Dacthal; CASRN 1861-32-1

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR Dacthal

File First On-Line 08/22/1988

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	08/01/1994
Inhalation RfC (I.B.)	not evaluated	
Carcinogenicity Assessment (II.)	not evaluated	

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Dacthal
CASRN — 1861-32-1
Primary Synonym — DCPA
Last Revised — 08/01/1994

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of

substances that are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
Effects on the lungs, liver, kidney, thyroid and thyroid hormones in males and females and eyes of females **2-Year Rat Feeding Study** **ISK Biotech Corp., 1993**	NOAEL: 1 mg/kg-day LOAEL: 10 mg/kg-day	100	1	1E-2 mg/kg-day

*Conversion Factors and Assumptions: None

I.A.2. Principal and Supporting Studies (Oral RfD)

Note: The RfD for dacthal was originally verified on February 18, 1987. The RfD was revised because of the availability of new information, including 2- year feeding/oncogenicity studies in rats and mice, a 2-generation reproduction study in rats, developmental toxicity studies in rats and rabbits and subchronic feeding studies in rats and mice.

ISK Biotech Corporation. 1993. MRID No. 42731001, 42998401. HED Doc. No. 010513. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Groups of Sprague-Dawley CD rats (70/sex/dose) were administered technical dacthal in the diet at dosage levels of 0, 1, 10, 50, 500 and 1000 mg/kg-day for 2 years. Dacthal utilized in this study contained 0.13% of the manufacturing impurity hexachlorobenzene (HCB). Test material intake was calculated based on the nominal concentration in the diet provided each week and the corresponding body weights and food consumption data for that week. Additionally, concentrations of HCB at each dose level were calculated as follows: 0.0013, 0.013, 0.065, 0.65 and 1.3 mg/kg-day for the 1, 10, 50, 500 and 1000 mg/kg-day dose levels, respectively.

Survival rates were comparable among the groups for both sexes for the first year of the study. Survival in treated males was lower for all groups compared with the control; males at the highest dose level displayed the highest mortality (73% vs 52% in the controls). A significant trend ($p<0.01$) in survival rates was observed when all male groups were included, but when the highest dose level was excluded, no significant dose-related trend was detected. Females displayed comparable survival among the groups. Males at the two highest dose levels displayed signs of poor physical health, such as anogenital staining, thin appearance, material around nose/mouth, and there was an increase in the findings of few or no feces, soft feces, dark urine and red urine/penile discharge. Females at the two highest dose levels appeared thin. No other findings were considered treatment related. The cause of death of some rats dying or sacrificed moribund during the first year included suppurative pyelonephritis, chronic nephropathy and suppurative inflammation in the kidney bladder, prostate and seminal vesicles.

In general, body weight was comparable among male groups during the first year of the study. From week 54 on, statistically significant ($p<0.01$) decreases were observed in males at 1000 mg/kg-day compared with control values. The 500 mg/kg-day females displayed the lowest body weights at study initiation, but were approximately 100% of control value. At weeks 6, 7, 13, 22 and from week 50 to termination, these females displayed statistically significant decreases ($p<0.01$) from the control value. At the highest dose level, females displayed decreased body weight compared with the controls at week 14 and from week 46 to termination. Additionally, the 50 mg/kg-day females displayed a statistically significant ($p<0.01$) decrease in body weight (dose related) at terminal sacrifice. Body-weight gains were comparable among males during the first year of the study, although at the highest dose, slight decreases from control values reached statistical significance at week intervals 0-5, 0-8 and 0-14. During the second year of the study, males at 1000 mg/kg-day displayed decreased gains compared with the control values. From the third week on, females at the two highest dose levels displayed decreased body-weight gains (dose related), although several intervals did not attain statistical significance.

A dose-related increase was observed in the incidence and severity of focal accumulations of foamy-appearing macrophages within the alveolar spaces (mainly in the subpleural areas, although in the peribronchiolar areas in several rats) in males at dose levels of 10 mg/kg-day and above in females at the two-highest dose levels. With the exception of the 10 mg/kg-day male group, these findings were statistically significant. These foci were correlated with the white foci observed in the lungs at necropsy. Similar findings were observed at the interim sacrifice in both sexes at dose levels of 50 mg/kg-day and above and in rats receiving 500 and 1000 mg/kg-day that died during the first year of the study.

Cholesterol clefts occurred in both sexes in the majority of the rats at the two highest dose levels (statistically significant), as well as in approximately 25% of the 50 mg/kg-day males. Additionally, cholesterol clefts were observed in rats in the other dose groups that had pulmonary foci. Reportedly these lesions may have occurred as a result of the breakdown of the foamy-appearing macrophages, resulting in the release of the lipid material that formed the cholesterol clefts. Also observed in the majority of the lungs of rats displaying focal accumulations of foamy macrophages was a thickening of the alveolar walls and fibrosis, as evidenced by the appearance of collagen under polarized light (statistically significant in males receiving 10 mg/kg-day and above and in females at 500 and 1000 mg/kg-day) and focal interstitial pneumonitis, characterized by foci of mixed inflammatory cells. When giant cells occurred in the areas of pneumonitis, a diagnosis of focal granulomatous pneumonitis was made (statistically significant at 500 and 1000 mg/kg-day, both sexes). Similar findings in the lungs were observed at the interim sacrifice and in rats dying during the final year of the study. Additionally, focal accumulations of brown granular pigment, thought to be hemosiderin, were increased (statistically significant) in the focal areas of interstitial pneumonitis at the 500 and 1000 mg/kg-day dose levels in both sexes at termination. Electron microscopy showed an increase of foci of foamy macrophages that were laden with lipid spheres, vacuoles, lamellar bodies and/or cholesterol clefts.

The liver, kidneys and thyroid are also known target organs for dacthal in both males and females at doses of 10 mg/kg-day and greater. Additionally, the eye appears to be a target organ in females. In females at study termination, a dose-related increase in the incidence of bilateral retinal atrophy was observed. Males at the 500 and 1000 mg/kg-day dose levels displayed a 12 and 16% increase, respectively, in absolute liver weight at interim sacrifice, and females at these dose levels displayed increases of 29 and 37%, respectively (statistically significant). At termination, the increases were 35 and 40% greater for males (statistically significant) and 18 and 22% greater in females.

A dose-related (statistically significant) increase in the incidence and severity of centrilobular hepatocytic swelling (hepatocytic hypertrophy) was observed in both sexes at dose levels of 50 mg/kg-day and above at both the interim and terminal sacrifices and in males at 10 mg/kg-day at terminal sacrifice. This lesion was characterized by an increase in cellular size, accompanied by a ground-glass appearance to the cytoplasm of the hepatocytes located in close proximity to the central vein of each hepatic lobule. As the severity of the lesion increased, larger portions of the lobule were affected, which the study's author points out is consistent with metabolic activation and an increase in smooth endoplasmic reticulum within the cell. Additionally, an increased incidence of eosinophilic foci in both sexes was observed at dose levels of 10 mg/kg-day and above and in rats dying during the second year of the study, compared with control groups, with statistical significance being attained at 500 and 1000 mg/kg-day in both sexes and at 50 mg/kg-day in males at the terminal sacrifice. Five high-dose males displayed eosinophilic cytoplasmic

inclusions at the interim sacrifice. The author stated that eosinophilic foci are focal areas of cellular alteration in the liver characterized by areas of hepatocytes with intensely eosinophilic cytoplasm, enlarged hepatocytes, increases in hepatocyte numbers, and distinct lesion borders occasionally resulting in compression of the adjacent parenchyma. An increase in osmiophilic membranes and smooth endoplasmic reticulum was observed in the hepatocytes of three high-dose males evaluated by electron microscopy.

An increase in the severity of chronic nephropathy in males and an increase in incidence and severity in females was observed at dose levels of 50 mg/kg-day and above compared with the respective control groups (statistically significant at the two highest dose levels, both sexes). Components of chronic nephropathy were listed as regenerative tubular epithelium, dilated tubules, casts, interstitial fibrosis and mononuclear cell infiltrates. The author noted that chronic nephropathy is a commonly observed progressive lesion in Sprague-Dawley rats, especially males. Moreover, the author stated that exacerbation of this common aging lesion was apparently the main cause of spontaneous death or moribundity, which led to the early sacrifice of high-dose males. Other findings in the kidneys of males at 500 and 1000 mg/kg-day that were considered most likely to be associated with the increased severity of chronic nephropathy included infarcts and cysts, pelvic hemorrhage, hyperplasia of transitional epithelium, papillary necrosis and pelvic dilatation. At interim sacrifice, similar kidney lesions were observed (increased incidence/severity of dilated tubules, mononuclear cell infiltrates, foci of regenerative tubular epithelium) in the high-dose groups and in males at 500 mg/kg-day. Tubular cell neoplasms of the kidney occurred only in treated males.

Effects in the thyroid included increased organ weight as well as an increase in the incidence and severity of follicular cell hypertrophy, hyperplasia and basophilic clumped colloid. Additionally, a dose-related decrease in thyroxine (T4) occurred throughout the study, and triiodothyronine (T3) was decreased in a dose-related manner at 52 weeks. Thyroid stimulating hormone (TSH) values were elevated at 52 weeks (dose related) and at 104 weeks (no dose response). As discussed by the study author, thyroid hormones are metabolized by the liver and excreted in the bile. Lower concentrations of the thyroid hormones can result following metabolic activation, which can lead to an increased release of TSH from the pituitary gland, via a feedback mechanism, and stimulation of the follicular cells. This in turn can result in follicular cell hypertrophy and hyperplasia following prolonged stimulation and ultimately follicular cell neoplasms. The findings in this study with respect to the liver and thyroid suggest a possible indirect effect of dacthal on the thyroid.

Based on effects observed in the lungs, liver, kidney, thyroid and thyroid hormones in both sexes and in the eyes of females, the LEL for systemic toxicity is 10 mg/kg-day. The NOEL for systemic toxicity is 1 mg/kg-day.

I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF — The uncertainty factor of 100 reflects 10 for interspecies extrapolation and 10 for intraspecies variability.

MF — None

I.A.4. Additional Studies/Comments (Oral RfD)

1) 2-Year Feeding Study: Principal study -- see previous description; Core grade minimum (ISK Biotech Corp., 1993)

2) 2-Year Feeding - dog: Core grade minimum (Diamond Alkali Co., 1963a)

Groups of purebred beagle dogs (4/sex/dose) were administered dacthal in the diet at dose levels of 0, 100, 1000 and 10,000 ppm (0, 2.5, 25 and 250 mg/kg-day). At the end of 1 year, one male and one female from the control and each of the test groups were sacrificed. At the end of 2 years all of the animals except one female from each group were sacrificed and the organs weighed. These female dogs were sacrificed during the 114 week of the study.

The general appearance and behavior of the test animals were comparable with those of the control animals. In general, the hematological picture for all four dose groups of animals appear to be comparable and no toxicological effects are evident. The organs of the male and female dogs from the three different dosage levels presented histologic variations that were not consistent nor indicative of a compound effect.

Since no effects were observed at any dose level tested, the NOEL for systemic toxicity is equal to or greater than 10,000 ppm (250 mg/kg-day).

3) 2-Generation Reproduction - rat: Core grade minimum (ISK Biotech Corp., 1990a)

Groups of Sprague-Dawley CD VAF/Plus (35/sex/dose) were administered dacthal in the diet at dosage levels of 0, 1000, 5000 and 20,000 ppm (Male: 0, 45, 233 and 952 mg/kg-day; Female: 0, 63, 319 and 1273 mg/kg-day) over two generations. On day 0 of lactation of the F2b litters, the low- and mid-dose level diets were replaced by diets containing 200 ppm (18 mg/kg-day) and 500 ppm (47 mg/kg-day), respectively, in order to ensure a NOEL for pup body weight. For the remainder of the study, including the F2 growth phase, the dietary concentrations were 200, 500 and 20,000 ppm. No change in the dietary concentration was made for F1 males or for F1 females that did not produce an F2b litter.

No differences were observed in reproductive performance at any dose level tested during the growth phase, mating, gestation and lactation for two generations and two litters per generation. Body weight and body-weight gain of parental animals of both generations were decreased mainly in the mid- and high-dose groups (with females affected more than males) and, although decreases were statistically significant, in general the difference compared with control values was slight. Food consumption was similarly affected, mainly for females, and only slightly. During gestation and lactation, the mid- and high-dose dams displayed decreases in body weight, which were also small in magnitude but again statistically significant. During lactation, the magnitude of the decrease from control value grew smaller with time. Offspring showed good viability, but body weight was affected at the mid- and high-dose levels. No effects on reproductive performance were observed. Based on decrease body weight and body-weight gain, the LEL for maternal toxicity is 5000 ppm (319 mg/kg-day). The NOEL for maternal toxicity is 1000 ppm (63 mg/kg-day). Based on decreased body-weight gain, the LEL for paternal toxicity is 20,000 ppm (952 mg/kg-day). The NOEL for paternal toxicity is 5000 ppm (233 mg/kg-day).

The NOEL for reproductive toxicity can be set at 1000 ppm (63 mg/kg-day) and the LEL at 5000 ppm (319 mg/kg-day) based on decreased pup body weight. There was an apparent increase in stillborn pups at the high-dose level, which was more pronounced in the second generation than in the first. Because decreases in pup body weights were observed at the mid- and high-dose levels in the F1a, F1b and F2a litters, the dose levels for the mid- and low-dose groups were lowered at the beginning of lactation of the F2b litters to ensure an NOEL for this parameter. The NOEL for offspring toxicity can be set at 200 ppm (18 mg/kg-day) and the LEL at 500 ppm (47 mg/kg-day) based on body-weight effects.

4) Developmental Toxicity - rat: Core grade minimum (SDS Biotech Corp., 1986)

Groups of pregnant Sprague-Dawley Crl:COBS CD rats (25/dose) were administered dacthal orally by gavage at dose levels of 0, 500, 100 and 2000 mg/kg-day from day 6 through 15 of presumed gestation.

No adverse effects were noted for maternal rats or their offspring. Although no effects were observed, the dose levels were deemed adequate. The NOEL for maternal and developmental toxicity can be set at 2000 mg/kg-day.

5) Developmental Toxicity - rat: Core grade minimum (SDS Biotech Corp., 1985)

Groups of pregnant Charles River Crl:COBS CD(SD)BR rats (25/dose) were administered dacthal diacid orally by gavage at dose levels of 0, 625, 1250 and 2500 mg/kg-day from day 6 through 15 of gestation.

The high-dose dams showed signs of toxicity manifested in slightly decreased body-weight gains on days 6-9 and significantly decreased food consumption on these days. Some overt signs of toxicity were also observed in the high-dose animals, including reddened anal exudate, labored breathing in one animal and red colored mucus in the feces. A few mid-dose as well as high-dose animals displayed excess salivation and soft or liquid stools. Based on food consumption changes and slight body-weight changes, the LEL for maternal toxicity is 2500 mg/kg-day. The NOEL for maternal toxicity is 1250 mg/kg-day.

No signs of developmental toxicity were observed. All parameters measured were within control values. There was a statistically significant decrease at all doses tested of percent live male fetuses/litter. Apparently, no dose- response relationship was evident in treated groups and the control value was somewhat high compared with historical controls. Treated values were within the historical control range. Based on the lack of developmental effects at any dose level tested, the NOEL for developmental toxicity is equal to or greater than 2500 mg/kg-day.

6) Developmental Toxicity - rabbit: Core grade minimum when considered with the other rabbit developmental toxicity study (Fermenta Plant Protection Co., 1989)

Groups of pregnant New Zealand White rabbits (20/dose) were administered dacthal orally by gavage at dose levels of 0, 125, 250 and 500 mg/kg-day from day 7 though day 19 of gestation.

Maternal reproductive parameters were not affected by treatment and no embryotoxicity, fetotoxicity or teratogenicity was observed at any dose level tested. When the results of the second rabbit developmental toxicity study (dose levels tested were 0, 500, 1000 and 1500 mg/kg-day) are considered along with the results of this study, a NOEL for maternal toxicity can be set at 250 mg/kg-day and a LEL of 50 mg/kg-day based on maternal deaths. The NOEL for developmental toxicity can be set at 500 mg/kg-day, the highest dose tested.

7) Developmental Toxicity - rabbit: Core grade minimum when considered with the other rabbit developmental toxicity study (Fermenta Plant Protection Co., 1989)

Groups of pregnant New Zealand White rabbits (20/dose) were administered dacthal orally by gavage at dose levels of 0, 500, 1000 and 1500 mg/kg-day from day 6 though day 19 of gestation. The doses for this study were based on a range-finding study in which doses of 500 to 4000 mg/kg-day were tested. Deaths occurred at 2000 and 4000 mg/kg-day but not at 1000 mg/kg-day and below.

Dacthal was toxic to the maternal animals, with deaths occurring in 4 low- dose, 13 mid-dose and 12 high-dose animals. A dose-related increase in adverse clinical signs was observed compared with control animals, which included decreased motor activity, ataxia, impairment or

loss of the righting reflex, morbundity and dried or absent feces. These clinical signs were mainly observed in those rabbits that died during the study. Also, a dose- related increase in the incidence of gastric ulcerations ws observed, with the mid- and high-dose animals displaying a statistically significant difference compared with controls. Maternal reproductive parameters were not affected by treatment and no embryotoxicity, fetotoxicity or teratogenicity was observed at the dose levels tested.

When the results from the other rabbit developmental toxicity study (dose levels tested were 0, 125, 250 and 500 mg/kg-day) are considered along with the results from this study, a NOEL for maternal toxicity can be set at 250 mg/kg-day and a LEL of 500 mg/kg-day based on maternal deaths. The NOEL for developmental toxicity can be set at 500 mg/kg-day, the highest dose tested.

Other Data Reviewed:

8) 2-Year Feeding/Oncogenicity - mouse: Core grade minimum (Fermenta Plant Protection Co., 1988)

Groups of CD-1 mice (90/sex/dose) were administered dacthal in the diet at dosage levels of 0, 100, 1000, 3500 and 7500 ppm (Male: 0, 12, 123, 435 and 930 mg/kg-day; Female: 0, 15, 150, 510 and 1141 mg/kg-day) for 2 years. Additionally, 20 animals/sex were used for health status purposes prior to study.

The only effects observed following exposure to the test material were on the liver, namely: 1) increased relative liver weight (7500 ppm at termination in both sexes); 2) increased glutamic-pyruvic transaminase (GPT, ALT) and sorbitol dehydrogenase (SDH) activities in both sexes at week 76 sacrifice in 1000, 3500 and 7500 ppm; not dose-related; SDH and GPT increased at termination only in 7500-ppm females; slight increases in ketones in the urine with increasing dose; increased cholesterol levels at week 76 in 3500- and 7500-ppm females (dose-related) and at termination in the 7500-ppm females; and 3) increased incidence of hepatocyte enlargement/vacuolation in both sexes at 7500 ppm.

The only other effect noted was an apparent increase in the incidence of corneal opacity with increasing dose (observed in males); however, the registrant provided additional information stating that the eye effect may have resulted from irritative effects of feed particles rather than from the test material. Additionally, the registrant conducted a 2 year rat ophthalmology study (Fermenta ASC Corp., 1990) that showed no eye effects at the highest dose tested, 20,000 ppm (1000 mg/kg-day).

Therefore, based on liver effects, the LEL for systemic toxicity is 7500 ppm (Male: 930 mg/kg-

day; Female: 1141 mg/kg-day). The NOEL for systemic toxicity is 3500 ppm (Male: 435 mg/kg-day; Female: 1141 mg/kg-day).

9) 2-Year Ophthalmology Study - rat: No core grade (Fermenta ASC Corp., 1990)

Groups of VAF Plus Crl:CD BR Sprague-Dawley rats (20/sex/dose) were administered dacthal in the diet at dosage levels of 0, 2000 (from weeks 1- 22), 1000 (from weeks 23-104) and 20,000 ppm (0, 100/50 and 1000 mg/kg-day) for 2 years. This study was performed specifically to investigate the effects of dacthal on the eye only because of an apparent increase in corneal opacity observed in the chronic feeding/oncogenicity study in mice (Fermenta Plant Protection Co., 1988).

In general, the animals of all dose groups were found to be without ocular lesions in either eye. A low incidence of viral infection (signs of sialodacroadenitis) was observed in all dose groups, which is common in laboratory animals. The findings at terminal sacrifice included changes expected in older rats (e.g., cataracts and corneal lesions); no increase in the incidence of these effects with test material exposure was noted.

Due to the lack of any evidence of ocular toxicity at any of the dose levels tested, the NOEL for eye effects is equal to 20,000 ppm (1000 mg/kg- day).

10) 2-Year Feeding/Oncogenicity - rat: Core grade supplementary (Diamond Alkali Co., 1963b)

Groups of rats (35/sex/dose) were administered dacthal in the diet at dosage levels of 0, 100, 1000 and 10,000 ppm (0, 5, 50 and 500 mg/kg-day). Interim sacrifices were made at 13 and 52 weeks.

The appearance and behavior of the test animals were generally comparable with the control animals throughout the study. Growth for the males and females in all three dose groups was comparable with controls. Food consumption from week 28 to week 52 for mid-dose males and high-dose males and females was significantly higher as compared with the corresponding controls. Food consumption for the control and test groups during the second year was not elevated statistically; however, inspection of the data revealed higher weekly mean values from week 80 through week 104 for high-dose males and mid- and high-dose females as compared with controls. At 104 weeks, the kidney weight for high-dose males and the adrenal weights for the high-dose females were found to be significantly higher than those for the corresponding controls.

Based on increased kidney weights in males and adrenal weights in females, the LEL for systemic toxicity is 10,000 ppm (500 mg/kg-day). The NOEL for systemic toxicity is 1000 ppm

(50 mg/kg-day).

11) 13-Week Feeding - rat: Core grade minimum (ISK Biotech Corp., 1991)

Groups of CD VAF/Plus Sprague-Dawley rats (15/sex/dose) were administered dacthal in the diet at dosage levels of 0, 10, 50, 100, 150 and 1000 mg/kg-day for 13 weeks. Two additional satellite groups (10/sex/dose) were administered dacthal in the diet at dosage levels of 0 and 1000 mg/kg-day for 60 days. The satellite groups were used to examine lungs only.

No treatment-related effects were observed on survival or clinical signs in either sex at any dose level tested. Body weight was comparable among the groups throughout the study for both sexes, although a significant trend toward lower body weight with increasing dose in females was observed. At study termination, body-weight gain for high-dose males and females was 8 and 14%, respectively, lower than the control values. Food consumption on a mean absolute basis was consistently lower in the high-dose females throughout the study compared with control values. Food consumption relative to body weight did not indicate any consistent difference for either sex. Dose-related effects were observed on the liver (increased weight and centrilobular hypertrophy), lung (increased accumulation of foamy macrophages), kidney (increased weight, epithelial hyperplasia, tubular hypertrophy, regenerative epithelium in males) and thyroid (follicular hypertrophy) in both sexes at dose levels of 50, 100, 150, and 1000 mg/kg-day.

Based on increased liver weight and microscopic findings, the LEL for systemic toxicity is 50 mg/kg-day. The NOEL for systemic toxicity is 10 mg/kg-day.

12) 13-Week Feeding - mouse: Core grade minimum (Fermenta Plant Protection Co., 1986)

Groups of CD-1 mice (15/sex/dose) were administered dacthal in the diet at dosage levels of 0, 625, 1250, 2500 and 7500 ppm (Males) and 0, 1000, 2500, 5000 and 10,000 ppm (Females) for 13-weeks. The group mean weekly achieved intakes of dacthal over the study for males was 0, 100, 199, 406 and 1235 mg/kg-day and for females was 0, 223, 517, 1049 and 2198 mg/kg-day.

No treatment-related effects were observed on survival, body weight/body- weight gain, food consumption or clinical signs in either sex. The only treatment-related effects observed were in the liver. An increased incidence of minimal centrilobular hepatocyte enlargement in the liver was noted, however, in the high-dose males and in the two highest doses in females, compared with their respective control groups. Fine vacuolation of centrilobular hepatocytes was observed in both sexes, but this was not considered to be related to liver enlargement and no dose-related difference in the incidence of the lesion was observed.

Based on histopathological effects observed in the liver, the LEL for systemic toxicity is 7500 ppm (1235 mg/kg-day) for males and 5000 ppm (1049 mg/kg-day) for females. The NOEL for systemic toxicity is 2500 ppm (Male: 406 mg/kg-day; Female: 517 mg/kg-day) for both sexes.

13) 36-Day Gavage Study - rat: Core grade supplementary (SDS Biotech, 1985)

Groups of CD Sprague-Dawley rats (10/sex/dose) were administered dacthal diacid by gavage at dose levels of 0, 100, 500 and 2000 mg/kg-day. Suspensions of dacthal diacid were prepared weekly in vehicle (0.5% w/v methyl cellulose solution). Doses were based on most recent body weight. Dose was a constant volume of 10 ml/kg, with controls receiving 10 mg/kg vehicle alone.

No treatment-related changes were observed in mortality, organ weights, or histopathology. Treatment-related effects were noted, however, in clinical chemistry and hematology in high-dose males. Hematocrit ($p<0.01$) and hemoglobin ($p<0.05$) were increased in high-dose males along with albumin ($p<0.05$) and potassium ($p<0.01$), whereas blood glucose in the animals decreased. Soft stools were evident in both high-dose males and females. No other treatment-related changes were evident.

Based on the effects observed at the highest dose tested, the LEL for systemic toxicity is 2000 mg/kg-day. The NOEL for systemic toxicity is 500 mg/kg-day.

14) 28-Day Feeding - rat: No core grade (ISK Biotech Corp., 1990b)

Groups of CD Sprague-Dawley rats (5/sex/dose) were administered dacthal in the diet at dosage levels of 0, 250, 1000 and 2000 mg/kg-day for 28 days. Food and water were available ad libitum.

No treatment-related effects were observed on survival, clinical signs, body weight, body-weight gain or food consumption in either sex at any of the dose levels tested. A dose-related effect was observed on the liver, that displayed an increase in weight and the incidence of hypertrophy of the centrilobular hepatocytes at dose levels. Other differences noted between control and treated animals could not be definitely attributed to the test material. Based on the effects observed in the liver at all dose levels tested, the LEL for systemic toxicity is 250 mg/kg-day. A NOEL for systemic toxicity was not established.

Data Gap(s): None

I.A.5. Confidence in the Oral RfD

Study — High
Database — High
RfD — High

The principal study was well conducted and is given a high confidence rating. Additional studies are of good quality and generally supportive of the principal study. Therefore, the database is given a high confidence rating. High confidence in the RfD follows.

I.A.6. EPA Documentation and Review of the Oral RfD

Source Document — This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation — None

Agency Work Group Review — 11/21/1985, 06/24/1986, 12/16/1986, 02/18/1987, 10/14/1987, 06/22/1988, 02/17/1994

Verification Date — 02/17/1994

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfD for Dacthal conducted in November 2001 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Dacthal
CASRN — 1861-32-1
Primary Synonym — DCPA

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Dacthal
CASRN — 1861-32-1
Primary Synonym — DCPA

This substance/agent has not undergone a complete evaluation and determination under US EPA's IRIS program for evidence of human carcinogenic potential.

III. [reserved]

IV. [reserved]

V. [reserved]

VI. Bibliography

Substance Name — Dacthal
CASRN — 1861-32-1
Primary Synonym — DCPA

VI.A. Oral RfD References

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VI.B. Inhalation RfD References

None

VI.C. Carcinogenicity Assessment References

None

VII. Revision History

Substance Name — Dacthal
CASRN — 1861-32-1
Primary Synonym — DCPA

Date	Section	Description
08/22/1988	I.A.	Oral RfD summary on-line
08/01/1994	I.A.	Oral RfD summary replaced; RfD changed
12/03/2002	I.A.6.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — Dacthal
CASRN — 1861-32-1
Primary Synonym — DCPA
Last Revised — 08/22/1988

- 1861-32-1
- 1,4-BENZENEDICARBOXYLIC ACID, 2,3,5,6-TETRACHLORO-, DIMETHYL ESTER
- BENZOIC ACID, 3,6-DICHLORO-2-METHOXY-
- CHLOROTHAL
- CHLORTHAL-DIMETHYL
- CHLORTHAL-METHYL
- DAC 893
- Dacthal
- DACTHALOR
- DCPA
- DIMETHYL TETRACHLOROTEREPHTHALATE
- DIMETHYL 2,3,5,6-TETRACHLOROTEREPHTHALATE
- FATAL
- TETRACHLOROTEREPHTHALIC ACID DIMETHYL ESTER
- 2,3,5,6-TETRACHLOROTEREPHTHALIC ACID, DIMETHYL ETHER

- 2,3,5,6-TETRACHLORPHTHALSAURE-DIMETHYLESTER