

IPRODIONE

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EXPLANATION

Iprodione was previously evaluated by the Joint Meeting in 1977 (Annex 1, reference 28) when an ADI of 0-0.3 mg/kg bw was established. The data reviewed in 1977 consisted of studies of pharmacokinetics, short-term toxicity in rats and dogs, long-term toxicity in mice and rats, and special studies on developmental toxicity, reproduction, and mutagenicity. The present review evaluates studies made available since the 1977 review. Relevant portions of the previous monograph have been incorporated into this toxicological monograph.

EVALUATION FOR ACCEPTABLE DAILY INTAKE**BIOLOGICAL DATA****Biochemical aspects****Absorption, distribution, and excretion****Rats**

The pharmacokinetics of iprodione following oral administration was studied using groups (5/sex) of Charles River CD rats. One group received a single low dose of 50 mg ¹⁴C-iprodione/kg bw (uniformly labelled phenyl ring). A second group received a single high dose of 900 mg ¹⁴C-iprodione/kg bw. A third group received multiple doses (14 daily doses) of 50 mg iprodione/kg bw/day of unlabelled (99.3% purity) followed by a single dose of ¹⁴C-iprodione. Blood, urine, and faeces were collected for 7 days after treatment at which time rats were sacrificed and tissues collected.

Following a single low dose, 90% of the administered dose was eliminated within 4 days primarily in urine. Urinary excretion accounted for 67% of the administered dose in males and 53% in females whereas faecal excretion accounted for 25% in males and 39% in females. Males may have absorbed the dose to a greater extent than females based on the greater urinary excretion and the larger area-under-the-curve (blood concentration-time curve) for males. Peak

blood concentrations were reached within 2-4 h. After 7 days, tissue residues in both sexes were less than 0.7 ppm in any one tissue and collectively accounted for no more than 0.3% of the administered dose. Tissue concentrations were highest in the liver and intestines. The elimination half-life was estimated to be 9 h for males and 7 h for females based on the blood-concentration time curves.

Following a single high dose, 90% of the administered dose was eliminated within 2 days in males and 3 days in females. The single high dose appeared to be absorbed to a lesser extent than the single low dose based on the greater faecal excretion of parent compound following the high dose compared to predominantly urinary excretion of the single low dose. Faecal excretion accounted for 56% of the administered high dose in males and 52% in females whereas urinary excretion accounted for 43% in male and 46% in females. The peak blood concentration was reached within 6 h and was about three times the peak concentration following the single low dose. After 7 days, tissue concentrations were less than 10 ppm in any one tissue and collectively accounted for no more than 0.2% of the administered dose. The elimination half-life of the single high dose was about twice that for the single low dose. The high dose elimination half-lives were 20 h for males and 13 h for females.

Following multiple low dose exposures, 90% of the administered dose was eliminated within 3 days, primarily in urine. The excretion pattern was similar to that for the single low dose. Urinary excretion accounted for 75% of the administered dose in males and 65% in females whereas faecal excretion accounted for 20% in male and 28% in females. Tissue concentrations were ≤ 1 ppm in any one tissue (Hallifax, 1989).

The dermal absorption of iprodione was 0.65% in 24 h for male and female rats. Groups of 3 male and 3 female hairless strain rats received a dose of 185 mg ^{14}C -iprodione /kg bw of (uniformly labeled phenyl ring) applied to a 12 cm² area of the back for 24 h. Ninety to 93% of the dose was recovered from the skin. Of the 0.65% absorbed, 0.45% of the radiolabel was found in urine and faeces and the remaining 0.15% was present mainly in the carcass (Laurent *et al.*, 1983).

Biotransformation

Rats

Following a single application of an oral dose of 200 mg iprodione/kg bw, 26% of the administered dose was eliminated in the urine and 59% in the faeces within 24 hours after application. The major portion of the dose excreted in the faeces was the parent compound, whereas only 3% of the administered dose was eliminated unchanged in the urine. Besides the principal urinary metabolites with a degraded isopropylcarbamoyl group (about 11% of the dose administered), metabolites with intact hydroxylated or non-hydroxylated aromatic rings were excreted in the urine. The isomer of the parent compound accounted for a small

proportion of the metabolites. Residues in the principal organs and tissues did not exceed 1.5% of the administered dose in rats sacrificed 4 days after dosage (Laurent and Buys, 1974).

In a similar study rats were dosed once with 100 mg/kg of ^{14}C aromatic ring labelled iprodione; 96 hours after administration 62% of the applied dose was eliminated via the urine and 36% via the faeces. About 16% was excreted as the parent compound in the faeces; the remaining radioactivity was mainly in the urine, in the form of the desisopropylated derivative (about 20% of the dose) and the N-(3,5-dichloro-4-hydroxyphenylbiuret) (approx. 13%). Tissues sampled 4 days after dosage contained about 1% of the administered dose (Laurent, et al, 1976).

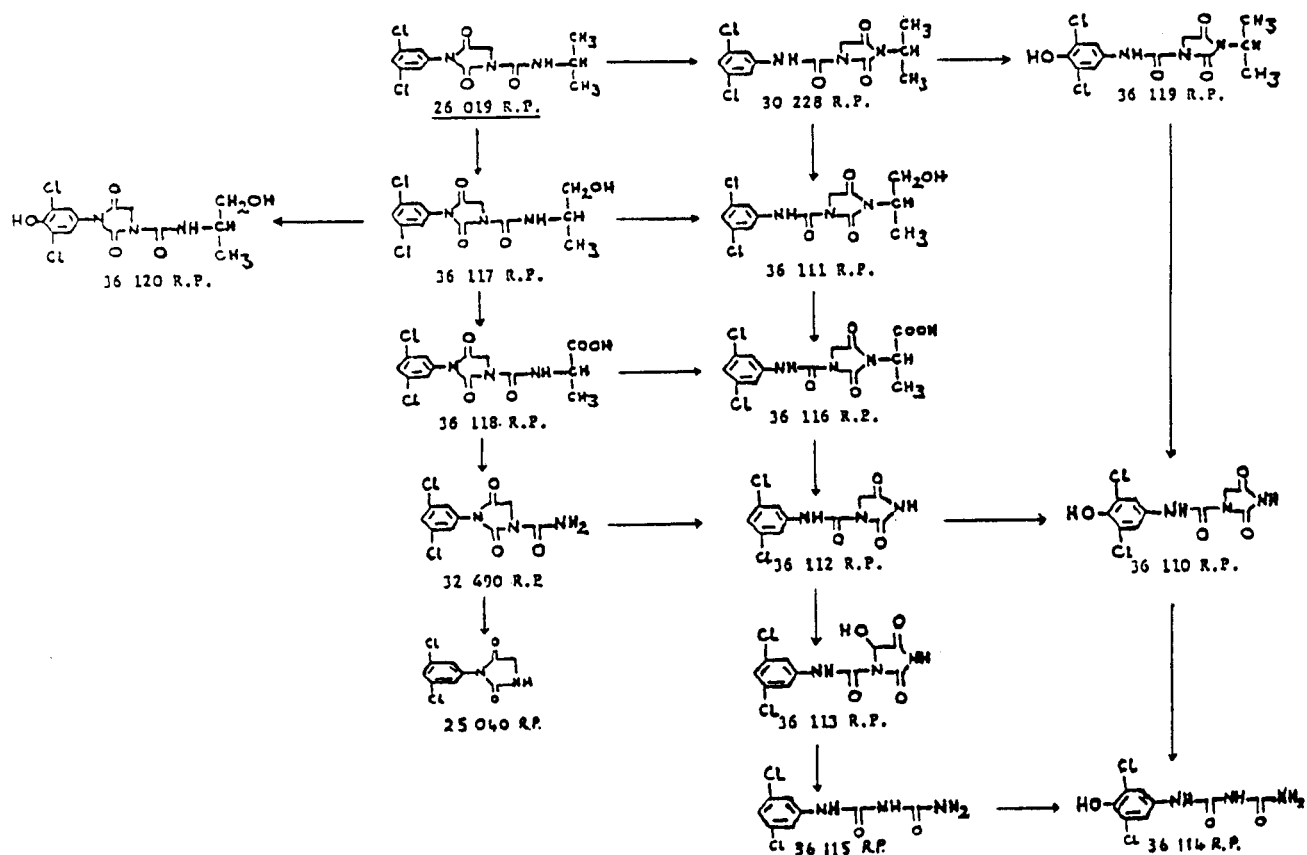
The metabolism of iprodione was studied in Charles River CD rats by analysing the urine and faeces obtained in the pharmacokinetics study described above (Hallifax, 1989). Metabolite identity was based on comparison of retention times with reference compounds by TLC and HPLC. A proposed metabolism scheme is shown in Figure 1. Iprodione was extensively metabolized by both males and females following single low or high doses or repeated low doses. Males and females of all groups eliminated in the urine relatively large amounts of a dealkylated metabolite corresponding to reference compound 32490 RP. The urine of all male and high dose females also contained large amounts of 36114 RP, a hydantoin ring-opened metabolite. Two major urinary metabolites, each representing 10-15% of the administered dose, were unidentified. Females in all groups eliminated a larger portion of the urinary radiolabel as the parent compound than males. Most of the extracted radiolabel in the faeces was the unchanged parent compound with small amounts of the same metabolites identified in the urine. The faeces of the high dose group contained relatively more parent compound than the single or repeated low dose groups, which is consistent with lower absorption of the high dose (Hallifax, 1989).

Iprodione and three metabolites were identified in hairless rats (3/sex) treated dermally with a dose (185 mg/kg bw) of ^{14}C -iprodione for 24 h. Iprodione was found unchanged in the urine, faeces, and intestines. Metabolite 30228 RP was found in the urine of males, 32490 was detected in the urine of males and females, and 36114 RP was detected in the urine, faeces, and intestines of males and females (Laurent *et al.*, 1983).

Humans

Small amounts of the metabolite 32490 RP were detected in the urine of 3 of 6 workers involved in mixing and diluting the formulation ROVRAL WP® (50% w/w iprodione). Unchanged iprodione was not detected in the urine (Jones, 1983).

Figure 1. Metabolic pathway for iprodione in the rat



Toxicological studies

Acute toxicity studies

The acute toxicity of iprodione is summarized in Table 1. Common signs of toxicity include decreased motor activity, ataxia, tearing, and paralysis. Tonic convulsions were noted in one study in mice.

Short-term toxicity studies

Mice

Groups (10-20/sex/dose) of CF-1 mice received iprodione (purity unspecified) in the diet daily for 28 days at 0, 600, 1900, 6000, 9500, or 15000 ppm (equal to 130, 390, 950, 1500 or 2300 mg/kg bw/day for males and 120, 420, 1000, 1500 or 2400 mg/kg bw/day for females). The highest dose produced mortality and depressed body-weight gain and food consumption. Exposure to 6000 ppm and above produced ataxia and lethargy during the first week of treatment. The liver was affected in groups receiving 6000 ppm and above. Absolute and relative liver weights were increased, livers had a stippled appearance on gross examination, and the incidence of hepatocyte vacuolation and focal eosinophilic degeneration was increased. At 15000 ppm granulomatous inflammation, (possibly in response to a foreign body), was observed in the heart, liver, and kidney. The NOAEL was 1900 ppm (equal to 390 mg/kg bw/day for males and 420 mg/kg bw/day for females) based on liver effects at 6000 ppm and above (Stevens, 1974).

Groups of 10 CF-1 Carworth mice/sex received iprodione (purity unspecified) in the diet daily for 4 weeks at 0, 600, 1900, 6000, 9500 or 15000 ppm, (equal to 115, 366, 1090, 1860 or 4030 mg/kg bw/day for males - the high dose based on first two weeks only - and 137, 439, 1310, 2090 or 2590 for females). The high dose produced mortality and depressed body-weight. Depression and ataxia were observed at 6000 ppm and higher. Relative liver weight was increased at 6000 ppm and above. Gross necropsy revealed white foci in the liver of mice receiving 1900 ppm and higher, a stippled appearance of the liver at 6000 ppm and higher, and liver enlargement at 9500 and 15000 ppm. White foci and granulomatous inflammation were observed in numerous tissues, primarily at the high dose. One granulomatous lesion was observed in the liver at 6000 ppm and 5 were observed in the bladder at 9500 ppm. The presence of spindle-shaped clear spaces in tissues and foreign body type giant cells suggested a reaction to crystal formation. Liver cell hypertrophy was increased at 6000 ppm and above. The NOAEL was 600 ppm (equal to 115 mg/kg bw/day for males and 137 mg/kg bw/day for females) based on gross changes in the liver at 1900 ppm and above (Huffman, 1974).

Table 1. Acute toxicity of iprodione

Species	Strain	Sex	Route	LD ₅₀ mg/kg bw	LC ₅₀ mg/l	Reference
Mouse	CD-1	M	oral	1870		Takehara <i>et al.</i> (1976b)
		F		2670		
	CD-1	M	i.p.	900		Takehara <i>et al.</i> (1976b)
		F		625		
	CD-1	M	subcutaneous	> 6700		Takehara <i>et al.</i> (1976b)
		F		> 6700		
Rat	CD	M	oral	> 2000		Cummins (1989)
		F		> 2000 ²		
	CD	M	oral	2060		Takehara <i>et al.</i> (1976a)
		F		1530		
Wistar	M&F	oral	3700		Babish (1976a)	
CD	M	i.p.	1330		Takehara <i>et al.</i> (1976a)	
	F		700			
CD	M	subcutaneous	> 4500		Takehara <i>et al.</i> (1976a)	
	F		> 4500			
Sprague-Dawley	M	inhalation (4-hr exp)		> 3.29	Coombs & Clark (1977)	
	F			> 3.29		
Rabbit	New Zealand white	M	dermal (24-hr exp)	> 2000	Plutnick <i>et al.</i> (1988)	
		F		> 2000		
	?	?	dermal (?-hr exp)	> 30000	Babish (1976b)	
Dog	Beagle	M	oral	> 2000	Pasquet & Mazuret (1974) (FAO/WHO, 1978)	
		F		> 2000		

¹ Purity of technical iprodione was 95.8%

² Purity of technical iprodione was 97.9%

The crystal formation in tissues was further evaluated using groups of 15 CD-1 mice/sex receiving iprodione (93.5%) in the diet daily for 4 weeks at 0, 1900, 6000, 9500 or 15000 ppm (equivalent to 290, 900, 1400, and 2300 mg/kg bw/day). The two highest dose levels produced mortality, clinical signs of toxicity, and depressed weight gain and food consumption. At 6000 ppm and above, crystalline deposits and effects on the liver were observed. Granulomatous lesions surrounding crystal deposits were found frequently in the urinary bladder and occasionally in liver parenchyma, myocardium, diaphragmatic muscle, and skeletal muscle. It was speculated that the crystals contained a major metabolite of iprodione, 32490 R.P., which was identified in the liver. Liver effects included increased weight, pale and mottled appearance on gross examination, and swelling of hepatocytes to form large homogeneous areas in the centrilobular region of the liver. Histopathological changes in the testes and spleen were observed at doses levels above 6000 ppm. A NOAEL of 1900 ppm (equivalent to 290 mg/kg bw/day) was determined based on crystalline deposits in the urinary bladder, liver enlargement, and hepatocellular swelling at 6000 ppm and above (Ganter *et al.*, 1979).

Groups of 10 Crl:CD-1(ICR)BR mice/sex received iprodione (95.7% purity) in the diet daily for 13 weeks at 0, 1500, 3000, 6000, or 12000 ppm, (equal to 260, 510, 1100 or 2100 mg/kg bw/day for males and 330, 660, 1300 or 2600 mg/kg bw/day for females). The high dose was associated with mortality, clinical signs of toxicity, weight loss, and reduced food consumption. The two highest dose levels produced crystalline deposits with associated multinucleated cells in a number of tissues, particularly in the urinary bladder. At the lowest dose level of 1500 ppm, liver and adrenal gland weights were increased in females. The incidence and severity of liver cell enlargement in males and females showed a dose-related increase beginning with the 1500 ppm dose level. Enlargement and vacuolation of adrenal cortex cells were increased in treated groups. The incidence of vacuolation of zona fasciculata cells was 0/10, 1/10, 3/10, 6/10, and 4/9 in females receiving 0, 1500, 3000, 6000 or 12000 ppm, respectively. At 3000 ppm and higher, effects were observed in the kidney, uterus, ovary, and spleen. The authors determined that dose levels of 6000 ppm or greater were unsuitable for a long-term study in mice because of crystal formation and accompanying effects in the urinary bladder. A NOAEL was not identified in this study. The lowest dose of 1500 ppm was associated with enlargement of the liver and adrenal glands and microscopic changes in these organs (Fryer *et al.*, 1990a).

Rats

Groups of 15 CD/CRJ rats/sex received iprodione (purity unspecified) in the diet daily for 3 months at 0, 300, 1000, or 3000 ppm, (equal to 21, 70 or 210 mg/kg bw/day for males and 24, 82 or 240 mg/kg bw/day for females). The high dose of 3000 ppm produced clinical signs of toxicity (i.e. piloerection, rough fur), depressed food and water consumption, and decreased body-weight (final weight

reduced 20-40%). A number of absolute and relative organ weights were decreased at the high dose including the liver, spleen, thymus, kidneys, and heart. Microscopic findings were observed at the high dose in the liver, spleen, and thymus. Swelling of the zona glomerulosa of the adrenal gland showed a dose-related increase at 1000 and 3000 ppm in both sexes. The NOAEL was 300 ppm (equal to 21 mg/kg bw/day for males and 24 mg/kg bw/day for females) based on microscopic changes in the adrenal cortex at 1000 ppm and above (Itabashi *et al.*, 1978).

Groups of 10 Crl:CD (SD) BR rats/sex received iprodione (95.7% purity) in the diet daily for up to 13 weeks at 0, 1000, 2000, 3000, or 5000 ppm (equal to 78, 150 or 250 mg/kg bw/day for males and 89, 180 or 270 mg/kg bw/day for females). The high dose group was terminated during week 8 due to excessive toxicity which included a progressive decrease in food intake and body-weight and the death of one male. Upon examination these animals showed abnormalities in the liver, adrenal glands, uterus, ovaries, prostate, and seminal vesicles. Clinical signs (i.e. hunched posture, piloerection, emaciation) occurred in males and females receiving 3000 ppm. Body-weight, food intake, and food efficiency were reduced at the 2000 and 3000 ppm. Ovary weight was decreased at 2000 and 3000 ppm, and uterus weight was reduced at 3000 ppm. Seminal vesicles and the prostate gland of males receiving 3000 ppm were reported as smaller than normal but no histological changes were noted. Histopathological changes were in the adrenal glands, uterus, and ovaries were increased at 2000 and 3000 ppm. Adrenal gland findings included enlarged cells of the *zona glomerulosa* in males and females and vacuolation of the *zone fasciculata* mainly in females. The uterus showed signs of atrophy and ovaries contained reduced numbers of corpora lutea. A NOAEL of 1000 ppm equal to 78 mg/kg bw/day for males and 89 mg/kg bw/day for females was determined, based on a reduced body-weight gain and histopathological changes at 2000 ppm and higher (Fryer *et al.*, 1990b).

Groups of 15 male and 15 female caesarean originated, barrier sustained, rats were fed 0, 150, 500 or 1000 ppm iprodione in the diet for 5 months. No effects were observed on mortality, food consumption, haematology (as judged by haemoglobin, haematocrit, erythrocyte count, or total and differential leucocyte count) clinical chemistry (as judged by BSP, SGOT, SGPT or SAP) or urinalysis. Body weight gain was slightly reduced (especially in males) at 500 and 1000 ppm. Absolute (but not relative) heart weight was reduced in males at 500 and 1000 ppm, and absolute kidney weight was reduced at 1000 ppm. In females, absolute liver and kidney weights were significantly reduced at 500 ppm only. Gross and histopathology were normal at all dose levels. In a parallel study, dichlozoline, a structurally related compound, induced cataracts. No such effect was seen with iprodione (Ganter *et al.*, 1973a).

Dogs

Groups of 2 male and 2 female dogs were maintained on a diet containing iprodione at dose levels of 0, 800, 2400 or 7200 ppm for a period of 3 months. At the top dose level the method of administration was altered after 6 weeks, to gelatine capsules. The treatment did not affect mortality. The recorded values of haematological determinations and urinalyses were within normal limits, as judged by haemoglobin, haematocrit, reticulocyte erythrocyte count, total and differential leucocyte count and prothrombine time, except for signs of mild anaemia in 1 male and 1 female at 2 months and 1 male at 3 months at the top dose level. At 7200 ppm a reduction of food consumption was observed, accompanied by reduced body-weight gain. Ophthalmoscopic examination of the animals did not reveal any pathological alterations. A transient increase in SGOT and SGPT was observed after 1 and 2 months of treatment at 7200 ppm. In treated male rats a dose-dependent increase of relative liver weights was observed, which was also observed in females at 2400 ppm and above. At 7200 ppm reduced relative weight of testes was found, but there was no histological indication of damage. The histopathological findings did not reveal any indication of treatment-related alterations of tissues (Coquet, 1973c; Gunter & Girard, 1973).

Groups of 6 beagle dogs/sex received iprodione (96.5% purity) in the diet daily for 52 weeks at 0, 100, 600, or 3600 ppm, (equal to 4.1, 24.9 or 145 mg/kg bw/day for males and 4.3, 28.3 or 153 mg/kg bw/day for females). Ophthalmology, haematology, clinical chemistry, and urinalysis tests were performed periodically over the course of the study. Slight retinal hyperreflection was noted more frequently in males receiving 3600 ppm and in females receiving 600 or 3600 ppm. The severity did not increase over time or with dose level and was not seen consistently in the same animals over time. Red blood cells were affected at 3600 ppm and possibly at 600 ppm. Compared to controls, high dose males showed a slight but consistent decrease in erythrocyte count, haemoglobin, and haematocrit over the course of the study. Females receiving the high dose showed a less consistent pattern of anaemia. Platelet count and partial thromboplastin time were increased over the course of the study in high dose males and females. The high dose was also associated with an increase in frequency and severity of erythrocytes containing Heinz bodies. After 52 weeks, 3/6 control males and 4/6 control females showed the presence of Heinz bodies compared to all males and females receiving the high dose. In control dogs the number of affected erythrocytes was 0-2 per field compared to 6-50 or over 50 per field in dogs receiving the high dose. During the first one-third of the study, the incidence and severity of Heinz bodies were also increased in males receiving 600 ppm. No treatment-related changes were noted in the bone marrow.

Plasma ALP was consistently increased over control values and was above the normal range in high dose males and females. In high dose females, serum ALT was transiently elevated early in the study and LDH was transiently increased

late in the study. Total bilirubin and albumin were slightly elevated during the study particularly in high dose females. Absolute and relative liver and adrenal gland weights were increased at the high dose in males and females. Absolute prostate gland weight was decreased 22% at 600 ppm and 41% at 3600 ppm. Relative prostate gland weight was also reduced at the high dose (39%). Two high dose females had enlarged adrenal glands and one high dose male had a swollen liver on gross examination. Nematode granulomas were found in various tissues of a number of control and treated dogs. Treatment-related microscopic changes were observed in the liver, adrenal glands, and urinary bladder of high dose males and females. In the urinary bladder, the majority of high dose males and females had submucosal granulomas and giant cells containing crystals. The majority of high dose males and females had fat vacuolation and/or pallid appearance of the adrenal cortex compared to an absence or lower incidence in controls. Hepatic centriacinar atrophy was observed in 3/6 males and 4/6 females receiving the high dose compared to no controls with the lesion. Pigmented macrophage agglomerates in the liver were more prominent in the high dose groups than in controls. An additional finding in females was lipofuscinosis in the proximal convoluted tubules of the kidney occurring in 2/6, 0/6, 4/5, and 4/6 in the 0, 100, 600, and 3600 ppm groups, respectively. No treatment-related histopathologic changes were noted in the prostate gland. A NOAEL of 100 ppm, equal to 4.1 mg/kg bw/day, was determined, 600 ppm representing a minimal toxic effect level with the majority of toxic changes occurring at the 3600 ppm dose level (Broadmeadow, 1984).

A second one-year dog study was conducted to determine the NOAEL between 100 and 600 ppm. Groups of 6 beagle dogs/sex received iprodione (96% purity) in the diet daily for 52 weeks at 0, 200, 300, 400, or 600 ppm, (equal to 7.8, 12, 18 or 25 mg/kg bw/day for males and 9.1, 13, 18 or 26 mg/kg bw/day for females). Eye examinations and haematology were performed during weeks 4, 8, 12, 20, 28, 36, and 52. The adrenal glands, kidneys, and prostate were the only organs weighed. Kidneys of females and prostate of males were the only tissues examined microscopically. Iprodione treatment had no effect on survival, body weight, body-weight gain, food consumption, or food efficiency. Most dogs treated with iprodione developed skin lesions consisting of redness and scab formation occurring primarily in the inguinal, hindlimb, and ventral abdominal areas. Skin lesions were less frequent and less severe in controls. The majority of lesions had cleared by study termination. Tests for mange and fungal infection were negative. It was noted that slight irritation of the skin was not uncommon in dogs fed powdered chow.

Eye examinations revealed no treatment-related abnormalities. Haematology parameters were within the normal range for all groups. In females receiving 600 ppm, erythrocyte count, haemoglobin, and haematocrit were reduced at week 4 (15%) and at week 36 (10%). In both males and females receiving 600 ppm, values for these erythrocyte parameters were consistently lower than control values through week 36, although the differences were not statistically significant.

Heinz bodies were not observed in any control or treated animal at any time point. Organ weights (kidney, adrenal glands, prostate) were unaffected, and no treatment-related histopathological changes were observed in the kidneys of females or prostate of males. Based on slight changes in erythrocyte parameters at 600 ppm, the NOAEL was 400 ppm, equal to 18 mg/kg bw/day (Kangas *et al.*, 1991).

Long-term toxicity/carcinogenicity studies

Mice

Groups of 60 male and 60 female mice were maintained on a diet containing the test compound at 0, 200, 500 or 1250 ppm for 18 months. No treatment-related effects on body-weight, food consumption or mortality were found. The recorded values of the haematological, blood chemistry and urinalyses tests, performed after 6, 12 and 18 months of the feeding period, were within the physiological range. Necropsy findings on mice that died during the last 6 months of the test and on those sacrificed at the termination date showed an increased number of enlarged lymph nodes in males at 200 ppm. Organ weight variations occurred sporadically in the various dose groups which were considered not to be treatment-related. The histopathological observations failed to reveal abnormal features. The distribution of neoplastic and non-neoplastic findings did not appear to demonstrate any significant dose dependence. The most common tumours were lymphosarcomas involving the spleen, lymph nodes and thymus (Hastings & Huffmann, 1975).

Rats

Groups of 60 male and 60 female rats were maintained on a diet containing 0, 125, 250 or 1000 ppm iprodione for 24 months. Slight reduction in body weight gain was observed at 1000 ppm. This was accompanied by some reduction in food intake. The treatment had no effect on food consumption, mortality or values of the haematologic, blood chemistry or urinalyses determinations. Necropsy findings did not reveal any drug-related gross alterations. Variations in organ weight did not show a group distribution and did not seem to be related to drug administration. Histopathology did not indicate a treatment relationship with neoplastic or non-neoplastic findings. At 24 months the most common tumours observed were pituitary adenomas and adenocarcinomas and fibroadenoma of the mammary glands (Hastings *et al.*, 1976).

Reproduction studies

Rats

Groups of 10 male and 20 female rats were maintained on a diet containing iprodione at concentrations of 0, 125, 250 or 1000 ppm for the first 5 weeks of

each generation and 0, 250, 500 or 2000 ppm for the next 8 weeks of treatment. The diet was fed through 3 generations. The treatment did not affect the growth rate, food consumption, mortality or fertility of the parent animals. The number of living delivered pups of the females treated with 2000 ppm was slightly reduced and the post-natal growth of the pups was slightly retarded. There was also a tendency for growth reduction at 500 ppm. Autopsy findings and microscopic examination of the major organs performed in rats of the third generation did not reveal abnormalities (Coquet, 1976).

The reproductive toxicity of iprodione was studied in two successive generations of Crl:CD BR/VAF/Plus rats. The first parental (F_0) animals were mated twice to produce F_{1a} and F_{1b} litters. F_{1a} animals were mated twice to produce F_{2a} and F_{2b} litters. Groups (28/sex) received diets containing 0, 300, 1000, or 3000 ppm of iprodione (96.2% purity) beginning at least 10 weeks prior to mating. The high dose of 3000 ppm was reduced to 2000 ppm at the time of the first mating of F_{1a} rats because of excessive toxicity. The administered doses were equal to 17, 55 or 160 mg/kg bw/day for F_0 males; 21, 71 or 210 mg/kg bw/day for F_0 females; 20, 68, and 150 mg/kg bw/day for F_1 males; and 25, 82 or 190 mg/kg bw/day for F_1 females. Toxicity in adult rats was observed at 1000 ppm and above. Body-weight, body-weight gain, and food consumption were reduced throughout the treatment period in F_0 and F_1 males receiving 3000 ppm and F_0 and F_1 females receiving 1000 or 3000 ppm. Reproductive performance was unaffected by iprodione exposure. Offspring toxicity was observed at the high dose. During lactation (16-21 days of age), F_{1a} and F_{1b} pups exhibited signs of toxicity including unkempt or hunched appearance, slow movement, and tremors during the last days of lactation. In both generations, litter size number of live pups, and pup weight were decreased at the high dose. The NOAEL was 300 ppm, equal to 21 mg/kg bw/day, for parental toxicity based on reduced parental body-weight at 1000 ppm and higher; for embryofetal toxicity, the NOAEL was 1000 ppm, based on clinical signs, reduced litter size, and reduced pup weight at 3000 ppm (Henwood, 1991).

Special studies on embryo/fetotoxicity

Rats

Groups of 25-30 rats were treated orally with 0, 100, 200 or 400 mg/kg bw/day iprodione on gestation days 5 to 15. Females at 400 mg/kg bw/day showed reduced fertility, reduced body weight gain and a dose-related reduction in food consumption, especially during the treatment period. The number of implantations was also reduced at the highest dose level. There was no indication of an embryotoxic or teratogenic effect of the test compound (Coquet, 1973a).

In a dose range-finding study in CD pregnant rats, treatment with 400 and 800 mg/kg bw/day resulted in mortality, weight loss, and pronounced clinical signs. Treatment with 240 mg/kg bw/day reduced weight gain and produced clinical signs, and 120 mg/kg bw/day occasionally produced clinical signs (i.e. flaccid

muscles). The lowest dose of 40 mg/kg bw/day had no effect on maternal health. It was concluded that dose levels should not exceed 240 mg/kg bw/day in a definitive developmental toxicity study (Tesh *et al.*, 1986a).

In the definitive study, iprodione (94.2%) was administered by oral gavage to groups of 25 mated female CD rats at doses of 0, 40, 90, or 200 mg/kg bw/day. Controls received the vehicle (aqueous methylcellulose). Rats were treated days 6-15 of gestation and sacrificed on day 21. The administered doses had no adverse effect on maternal health as assessed by mortality, clinical signs, body-weight, and food consumption. In the offspring, the incidence of space between body wall and organs was slightly increased at the high dose. The incidences were 4.3%, 5.3%, 5.8%, and 11.2% on a fetal basis and 15%, 20%, 20%, and 32% on a litter basis at 0, 40, 90 and 200 mg/kg bw/day, respectively. The majority of affected fetuses were small in size. It was noted that this observation was associated with fetuses of low body-weight in previous studies and was indicative of slight immaturity. The incidence of small fetuses (<2.7g) in this study was 2.9%, 5.1%, 4.9%, and 8.0% (fetal basis). Group mean fetal body-weights were 3.27, 3.18, 3.16, and 3.15 g. The findings collectively were suggestive of a slight effect on fetal developmental at the high dose despite the fact that none of the differences were statistically significant and values at the high dose were within the historical control range. A NOAEL for maternal toxicity of 200 mg/kg bw/day and a NOAEL for embryo-fetal toxicity of 90 mg/kg bw/day were determined, based on slightly delayed fetal development at 200 mg/kg bw/day. There was no evidence of teratogenic potential at the highest dose tested (200 mg/kg bw/day) (Tesh *et al.*, 1986b).

Rabbits

Groups of 15-17 New Zealand white rabbits were intubated on gestation days 6-16 inclusive with 0, 100, 200 or 400 mg/kg bw/day iprodione. Body-weight gain, over the period of treatment, was slightly reduced at 100 mg/kg bw/day, and a dose-related weight loss occurred at 200 and 400 mg/kg bw/day. Food intake was reduced at 200 mg/kg bw/day and above. At 400 mg/kg bw/day 9 of 17 females died, and only one of the four remaining pregnant animals carried to term. Fetal loss was increased at 200 mg/kg bw/day, and the fetal weight was reduced at 200 mg/kg bw/day and above. Multiple malformations occurred in 1 of 68 living fetuses at 200 mg/kg bw/day. Minor malformations were noted in all groups (Coquet, 1973b).

The developmental toxicity of iprodione was studied in New Zealand white rabbits. Iprodione (95.0% purity) was administered by oral gavage to groups of 18 artificially inseminated females at doses of 0, 20, 60, or 200 mg/kg bw/day. The control group received the vehicle (aqueous methylcellulose). Rabbits were treated on days 6-18 of gestation and sacrificed on day 29. Maternal toxicity was produced at 60 and 200 mg/kg bw/day. The high dose group experienced weight loss and reduced food consumption during the entire treatment period. Clinical signs associated with the high dose included hair loss, diarrhoea, and decreased

urination and defecation. The group receiving 60 mg/kg bw/day experienced slight body-weight loss during the first six days of treatment compared to positive weight gain by controls. Seven of 18 females receiving the high dose aborted compared to 1/18, 0/18, and 1/18 for the 0, 20, and 60 mg/kg bw/day groups. Ten does receiving the high dose delivered litters, two of which had totally resorbed litters (compared to 1/13 controls) resulting in only 8 viable litters at the high dose. A NOAEL of 20 mg/kg bw/day was determined based on depressed maternal weight gain at 60 mg/kg bw/day and above. The high dose of 200 mg/kg bw/day was considered an excessive dose for a teratology evaluation. Some skeletal variations appeared increased at the high dose, but the incidences were within the historical control range. The NOAEL for maternal toxicity was 20 mg/kg bw/day based on depressed weight gain at 60 mg/kg bw/day. The NOAEL for embryo-fetal toxicity was 60 mg/kg bw/day based on increased abortions and post-implantation losses at 200 mg/kg bw/day (Keets *et al.*, 1985).

Special studies on eye and skin irritation and hypersensitivity

Technical iprodione caused mild, transient eye irritation in rabbits. The irritation was lessened by washing the eye immediately after exposure (Babish, 1976c; Bonnette, 1991a).

Technical iprodione is not a dermal irritant in rabbits (Babish, 1976d; Bonnette, 1991b) or a dermal sensitizer in guinea-pigs (Trimmer *et al.*, 1988).

Special studies on genotoxicity

The results of genotoxicity studies are summarized in Table 2. Iprodione has been consistently negative in assays for point mutation, chromosomal aberration, and sister chromatid exchange. A questionable positive result was reported for DNA damage in *Bacillus subtilis*.

Observations in humans

No data available.

COMMENTS

Iprodione is extensively absorbed from the gastrointestinal tract. It was extensively metabolized and rapidly excreted, primarily in the urine, although relative faecal excretion of the parent compound increased at high doses. Higher doses (for example 900 mg/kg bw) appeared to be absorbed to a lesser extent and eliminated at a slower rate than lower doses (for example 50 mg/kg bw). The elimination half-life was 7-9 h following a single low dose and 13-20 h following a single high dose. The metabolic pathways elucidated in rats involve dealkylation on the isopropyl carbamoyl chain, hydroxylation of the aromatic ring and rearrangement and opening of the hydantoin ring.

Table 2. Results of genotoxicity assays on iprodione

Test system	Test object	Concentration of iprodione	Purity	Results	Reference
Ames test (1)	<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537, TA1538	1-5000 µg/plate dissolved in DMSO	96.2%	Negative	Lawlor & Valentine (1990)
	<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537, TA1538	25-200 µg/plate dissolved in DMSO	95.1 99.3%	Negative	Bouanchaud & Cartier (1982a,b)
	<i>S. typhimurium</i> Ta98, TA100, TA1535, TA1537	12.5-250 µg/plate dissolved in DMSO	?	Negative	Benazet & Cartier (1979)
<i>E. coli</i> mutation assay (1)	<i>E. coli</i> K12, GY 5057 strain	0.05-1000 µg/ml dissolved in DMSO	95.1 99.3%	Negative	Bouanchaud & Cartier (1982a,b)
	<i>E. coli</i> , W3110 (pol A.), p3478 (pol A)	12.5-200 µg/plate dissolved in DMSO	95.1 99.3%	Negative	Bouanchaud & Cartier (1982a,b)
<i>B. subtilis</i> mutation assay (1)	<i>B. subtilis</i> rec. exc. pol strains (19 strains)	20-1670 µg/ml dissolved in DMSO	96.8%	Positive (3)	Felkner (1985a)
<i>Saccharomyces cerevisiae</i> mutation assay (1)	<i>Saccharomyces cerevisiae</i> D7 strain	62.5-500 µg/ml dissolved in DMSO	99.3%	Negative	Bouanchaud & Cartier (1982a,b)
(2)	<i>Saccharomyces cerevisiae</i> D7 strain	250 µg/ml dissolved in DMSO	?	Negative	Benazet & Cartier (1979)
CHO/HGPRT mutation assay (1)	Chinese hamster ovary cells (CHO-K ₁ -BH ₄)	5-1500 µg/ml dissolved in DMSO	?	Negative	Godek <i>et al.</i> (1985)
<i>In vitro</i> cytogenetics (1)	Chinese hamster ovary cells (CHO-K ₁ -BH ₄)	15-400 µg/ml dissolved in DMSO	?	Negative	San Sebastian <i>et al.</i> (1985)
<i>In vitro</i> sister chromatid exchange (1)	Chinese hamster ovary cells (CHO-K ₁ -BH ₄)	5-400 µg/ml dissolved in DMSO	?	Negative	Felkner (1985b)
Dominant lethal assay	CF-1 mice	0, 1500, 6000 ppm X 49 days	?	Negative	Hastings <i>et al.</i> (1974) (WHO, 1978)

(1) Both with and without metabolic activation.

(2) Without metabolic activation.

(3) Positive at highest and lowest doses without metabolic activation. Problem with precipitation of test material, inadequate negative and positive controls.

Iprodione had low acute toxicity by all routes of exposure. The oral LD₅₀ was greater than 1500 mg/kg bw in mice, rats, and dogs. The World Health Organization has classified iprodione as unlikely to present acute hazard in normal use (WHO, 1992).

In three 4-week studies in mice at dietary concentrations of 0, 600, 1900, 6000, 9500, or 15000 ppm, the lowest NOAEL was 600 ppm, equal to 115 mg/kg bw/day, based on macroscopic hepatic changes at 1900 ppm. At 6000 ppm and above, the test material crystallized in the tissues. In a 3-month study in mice at dietary concentrations of 0, 1500, 3000, 6000, or 12000 ppm (equal to 260, 510, 1100, and 2100 mg/kg bw/day) an increase in liver and adrenal gland weights and hypertrophy and/or vacuolation of hepatocytes and adrenal cortical cells were observed in all treated groups.

In a 3-month study in rats at dietary concentrations of 0, 300, 1000, or 3000 ppm, the NOAEL was 300 ppm, equal to 21 mg/kg bw/day. Higher doses produced swelling in the zona glomerulosa of the adrenal cortex. In another 3-month study in rats at dietary concentrations of 0, 1000, 2000, 3000, or 5000 ppm, the NOAEL was 1000 ppm, equal to 78 mg/kg bw/day, based on reduced body-weight gain and histopathological changes in the adrenal glands, ovaries and uterus at 2000 ppm and higher.

In a one-year study in dogs at dietary concentrations of 0, 100, 600, or 3600 ppm, the NOAEL was 100 ppm, equal to 4.1 mg/kg bw/day, based on the detection of Heinz bodies in erythrocytes and decreased prostate gland weight at 600 ppm and higher. In a second one-year study at dietary concentrations of 0, 200, 300, 400, or 600 ppm, the NOAEL was 400 ppm, equal to 18 mg/kg bw/day, based on decreased erythrocyte values at 600 ppm.

In a two-generation reproduction study in rats at dietary concentrations of 0, 300, 1000, or 3000/2000 ppm, the NOAEL was 300 ppm, equal to 21 mg/kg bw/day, based on depressed body-weight at 1000 ppm and above. Reproductive performance was unaffected. Offspring survival and growth were reduced at 3000/2000 ppm.

In a teratology study in rats using gavage doses of 0, 40, 90, or 200 mg/kg bw/day, the NOAEL for maternal toxicity and teratogenicity was 200 mg/kg bw/day. The NOAEL for embryofetal toxicity was 90 mg/kg bw/day, based on slightly delayed fetal development at 200 mg/kg bw/day. In rabbits administered 0, 20, 60, or 200 mg/kg bw/day by gavage, the NOAEL for maternal toxicity was 20 mg/kg bw/day based on depressed weight gain at 60 mg/kg bw/day. The NOAEL for embryofetal toxicity was 60 mg/kg bw/day based on increased abortions and post-implantation loss at 200 mg/kg bw/day. No teratogenic effects were found.

After consideration of the available genotoxicity data, the Meeting concluded that iprodione was not genotoxic.

The former ADI, based on a multi-generation reproduction study in rats, was revised. The new ADI was based on the results of several studies, including the reproduction study in rats, the teratology study in rabbits, and the one-year study in dogs. A safety factor of 100 was applied to the NOAELs from these studies.

TOXICOLOGICAL EVALUATION

Level causing no toxicological effect

Mouse:	600 ppm in the diet, equal to 115 mg/kg bw/day (four-week study)
Rat:	300 ppm in the diet, equal to 21 mg/kg bw/day (two-generation reproduction study)
	500 ppm in the diet, equivalent to 25 mg/kg bw/day (reproduction study reviewed by the 1977 Joint Meeting)
Rabbit:	20 mg/kg bw/day (teratology study, maternal toxicity)
Dog:	400 ppm in the diet, equal to 18 mg/kg bw/day (one-year study)

Estimate of acceptable daily intake for humans

0-0.2 mg/kg bw/day

Studies which will provide information valuable in the continued evaluation of the compound

1. Ongoing toxicological studies.
2. Observation in humans.

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