOE_{Inhalation\ (oral\ equivalent)}}}$$

III. FQPA CONSIDERATIONS

1. Neurotoxicity Data

In an acute neurotoxicity study, groups of Crl:CD BR VAF/Plus rats (10/sex/dose) received a single oral administration of Dicofol(95.5%) in corn oil at doses of 0, 15, 75, or 300 mg/kg. Treatment-related effects observed included: urine or feces stained fur (both sexes at 350 mg/kg); change in air righting response as indicated by increased incidence of uncoordinated landing (females at 75 and 350 mg/kg); increased incidence of sleeping (females at 350 mg/kg) decrease in motor activity (both sexes at 350 mg/kg); and decreases in body weights as well as food consumption (both sexes at 75 and 350 mg/kg). The NOAEL was 15 mg/kg/day and the LOAEL was 75 mg/kg/day based on decreased body weights and reduced food consumption (MRID No. 42633303).

In a subchronic neurotoxicity study, groups of Crl:CD BR VAF/Plus rats (10/sex/dose) were fed diets containing Dicofol (95.1%) at 0, 5, 100 or 500 ppm (0, 0.3,5.6, or 27.8 mg/kg/day for males and 0, 0.3, 6.5, or 31.3 mg/kg/day for females, respectively). Both sexes of rats at 500 ppm exhibited decreases in body weight gain and food consumption, decreases in the incidence of rears in the open field, a slight and persistent decrease in the forelimb and hindlimb grip strength, a slight increase in the landing foot splay and a significant increase in absolute brain weight (males only). The NOAEL was 100 ppm (5.6 mg/kg/day) and the LOAEL was 5 ppm (0.3 mg/kg/day) based on decreased motor activity and increased liver weights. The Committee judged that the brain weight increases were not attributed solely to the body weight gain decrements. There was no evidence of neuropathological changes in the central or peripheral nervous system **[Note: The Executive Summary should be revised to state that there was a significant increase in absolute brain weight, not a decrease.]** (MRID No. 42971401).

Overt clinical signs of neurotoxicity were not prevalent in the data base; salivation in the prenatal toxicity study in rats was suggestive of a neurotoxic effect. Additionally, abnormalities in electrocardiograms (increased QT and PR intervals) in male and female dogs at 300 and 1000 ppm (approx. 10 and 26 mg/kg/day) in the 13-week subchronic study may have been related to neurotoxicity.

There were no indications of decreased brain weight or histopathology of the brain or peripheral nervous system, following processing of tissues without perfusion, in any of the guideline subchronic or chronic studies.

2. Determination of Susceptibility

There is no indication of additional sensitivity to young rats or rabbits following pre- and/or postnatal exposure to Dicofol in the developmental and reproductive toxicity studies; however, there is a need for the re-evaluation of the length and periodicity of estrous cycle in the special one-generation reproduction study.

(I) Developmental Toxicity:

In a prenatal developmental toxicity study, pregnant Crl: COBS CD (SD) rats (25/group) received oral administration of Dicofol (95.6%) in corn oil at doses of 0, 0.25, 2.5 or 25 mg/kg/day during gestation days 6 through 15. The Committee discussed the conclusions reached in the DER and concluded that the NOAEL for maternal toxicity should be revised from 0.25 mg/kg/day to 2.5 mg/kg/day, since the only observation at the 2.5 mg/kg/day dose level was salivation. This finding did not occur consistently across studies in the database, and it is not related to other evidence of toxicity of this chemical. Therefore, for maternal toxicity, the revised NOAEL was 2.5 mg/kg/day and the LOAEL was 25.0 mg/kg/day, based on significantly increased incidences of salivation during the period of dosing, decreased body weight, body weight gain, and food consumption, increased relative liver weight, and increased histopathological changes in the liver (increased incidence of centrilobular hepatocyte hypertrophy). No developmental toxicity was observed. For developmental toxicity, the NOAEL was $\geq$25 mg/kg/day (HDT); a LOAEL was not attained (MRID No. 40042046)

In a prenatal developmental toxicity study, pregnant New Zealand White rabbits (20/dose) received oral administration of Dicofol (95.6%) in 1% methylcellulose at dose levels of 0, 0.4, 4.0 or 40.0 mg/kg/day during gestation days 7 through 18. For Maternal Toxicity, the NOAEL was 4 mg/kg/day and the LOAEL was 40 mg/kg/day based on significant decreases in body weight gain and food consumption as well as clinical signs (abnormal feces), increase in relative liver weights, increase in the incidence of cytoplasmic hyalinization and of diffuse vacuolation in hepatocytes. For Developmental Toxicity, the NOAEL was 4 mg/kg/day and the LOAEL was 40 mg/kg/day based on increase in abortions (4/19) when compared to concurrent (1/18) and historical controls (1/14 to 2/15) (MRID No. 40042047).

(ii) Reproductive Toxicity:

In a two-generation reproduction study, groups of Crl:CD BR rats (25/sex/group) were fed diets containing Dicofol (93.3%) at dose levels of 0, 5, 25, 125 or 250 ppm (equivalent to 0.4, 1.9, 9.5, or 18.9 mg/kg/day for males and 0.4, 2.1, 10.5, or 20.5 mg/kg/day for females). One litter was produced in the first generation, and two litters were produced in the second generation (MRID No. 41606601).

For parental systemic toxicity, the NOAEL was 5 ppm (0.4 mg/kg/day) and the LOAEL was 25 ppm (1.9/2.1 mg/kg/day for M/F) based upon histopathological changes in P generation and F1 generation livers (hypertrophy of centrilobular hepatocytes with associated vacuolation) and F1 generation ovaries (increased vacuolation). In addition, at 250 ppm (18.9/20.5 mg/kg/day in M/F), hypertrophy /vacuolation of the adrenal glands was observed in P generation and F1 generation females (MRID No. 41606601).

For reproductive toxicity, the NOAEL was 5 ppm (0.4 mg/kg/day) and the LOAEL was 25 ppm (1.9/2.1 mg/kg/day in M/F, based on the ovarian vacuolation in the F1 females, which was judged to be an effect on reproductive physiology (MRID No. 41606601).

For offspring toxicity, the NOAEL (not specifically defined in the DER) could be defined at 25 ppm (1.9/2.1 mg/kg/day for M/F) and the LOAEL at 125 ppm (9.5/10.5 mg/kg/day for M/F) based on decreased F2 pup viability (increased numbers of stillborn pups, postnatal day 0-4 pup deaths, and total litter loss). Additionally, at 250 ppm (18.9/20.5 mg/kg/day in M/F), viability of F1 pups and F1 and F2a pup weight (Days 7 and 14) were decreased (MRID No. 41606601).

In a special one-generation special postnatal toxicity study in Sprague-Dawley rats (30/sex/group), 96.4% Dicofol was administered at dietary concentrations of 5, 25, and 125 ppm (0, 0.3, 1.7, and 8.7 mg/kg/day for males and 0, 0.4, 2.0, and 9.8 mg/kg/day for females during premating). Parental animals were treated for 10 weeks, then mated. Selected F1 rats were weaned and maintained on treated diets until 70-100 days of age. A satellite group consisting of 10 treated F0 females/dose were mated with F0 males from the main study to produce F1 offspring. These offspring were used for evaluation of test material and metabolite residues in: serum during the premating phase of the study; in milk on days 2 and 12 postpartum; in prenursing neonate tissue; and in serum from weanling pups. The animals were adequately exposed to the test material during all phases of the study as shown by quantifiable levels of the Dicofol and metabolites in adult serum, milk, prenursing neonate tissue, and weanling serum (MRID No. 44253801).

For parental systemic toxicity, the NOAEL was 25 ppm (1.7/2.0 mg/kg/day in M/F) and the LOAEL was 125 ppm (8.7/9.8 mg/kg/day in M/F) based on increased absolute and relative liver weights and on histopathologic findings in the liver of adult F0 and F1 male and female rats (centrilobular hypertrophy of hepatocytes with increased cytoplasmic eosinophilia) (MRID No. 44253801).

For offspring toxicity, the NOAEL was also 25 ppm (1.7/2.0 mg/kg/day in M/F) and the LOAEL was 125 ppm (8.7/9.8 mg/kg/day in M/F) based on histopathologic findings in the liver of F1 weanlings (vacuolization of centrilobular hepatocytes in both sexes and hypertrophy of centrilobular hepatocytes with or without increased cytoplasmic eosinophilia in females) (MRID No. 44253801).

No treatment-related effects were observed on the number of stillborns, mean litter sizes at birth, sex ratio, viability, clinical signs, or body weight of offspring. No treatment-related effects were observed on parameters of reproductive function or performance: length of estrous cycle; epididymal sperm count, concentration, motility, and morphology; testicular spermatid count and concentration; sexual maturation as evidenced by age of vaginal opening in females and preputial separation in males; mean precoital interval; mating and fertility indices; and median gestation length. For reproductive toxicity, the NOAEL was >125 ppm (MRID No. 44253801).
It was determined by the reviewer that additional information regarding the periodicity of estrous cyclicity and the ovarian follicle count data will need to be submitted by the registrant prior to final acceptance of the DER. Note: the DER for this study has not yet been finalized in HED.] (MRID No. 44253801).

4.. Recommendation for a Developmental Neurotoxicity Study

The HED RfD Peer Review Committee (10/16/94) had placed the requirement for a developmental neurotoxicity study in rats in *reserve* status, pending completion of the acute and subchronic rat neurotoxicity studies. These studies have since been received and reviewed by the Agency. The developmental neurotoxicity study had been requested by Data-Call-In prior to the RfD decision. Based on a weight-of-the-evidence evaluation, the Hazard Identification Assessment Committee *reaffirmed the need for a developmental neurotoxicity study* in rats. The protocol should ensure that equilibrium maternal blood levels of Dicofol are achieved at least prior to implantation. The following information was considered by the Committee in support of this recommendation:

(I). Evidence that support requiring a developmental neurotoxicity study:

- Dicofol produces neurotoxic effects.
- SAR: Dicofol is an organochlorine and is structurally similar to DDT, which is neurotoxic
- Neurobehavioral effects (decreased motor activity, urine/feces staining, decreased air righting response, increased somnolence) were noted in the

acute neurotoxicity study in rats (without histopathological correlation) at 75 and 350 mg/kg.

- Neurobehavioral effects (decreased motor activity at 100 and 500 ppm [5.6/6.5 and 27.8/31.3 mg/kg/day in M/F, respectively], and decreased number of rears, decreased fore- and hindlimb grip strength, and increased landing foot splay at 500 ppm) were noted in the subchronic neurotoxicity study in rats (without histopathological correlation).

- Brain weight was decreased in males at 500 ppm (31.3 mg/kg/day) in the subchronic neurotoxicity study in rats.

- Dicofol is an endocrine disruptive chemical.

- Endocrine toxicity (adrenal and thyroid) is noted throughout the data base. The RfD is based upon inhibited adrenal cortisol release in the chronic dog study.

- Ovarian toxicity which is consistent with enhanced steroidogenic activity was noted in the two-generation reproduction study in rats (ovarian vacuolation).

(ii). Evidence that do not support asking for a developmental neurotoxicity study:

- No effects on histopathology of the brain or peripheral system (without perfusion) were observed in any of the guideline subchronic or chronic studies in which these parameters were measured. In addition, no effects on histopathology of the nervous system were observed following perfusion in the acute and subchronic neurotoxicity studies in rats.

- No evidence of developmental anomalies, including abnormalities in the development of the fetal nervous system, were observed in the prenatal developmental toxicity studies in either rats, or rabbits, at maternally toxic oral doses up to 25.0 or 40.0 mg/kg/day, respectively. In addition, no evidence of neurological deficits were noted in the offspring in a two-generation reproduction study in rats.

- No evidence of endocrine toxicity was noted in the offspring on a one-generation reproduction study in rats, with a postnatal exposure phase; however, some questions regarding periodicity of estrous cyclicity and ovarian follicle count still remain.

V. DATA GAPS

§83-6 Developmental Neurotoxicity Study in Rats.

IV. SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

The doses and toxicological endpoints selected as well as the Uncertainty Factor and Margins of Exposures for various exposure scenarios are summarized below.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary	NOAEL = 15.0 U.F. = 100	Decreases in body weight gain and food consumption	Acute Neurotoxicity - Rat
		Acute RfD = 0.15 mg/kg	
Chronic Dietary	NOAEL=0.12 U.F. = 100	Inhibition of ACTH stimulated release of cortisol.	Chronic Toxicity - Dog
		Chronic RfD = 0.0012mg/kg	
Dermal (Short-Term)	Dermal NOAEL = 75	Lack of Inhibition of ACTH stimulated release of cortisol.	90-Day Dermal Toxicity - Dog
Dermal (Intermediate-Term)	Dermal NOAEL = 3.0	Inhibition of ACTH stimulated release of cortisol.	90-Day Dermal Toxicity - Dog
Dermal Long-Term)[1]	Oral NOAEL = 0.12	Inhibition of ACTH stimulated release of cortisol.	Chronic Toxicity - Dog
Inhalation (Short-Term)[2]	Oral NOAEL = 15.0	Decreases in body weight gain and food consumption	Acute Neurotoxicity - Rat
Inhalation (Intermediate-Term)[2]	Oral NOAEL = 0.29	Inhibition of ACTH stimulated release of cortisol.	90-Day Oral Toxicity - Dog
Inhalation (Long-Term)[2]	Oral NOAEL=0.12	Inhibition of ACTH stimulated release of cortisol.	Chronic Toxicity - Dog

[1]Use 30% dermal absorption factor for long-term dermal risk assessments.

[2]Use 100% inhalation absorption factor for inhalation risk assessments (all durations).