

PENCONAZOLE

First draft prepared by
J.E.M. van Koten-Vermeulen and E.M. den Tonkelaar
National Institute of Public Health and Environmental Protection
Bilthoven, Netherlands

EXPLANATION

Penconazole is a systemic triazole fungicide with preventive and curative properties for the control of powdery mildew. It stops the development of fungi by interfering with the biosynthesis of sterols in cell membranes. It is used on fruit, especially apples and grapes, and vegetables. The compound was considered for the first time by the present Meeting.

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

Groups of Cr:CD(ICR)BR mice (20/sex/group) were fed diets containing 0, 10, 100, 300, 500, 1000 or 2400 ppm penconazole; purity 98.7%) for 13 weeks. At the end of the study the mice were given orally (10 mice/sex) or intravenously (10/mice/sex) a tracer dose of triazole-¹⁴C-penconazole. Urine was collected 24 and 48 h after dosing and faeces were collected at 48 h after dosing. Most of the ¹⁴C in urine was excreted in the first 24 h after dosing both after oral and i.v. administration. Total recovery of ¹⁴C in urine amounted to 47-66% for males and 63-78% for females irrespective of the previously administered dose or the route of administration. After i.v. or oral administration, male mice excreted more ¹⁴C in the faeces than female mice, 19-31% and 9-17%, respectively (Hiles, 1987b).

Rats

Groups of two Tif:RAIf (SPF) rats/sex were given a single oral dose of 0.5 or 25 mg/kg bw ¹⁴C-penconazole (triazole-labelled, purity >98%) in ethanol/PEG 200/water (2/3/5, v/v) by gavage. One rat/sex served as a control. Urine, faeces and expired CO₂ were collected at 24 h intervals. The rats

were sacrificed after 6 days and tissues were collected and analyzed for radioactivity. In both dose groups most of the radioactivity was eliminated in the urine (62-65% in males and 74-85% in females) and faeces (34-43% in males and 13-32% in females). Most of the excretion occurred within the first 24 h after administration. Especially at the high-dose level, females excreted a higher amount in the urine than the males. Minor amounts were detected in the expired air (ca 0.1%). At the 0.5 mg/kg bw dose level, most tissue residues were at or below the detection limit. Only in lungs (0.003-0.005 mg/kg), liver (0.003-0.004), kidney (0.002 mg/kg) and carcass (0.003 mg/kg) were detectable amounts of radioactivity found. The residues found at 25 mg/kg bw were about 20 times higher than those found at the 0.5 mg/kg bw dose level (Hamböck, 1980).

Groups of Crl:CD(SD)BR rats (5/sex/group) were given a single dose of unlabelled penconazole (purity 98.7%) corresponding to 0, 10, 100, 300, 500, 1000 or 2400 ppm in the diet, immediately followed by the administration by gavage of 0.1 mg ¹⁴C-triazole-labelled penconazole. Urine was collected 24 and 48 hours after dosing and faeces were collected 48 h after dosing. Rats were sacrificed 48 h after dosing. Most of the radioactivity was recovered in the first 24 h urine: 34-46% and 56-86% in males and females, respectively. After 48 h, the urinary excretion ranged from 46-55% in males and from 69-90% in females. Recoveries in faeces ranged from 19-27% in males and from 9-13% in females. Average total recoveries were 80% and 93% for males and females, respectively. In female rats, total recoveries were higher at all dose levels but there was no apparent correlation between excretion of radioactivity and the pretreatment dose level (LeVan, 1987).

Groups of Crl:CD(SD)BR rats (13/sex/group) were fed diets containing 0, 10, 100, 300, 500, 1000 or 2400 ppm non-labelled penconazole (purity 98.7%), for at least 13 weeks prior to a single oral or i.v. administration of 0.1 mg of ¹⁴C-penconazole (triazole ring-labelled) to 5 rats/sex/group; 3 rats/sex/group were available for replacement. Rats were sacrificed 48 h after receiving the radioactive dose. Urine was collected for 0-24 h and 24-48 h after radioactive dosing and faeces for 48 h. The samples were analyzed for radioactivity.

The administered radioactivity was recovered primarily in the first 24 h urine sample after both oral and i.v. dosing, with considerably higher amounts in female rats than in male rats. Total recovery in urine ranged from 73-77% in female rats and from 49-53% in male rats after an i.v. dose, and from 74-79% in female rats and from 48-59% in male rats after an oral dose. In faeces, 22-29% was recovered in males and 12-17% in females after i.v. administration. After oral administration, 26-31% was recovered in male rats and 13-16% in female rats. There was no relationship between pre-treatment doses and excretion of radioactivity (Hiles, 1987a).

Five Wistar rats/sex received a single oral dose of 0.5 or 50 mg penconazole/kg bw (^{14}C -phenyl-labelled; purity >99%). Urine and faeces were collected up to 96 h. Independent of the administered dose, male rats excreted equal amounts via the urine (46.9% and 41.1%) and faeces (43.5%-47.0%), female rats excreted 69.0% and 72.2% via the urine and 21.1% and 18.1% in the faeces in the low- and high-dose, respectively. No radioactivity (<0.01%) was found in the expired air. In both sexes, detectable tissue residues at 0.5 mg/kg bw were found only in liver, kidney, femur and intestinal tract. In males at 50 mg/kg bw the highest residual activity was found in the intestinal tract (4.08 ppm penconazole equivalents) followed by liver, kidney, adrenals, skin, carcass, blood and plasma (0.15 to 1.46 ppm). In females at 50 mg/kg bw the residual activity was 2 to 9 times lower than in males (Van Dijk, 1987).

In a bile excretion study, 9 h after the oral administration of 0.5 mg ^{14}C -penconazole/kg bw to males and females, 48.7% and 28.8% of the administered dose was excreted via the bile, respectively. After 48 h, biliary, urinary and faecal excretion represented 54.6%, 28.2% and 4.7% of the administered radioactivity for male rats and 40.2%, 47.9% and 2.0% for female rats. Fourteen daily treatments with 0.5 mg penconazole/kg bw/day followed by a final treatment with ^{14}C -labelled penconazole had no influence on the rate and route of excretion (Van Dijk, 1987).

Hens

Groups of two laying hens received oral doses equivalent to 5 ppm in the feed of ^{14}C -triazole-labelled penconazole or ^{14}C -phenyl ring-labelled penconazole for 16 consecutive days. Excreta and eggs were collected daily. Regardless of the radiolabel, nearly 99% of the radioactivity was eliminated with the excreta. Total radioactivity in the tissues amounted to 0.008% and 0.025-0.08% for the triazole and phenyl labels, respectively. Individual tissue residues for both labels ranged from <0.003 ppm to 0.025 ppm. The radioactivity recovered in the eggs reached a plateau on day 10 with 0.022 ppm (yolks) and 0.010 ppm (whites) for the triazol label, and on day 11 with 0.022 ppm (yolks) and 0.005 ppm (whites) for the phenyl label (Murphy & Capps, 1988a).

Goats

Two lactating goats were given an oral dose equivalent to 5 ppm in the feed of ^{14}C -triazole-labelled penconazole or ^{14}C -phenyl ring-labelled penconazole for 10 consecutive days. Daily samples of urine, faeces and milk as well as samples of blood, expired CO_2 , and volatiles were collected. The goats were sacrificed 24 h after the last dose. Excretion in the urine amounted to 92% and 77% for the triazole and phenyl label, respectively; 8% of the radioactivity was recovered in the faeces for both labels. About 0.2 and 0.1% of the administered dose was recovered as total tissue residue for the triazole- and

phenyl-label, respectively. Individual ^{14}C tissue levels were lower than 0.017 ppm penconazole equivalents except for kidney and liver with ^{14}C levels of 0.061 and 0.103 ppm for the triazole-label, and 0.036 and 0.075 ppm for the phenyl-label, respectively. The radioactivity recovered in milk reached a plateau around day 4 with 0.013 ppm for the triazole-label and 0.009 for the phenyl-label. Total recovery for the phenyl-label was lower, but this was due to a technical error (Murphy & Capps, 1988b).

Biotransformation

Rats

Twenty male Tif:RAIf (SPF) rats were given by gavage single oral dosages of 22.8 mg ^{14}C -triazole-labelled penconazole (> 98% purity)/kg bw. Urine and faeces were collected 24 h and 48 h after dosing and analyzed for radioactivity. The pooled 0-48 h urine and faeces samples contained 62% and 33% of the dose, respectively. Numerous metabolites, mostly conjugated, were identified in urine and faeces (13 urinary metabolites were identified by mass and NMR spectroscopy). Only 0.8% of the administered dose was excreted with the faeces as unchanged penconazole. A major pathway of metabolism is the stepwise oxidation and shortening of the alkyl side chain (see Figure 1). Also free triazole (about 15%) was excreted in urine and faeces, demonstrating another major independent pathway, namely cleavage at the nitrogen-carbon bond between the triazole ring and the pentyl moiety. Also oxidation of the triazole ring moiety, producing the 3-(or 5-)-hydroxy derivative, is observed. Conjugation, in particular glucuronidation, of the hydroxylated metabolites was also found (Hamböck, 1982, 1984).

Quantitative differences of the metabolite pattern of male and female urines were studied in groups of two male and female rats following a single oral dose of 0.5 mg/kg bw or 25 mg/kg bw triazole-labelled penconazole (Hamböck, 1980). Renal excretion was 60-63% for the males and 73-85% for the females. Males excreted more via the faeces (35-37%) than females (14-31%). Although the pattern of metabolites found in the 0-24 h urine samples was qualitatively the same in males and females (irrespective of the dose), polar metabolites, consisting of conjugated hydroxy derivatives, were much more abundant in females, accounting for 45% of the administered dose as compared to 3% in males. Males tend to excrete more free triazole (7% of the dose) than females (1%). Carboxylic acid metabolites are also more abundant in males. (Hamböck, 1985).

In a toxicokinetic study with ^{14}C phenyl-labelled penconazole, similar metabolite patterns were found in urine, bile and extractable faeces of males and females given one oral dose of 0.5 or 50 mg/kg bw. A total of 5 metabolites were in common to both sexes in urine, faeces and bile. Quantitatively more polar conjugated metabolites were found in the metabolite

patterns of the females. Conjugated CGA 127841 was found in urine, faeces and bile. Unconjugated CGA 127841 was found in bile, liver and kidney and CGA 189659 was found in faeces, liver and kidney (Van Dijk, 1987). These metabolites were not found by Hamböck, but they are essential intermediates in the metabolic pathway of penconazole (see Figure 1).

Hens

Characterization of the radioactivity in the excreta of laying hens dosed with triazole or phenyl ¹⁴C-labelled penconazole for 16 consecutive days revealed only 0.8% and 3.7% unchanged parent compound, respectively. After administration of both labels a carboxylic acid (metabolite 1) was the major metabolite accounting for 22% of the radioactive extractables. The metabolic pattern was comparable to female rats (no free triazole being detected) (Murphy & Capps, 1988a).

Goats

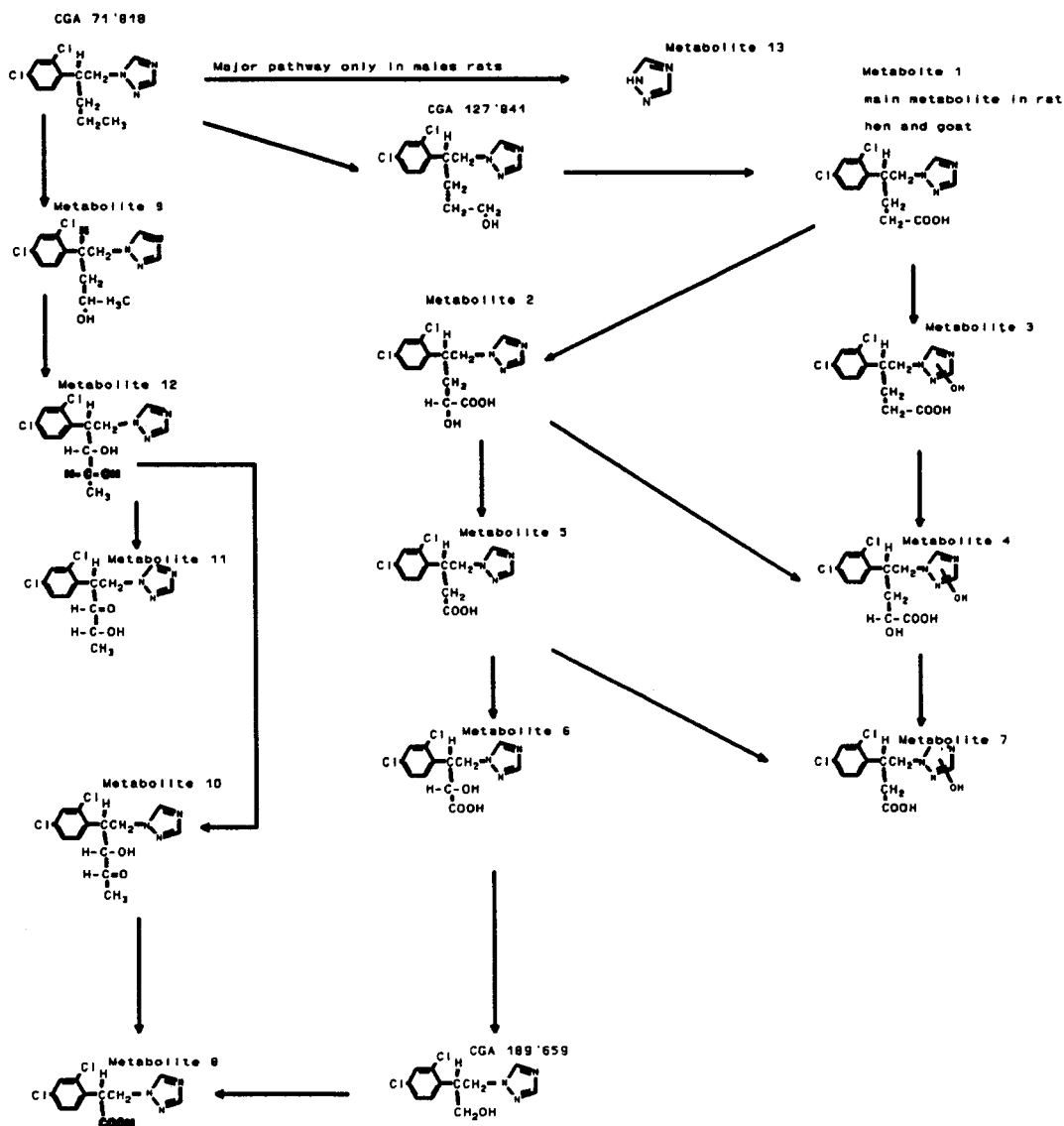
In goats fed a diet containing 5 ppm of ¹⁴C-labelled penconazole (triazole as well as phenyl ring) no parent compound was detected in the urine, while in faeces 17 and 21% parent compound were detected following administration of the phenyl- and triazole-label, respectively. The metabolic patterns in tissues, excreta and milk were the same for both labels, with the major metabolite identified as a carboxylic acid (metabolite 1). The metabolic pattern was comparable to female rats (no free triazole being detected) (Murphy & Capps, 1988b).

Effects on drug metabolizing liver enzymes

Groups of 6 male RAI albino rats or groups of 6 male Mag mice were orally administered 14 daily doses of 0, 10, 80, 160 or 320 mg penconazole/kg bw/day (purity 98,7%). The animals were fasted for 24 h after the last administration and then killed. The livers were removed and biochemical determinations were performed in the homogenates, microsomal and cytosolic fractions. Part of the livers from mice and rats from the control and the high-dose group were fixed for electron microscopy.

Relative liver weight was increased at doses \geq 80 mg/kg bw/day in both rats and mice. At the highest dose, total liver DNA content was increased to 120% in rats and to 125% in mice. Microsomal protein, phospholipid contents and enzyme activities were significantly increased in both mice and rats at 80 mg/kg bw/day and above. Cytochrome P-450, ethoxycoumarin O-deethylase and epoxide hydrolase were also significantly increased in rats at 10 mg/kg bw/day. Electron microscopy revealed proliferation of smooth endoplasmic reticulum membranes in both species (Waechter *et al.*, 1985).

Figure 1: Proposed metabolic pathways of penconazole



- Metabolite 1: 4-(2,4-dichlorophenyl)-5-(1H-1,2,4-triazol-1-yl)-pentoic acid. CGA 177279.
- Metabolite 2: 4-(2,4-dichlorophenyl)-2-hydroxy-5-(1H-1,2,4-triazol-1-yl)-pentoic acid.
- Metabolite 3: 4-(2,4-dichlorophenyl)-5-[3-(or 5)-hydroxy-1H-1,2,4-triazol-1-yl]-pentoic acid.
- Metabolite 4: 4-(2,4-dichlorophenyl)-2-hydroxy-5-[3-(or 5)-hydroxy-1H-1,2,4-triazol-1-yl]-pentoic acid.
- Metabolite 5: 3-(2,4-dichlorophenyl)-4-(1H-1,2,4-triazol-1-yl)-butanoic acid. CGA 177280
- Metabolite 6: 3-(2,4-dichlorophenyl)-2-hydroxy-4-(1H-1,2,4-triazol-1-yl)-butanoic acid. CGA 177282
- Metabolite 7: 3-(2,4-dichlorophenyl)-4-[3-(or 5)-hydroxy-1H-1,2,4-triazol-1-yl]-butanoic acid.
- Metabolite 8: 3-(2,4-dichlorophenyl)-3-(1H-1,2,4-triazol-1-yl)-propanoic acid. CGA 179944
- Metabolite 9: 2-(2,4-dichlorophenyl)-1-(1H-1,2,4-triazol-1-yl)-pentane-4-ol. CGA 132465
- Metabolite 10: 2-(2,4-dichlorophenyl)-3-hydroxy-1-(1H-1,2,4-triazol-1-yl)-pentane-4-one.
- Metabolite 11: 2-(2,4-dichlorophenyl)-4-hydroxy-1-(1H-1,2,4-triazol-1-yl)-pentane-3-one.
- Metabolite 12: 2-(2,4-dichlorophenyl)-1-(1H-1,2,4-triazol-1-yl)-3,4-pentandiol.
- Metabolite 13: 1H-1,2,4-triazole. CGA 71019

Metabolites 9, 10, 11 and 12 were mainly found as glucuronides or other conjugates.

Toxicological studies

Acute toxicity studies

Table 1. Acute toxicity of penconazole

Species	Sex	Route	LD ₅₀ mg/kg bw	LC ₅₀ mg/m ³	Purity	Reference
Mouse	M&F	oral	2444		88.4	Sarasin (1980)
Rat	M&F	oral	2125		88.4	Bathe & Gfeller (1980a)
	M&F	dermal	>3000		88.4	Bathe & Gfeller (1980b)
	M&F	inhal		>4046	96.1	Hartmann & Gfeller (1987)
Chinese hamster	M&F	oral	>5000		88.4	Bathe & Gfeller (1980c)
Rabbit	M&F	oral	971		88.4	Kobel (1981)

Penconazole shows low acute oral toxicity to mice, rats and hamsters, but is slightly more toxic to rabbits.

Short-term toxicity studies

Mice

Groups of Cr:CD(ICR)BR mice (15/sex/group) were fed diets containing 0, 10, 100, 300, 500, 1000 or 2400 ppm penconazole (purity 98.7%) equivalent to 0, 1.5, 15, 45, 75, 150 or 360 mg/kg bw/day for 13 weeks. Histopathology was only reported for the liver. No treatment-related effects were observed on clinical signs, mortality, ophthalmoscopy, food consumption, food efficiency, haematology or urinalysis. Body-weight was lower at 2400 ppm. Cholesterol levels were decreased at 1000 and 2400 ppm, ALAT increased in high-dose males and total protein and albumin were decreased in females at 2400 ppm. Relative liver weight was significantly increased at 500, 1000 and 2400 ppm. An increased incidence of centrilobular hypertrophy of the liver was observed in males at doses \geq 500 ppm and in females at the highest dose. Hepatic degeneration and vacuolisation was also observed in high-dose males. Coagulative necrosis in the liver was observed in males at 1000 and 2400 ppm. The NOAEL in this study was 300 ppm in the diet, equivalent to 45 mg/kg bw/day (Hiles 1987b).

Rats

Groups of Tif:RAIf(SPF) rats (10/sex/group) were orally administered 0, 20, 100 or 500 mg penconazole (purity 91.7%)/kg bw/day for 28 days. Since no marked symptoms of toxicity showed up during the first week of treatment the doses were increased to 100, 500 or 1000 mg/kg bw/day on day 8 of treatment.

After increasing the doses, 3 male and 3 female high-dose rats showed marked apathia and lateral body position at day 10 but the animals recovered on day 11. No effects were observed on mortality, ophthalmic or hearing examinations. In the mid- and high-dose groups male mean body weight was decreased, food consumption and food conversion were decreased in males and females, haemoglobin and haematocrit values were decreased in females and ALP and ALAT as well as cholesterol and total proteins were increased in males and females and total globulin was increased and A/G ratio was decreased in females. Phosphate and glucose were increased in high-dose females. Albumin increased in high-dose males and females. Urine volume was increased in males at the highest dose and in females at the mid- and high-dose. Relative liver, kidney and adrenal weight was increased in mid- and high-dose males and females. Relative brain, spleen and thyroid weight were increased in high-dose females. Enlarged livers with slight hypertrophy of the hepatocytes were observed in 8/10 and 3/10 males and females at the mid-dose and in all animals at the highest dose. The lowest dose (20-100 mg/kg bw/day) was considered as the NOAEL (Basler *et al.*, 1984).

Groups of Tif:RAIf(SPF) rats (20/sex/group) were fed diets containing 0, 30, 300 or 3000 ppm (equal to 2.1, 19.4 or 202.3 mg penconazole/kg bw/day for males and 2.1, 20.7 or 208.6 mg penconazole/kg bw/day for females, respectively) (purity 91.7%) for 3 months. No effects were observed on clinical signs, mortality, food and water consumption, food conversion, hearing tests or eye examinations. Body weight was decreased in males and females at the highest dose. An increase in total plasma protein and albumin was observed in male rats at all doses and a trend to an increase in total plasma proteins was seen in females at 3000 ppm. GGT was slightly increased in females at 300 and 3000 (significantly) ppm. Cholesterol levels were increased in both sexes at 3000 and also in females at 300 ppm. A significant dose-related increase in relative liver weight was observed at all dose levels. Relative testes weights were increased in males at 3000 ppm and brain, kidney and thymus weight were increased in high dose females. At histopathology minimal hypertrophy of the hepatocytes was seen in 20/20 male rats and 9/20 female rats at 3000 ppm. In this study no NOAEL was identified, although the liver weight increase at 30 ppm was marginal (Basler *et al.*, 1982).

In another 3 month feeding study groups of Tif:RAIf(SPF) rats (20/sex/group) were fed diets containing 0, 10, 30 or 100 ppm penconazole (purity 91.7%) (equal to 0.8, 2.1 or 7.1 mg penconazole/kg bw/day for males and 0.8, 2.1 or 7.3 mg penconazole/kg bw/day for females, respectively). No effects were observed on clinical signs, mortality, body-weight, food and water consumption, food conversion, eye examinations, hearing tests, organ weight or histopathology. Total proteins were increased in male and female rats at 30 and 100 ppm. Total globulin was increased in high dose females. GGT was slightly increased in females at both 30 and 100 ppm. Liver weight was increased at 10 and 30 ppm in male rats only, but not at 100 ppm. No liver histopathological

effects were observed. The NOAEL in this study was 10 ppm penconazole, equal to 0.8 mg/kg bw/day (Basler *et al.*, 1983).

In an additional study groups of albino [CrI:CD(SD)BR] rats (15/sex/group) were fed diets containing 0, 10, 100, 300, 500, 1000 or 2400 ppm penconazole (purity 98.7%) equivalent to 0.5, 5, 15, 25, 50 or 120 mg penconazole/kg bw/day for 90 days. In this study only the liver as target organ was studied histopathologically. Observations included clinical signs mortality, body-weight, food consumption, food efficiency, ophthalmoscopy, haematology, clinical chemistry (including GGT), urinalysis, organ weights, macroscopy and histopathology. Female body weight gain was lower at 500, 1000 and 2400 ppm and food consumption was decreased at the highest dose. Urea nitrogen was increased in males at all dose levels, but not clearly dose-related. Relative liver weight was significantly increased in rats at 500 (females only), 1000 and 2400 ppm. Relative kidney weight was increased in rats at 2400 ppm. At histopathology the incidence of vacuolization, degeneration and centrilobular hypertrophy of hepatocytes was increased at 500 ppm and above. The NOAEL in this study was 300 ppm, equivalent to 15 mg/kg bw/day (Hiles, 1987c).

Rabbits

Groups of New Zealand white rabbits (5/sex/group) were given 1000, 1500 or 2000 mg penconazole/kg bw/day (purity 91.7%) by dermal application once/day for 5 days/week for 21 days. Two satellite groups received 0 or 2000 mg penconazole/kg bw/day for 21 days followed by a recovery period of 14 days. Transient signs of dyspnea, curved body position and ruffled fur were observed at all dose levels including control rabbits, but symptoms disappeared during the recovery period. No dose-related effects were observed on mortality, body-weight, food consumption and food conversion, haematology, clinical chemistry, macroscopy and histopathology. The NOAEL in this study was \geq 2000 mg/kg bw/day (Seifert *et al.*, 1983).

Dogs

Groups of beagle dogs (10/sex/group) were fed diets containing 0, 100, 500, or 5000/2500 ppm penconazole (purity 91.7%), equal to 3.0, 16.9 or 133 mg penconazole/kg bw/day for males and 3.3, 16.7 or 139 mg penconazole/kg bw/day for females, respectively, for 12 months. Due to poor feed intake the highest dose was lowered to 2500 ppm in week 20. An interim kill on 4 dogs/sex/group was carried out at week 14 and 2 dogs/sex/group were kept for a 4-week recovery period. Observations included clinical signs, mortality, body-weight, food consumption, food conversion, ophthalmoscopy, auditory perception, haematology, blood chemistry, urinalysis, macroscopy, organ weights and histopathology.

An increased incidence of vomiting was observed in high-dose dogs during the first three months of treatment; thereafter occasionally vomiting was observed only in females. The high-dose dogs lost body-weight and had a reduced food consumption during the first months. After lowering the dosage food consumption and male bodyweights were comparable to the controls but the mean weight of the females remained lower than the control value. ASAT, ALP, OCT, GGT and ALAT activities were increased in dogs at the highest dose during the whole administration period. Total globulin concentration was increased in males at the highest dose during weeks 13, 26 and 53, consequently the total protein was slightly increased and the A/G ratio was decreased. Terminal body-weight of high-dose male and female dogs were decreased after 3 months. At this time relative liver weights were increased at 500 and 5000 ppm. Relative kidney weight was increased at the highest dose in both males and females. Relative brain and adrenal weight were increased and relative heart weight was decreased in high-dose females. All males at 5000 ppm showed a reduction in testes weights and atrophy of the seminiferous epithelium. At macroscopy emaciation was observed in dogs at the highest dose after 3 months. At histopathology after 3 months, minimal lesions characterized by monocellular hepatocyte necrosis associated with inflammatory cell infiltration were noticed in nearly all interim sacrificed dogs at the highest dose and in one male dog at 500 ppm. After 12 months, testes weights were reduced in males at 2500 ppm and liver weight was increased in females at 500 and 2500 ppm. At histopathology, bilateral tubular atrophy and reduced spermatogenesis in the testes was observed in the high-dose males and an increased incidence of inflammation with fibrosis in the peripheral lobular region of the liver occurred in the mid- and high-dose animals. The only abnormalities found after the recovery period were decreased relative testes weights and tubular atrophy at 2500 ppm. The NOAEL in this study was 100 ppm, equal to 3.0 mg/kg bw/day for males and 3.3 mg/kg bw/day for females (Gfeller *et al.*, 1984).

Long-term toxicity/carcinogenicity studies

Mice

Groups of Tif:MAGf(SPF) mice (80/sex/group) were fed diets containing 0, 5, 75, 150 or 300 ppm penconazole (purity 91.7%), equal to 0.75, 9.8, 19.3 or 40.8 mg/kg bw/day for males and 0.67, 8.8, 17.2 or 35.7 mg/kg bw/day for females, for 24 months. An interim kill was carried out on 10 mice/sex/group at 52 weeks. No effects were observed on mortality, clinical signs, body-weight, food and water consumption, food conversion, ophthalmic and hearing inspections, haematology, blood chemistry, urinalysis, macroscopy or histopathology. Relative liver weight was increased in high-dose males and females at the interim kill. At the end of the study adrenal weight (not dose-related) and prostate weight were increased in males at 75, 150 and 300 ppm. There was no treatment-related increase in tumour incidence (Basler *et al.*, 1985b). Since weighing of prostate glands is not very reliable and the increased

weight was not found at 53 weeks, the Meeting concluded that this effect was probably biologically insignificant. The NOAEL was therefore 150 ppm, equal to 19.3 mg/kg bw/day for males and 17.2 mg/kg bw/day for females based on the increased liver weight.

Rats

Groups of Tif:RAIf(SPF) rats (80/sex/group) were fed diets containing 0, 5, 75, 150 or 300 ppm penconazole (purity 91.7%) for 24 months. An interim kill was carried out on 10 rats/sex/group at 12 months. Twenty rats/sex/group were maintained for laboratory investigations and sacrificed after 24 months. The remaining 50 rats/sex/group were sacrificed after 116/117 weeks. No effects were observed on mortality, clinical signs, body-weight, food and water consumption, food conversion, ophthalmic and hearing inspections, haematology, blood chemistry, urinalysis, macroscopy or histopathology. At the interim kill, liver weight was increased in females at 150 and 300 ppm and pituitary weight was decreased in high-dose males. A tendency to increased liver weight was still observed in females at the highest dose at 104 weeks. Tumour incidence was not enhanced. The NOAEL in this study was 75 ppm, equal to 3.8 and 4.0 mg/kg bw/day for males and females, respectively (Basler *et al.*, 1985b).

Reproduction studies

Rats

Penconazole (purity 91.7%) was administered in the diet to groups of 20 Tif:RAIf(SPF) rats/sex at concentrations of 0, 80, 400 or 2000 ppm (continuously over a period of 110 days to the parental generations (F_0 and F_1), including a 12-day mating period for each generation at the age of 3 months. These dose levels were equal to 5.5-6.5, 28.5-31 or 146-166 mg/kg bw/day for males and 7.5-8.5, 40-42.5 or 202-227 mg/kg bw/day for females during the whole period. Parental rats were killed after weaning of the F_1 and F_2 generation, respectively. Observations included clinical signs, body-weight, food consumption, fertility index, implantation rate, litter size, live and dead fetuses, sex ratio, organ weight, macroscopy and histopathology.

A slightly depressed body-weight gain and food consumption was seen at the highest dose in F_0 females. Parturition was delayed and the average duration of pregnancy was 21.1, 21.2, 21.3 and 21.6 days for the 0, 80, 400 and 2000 ppm group. Four dams died, two (1 at 400 and 1 at 2000 ppm) at or a short time after parturition, one (at 2000 ppm) after 4 days and one (at 2000 ppm) after 11 days. Testes weights of F_0 males were slightly increased at 2000 ppm (liver weight was not determined).

Body-weight gain of F₁ pups was slightly reduced at 2000 ppm. The activity index (ELP, exploratory locomotion pattern) was slightly but not significantly depressed at 400 and 2000 ppm; there was however no effect on general development and behaviour. At 2000 ppm, relative liver weight was increased in male and female F₁ pups and brain and ovary weight was increased in F₁ female pups. Body-weight gain and food consumption of F₁ parents was slightly reduced at 2000 ppm. One dam died at 400 ppm and 2 at 2000 ppm at or some days after parturation. The average pregnancy duration was increased at the highest dose (21.3, 21.4, 21.2 and 21.8 days at 0, 80, 400 and 2000 ppm, respectively). At 2000 ppm, relative liver weight and relative ovary weight were increased in F₁ parents, while relative brain and testes weight were increased in F₁ males. A decreased implantation rate was observed at 2000 ppm.

The ELP was slightly but not significantly decreased in high-dose F₂ pups without any effect on general development and behaviour. Relative liver weight was increased in high-dose F₂ pups.

Histopathological examination of the livers of F₁ adults revealed slight hypertrophy of the hepatocytes mainly in the centrilobular region in 17/20 males and in 16/16 females at 2000 ppm and in 5/19 males and 14/16 females at 400 ppm. Additionally, small recent necrosis in the liver was observed in 2/16 high-dose females. No histopathological changes were seen in weanling rats from both F₁ and F₂ generations. The NOAEL in this study was 80 ppm, equal to 5.5-6.5 mg/kg bw/day and 7.5-8.5 mg/kg bw/day for males and females, respectively (Fritz *et al.*, 1983a; Fritz *et al.*, 1983b).

Groups of 30 Charles River COBS CD rats/sex were fed diets containing 0, 25, 250 or 2500 ppm penconazole (purity not given). After 63 days of treatment the rats were mated to start a two-generation (1 litter/generation) study. The F₁ parents (randomly selected) were mated after 84 days of treatment. Only weights of ovaries and testes were determined. At 2500 ppm body-weight and food consumption were decreased in F₀ females and body-weight was decreased in F₁ parents. Mating indices were slightly reduced in the F₀ and F₁ generations at 2500 ppm, but fertility indices were not affected. Reduced pup weight and an increase in the number of stillborn pups or pups that died during the first days of lactation was observed at the highest dose. Relative ovary weight was significantly increased in females of the F₀ and the F₁ generation at 2500 ppm. The NOAEL in this study is 250 ppm, equivalent to 12.5 mg/kg bw/day (Schardein, 1987)

Special studies on embryotoxicity and/or teratogenicity

Rats

Groups of 25 pregnant Tif:RAIf(SPF) female rats were administered orally by intubation 0, 30, 100 or 300 mg penconazole (purity 88.4%)/kg bw/day

suspended in CMC from days 6 to 15 of gestation. The dams were observed for clinical signs, body-weight and food consumption and were killed at day 21 of gestation. The number of total implantations, resorptions, live and dead fetuses were recorded and the uterus was weighed. Fetuses were weighed, sexed and examined for external, visceral and skeletal malformations. Two dams at 300 mg/kg bw/day died shortly before autopsy. Maternal bodyweight gain in the highest dose group was slightly reduced. Food consumption was reduced in all experimental groups. An increase in the numbers of unossified phalangeal nuclei of the hind limb was observed at 100 and 300 mg/kg bw/day (not dose-related). At the highest dose, acaudia (taillessness) was observed in 1/182 fetuses, and the overall incidence of skeletal anomalies including irregularly shaped sternebrae was increased at the highest dose. The NOAEL for maternal and embryofetal toxicity was 30 mg/kg bw/day.

In a supplementary study, 0 or 300 mg penconazole/kg bw/day was administered by gavage to groups of 15 pregnant rats from days 6-15 of gestation and another group of 15 rats received 450 mg penconazole/kg bw/day from days 10-14 of gestation. Body-weight gain and food consumption were decreased at both dose levels. Four and 2 females died shortly before autopsy at 300 and 450 mg/kg bw/day, respectively. The average weight of live fetuses was decreased at 300 and 450 mg/kg bw/day. The incidence of unossified phalangeal nuclei of the forelimb was increased at 450 mg/kg bw/day and the incidence of unossified phalangeal nuclei of the hind limbs and calcaneus were increased at both 300 and 450 mg/kg bw/day. No irregular ossification of sternebrae was observed at 300 mg/kg bw/day. At 450 mg/kg bw/day an irregularly ossified sixth sternebrae was recorded in one foetus (Fritz & Giese, 1981). The increased incidence of these variants may indicate delayed fetal development, but in the absence of any associated malformations should not be considered as indicative of teratogenicity.

Groups of 25 pregnant Charles River rats were administered by gavage 0, 5, 100, or 500 mg penconazole (purity 98.7%)/kg bw/day in corn oil from days 6-15 of gestation. The females were observed for clinical signs, body-weight and food consumption and sacrificed on day 20 of gestation. The number of implantation sites, resorption sites, corpora lutea were recorded. Fetuses were weighed, sexed and examined for external, internal and visceral anomalies. Two high-dose dams and 1 dam at 5 mg/kg bw/day died during the study. High-dose dams exhibited damp fur, crusty eye, crusty muzzle, crusty nose, and yellow/brown stained fur as well as staggered gait, emaciated loose stools, weakness and/or lethargy (5/25) and clear salivation (4/25). Body-weight and body-weight gain were significantly decreased at the highest dose. Food consumption was decreased from days 6-13 at 100 and 500 mg/kg bw/day. At the highest dose, the number of early and late resorption sites was increased and the number of viable fetuses as well as the fetal weight were decreased. The number of runts and litters with runts as well as the occurrence of cervical ribs was increased at 500 mg/kg bw/day. No teratogenic effects were observed.

The NOAEL for maternal and embryofetal toxicity in this study was 100 mg/kg bw/day (Salamon, 1985).

Rabbits

Groups of 20 pregnant chinchilla rabbits received 0, 25, 75 or 150 mg penconazole (purity 91.7%)/kg bw/day orally by intubation from day 6 to 18 of pregnancy. Observations included clinical signs, body-weight gain, food consumption. Dams were killed on day 28 of pregnancy and fetuses were removed by caesarean section. No effects were observed on the number of corpora lutea, total implantations, early and late resorptions, live and dead fetuses, sex ratio uterus and fetal weight, external and visceral examination and skeletal malformations.

At 150 mg/kg bw/day average food consumption was slightly reduced and the number of early resorptions was slightly but not significantly increased. At the highest dose, one fetus with microphthalmia and one fetus showing microphthalmia associated with internal hydrocephaly were seen. The NOAEL for maternal toxicity and for embryotoxicity was 75 mg/kg bw/day (Giese & Suter, 1982).

Groups of 20 pregnant New Zealand white rabbits were orally dosed by gavage with 0, 10, 50 or 200 mg penconazole/kg bw/day from days 7 to 19 of gestation. Observation included clinical signs, body-weight and food consumption. All dams were killed on gestation day 29 and fetuses were delivered by caesarean section. During the treatment period decreased defecation and urination were observed in high-dose animals and body-weight and food consumption were decreased. A significant increase in body-weight and mean food consumption was observed from gestation day 20-29. The number of early resorptions was slightly increased and the number of viable fetuses was slightly lower at the highest dose. At 200 mg/kg bw/day, a slightly increased incidence of the number of fetuses with unossified hyoid body and/or arches (marginal at 50 mg/kg bw/day) and of fetuses with reduced ossification of the skull was observed. No teratogenic effects were observed. The NOAEL in this study for maternal and/or embryotoxicity was 50 mg/kg bw/day (Nemec *et al.*, 1985).

Special studies on mutagenicity

A number of genotoxicity tests have been carried out with penconazole. The results are summarized in Table 2.

Table 2. Results of mutagenicity assays on penconazole

Test system	Test object	Concentration of penconazole	Purity (%)	Results	References
<i>In vitro</i> Ames test ^{a,b}	<i>S. typhimurium</i> TA100, TA98 TA1535, TA1537	250-20250 µg/ml in DMSO; ^a > 6750 µg/ml toxic, and ^b 20250 µg/ml toxic	92.8	negative	Armi & Müller (1980)
Ames test ^{a,b}	<i>S. typhimurium</i> TA98, TA100 TA1535, TA1537	100-25600 µg/ml in acetone	91.7	negative ^c	Depratade & Armi (1984)
Yeast test ^{a,b} (mitotic gene conversion)	<i>S. cerevisiae</i> D7	0.1-40 µg/ml in DMSO	91.7	negative	Armi & Müller (1983)
Transformation assay	mouse embryofibro- blasts BALB/3T3	2.625, 5.25, 10.5, 21.0 and 42.0 µg/ml in DMSO	91.7	negative ^c	Beilstein & Müller (1984a)
Mouse lymphoma assay ^{a,b}	L5178Y mouse lymphoma cells (TK + /-)	(-): 6.75-100 µg/ml, 100 µg/ml toxic; (+): 8.25-110 µg/ml, ≥ 110 µg/ml toxic; both in DMSO	91.7	negative ^c	Beilstein & Müller (1984b)
DNA repair test	human fibroblasts	0, 0.32, 1.6 and 40 µg/ml.	91.7	negative ^c	Puri & Müller (1983)
DNA repair test	rat hepatocytes	0, 0.32, 1.6, 8.0, 40 µg/ml	91.7	negative ^c	Puri & Müller (1984)

Table 2 (cont'd)

Test system	Test object	Concentration of penconazole	Purity (%)	Results	References
<i>In vivo</i> Host mediated assay (intra sanguine)	<i>S. typhimurium</i> TA98, TA100 and TA1535 in male NMRI mice	0, 350, 700 and 1400 mg/kg orally	91.7	negative	Arni & Müller (1984)
Host mediated assay	L 5178Y-cells in DBA/Bom/SPF mice	0, 813 mg/kg bw orally	91.7	negative	Strasser & Müller (1982)
Nucleus anomaly test	Chinese hamster bone marrow cells	0, 417, 834 and 1668 mg/kg orally in PEG 400 per day on 2 consecutive days	92.8	negative ^c	Hool & Langauer (1982)
Sister chromatid exchange assay	Chinese hamster bone marrow	0, 417, 834 and 1668 mg/kg orally in PEG 400	91.7	negative ^c	Hool & Arni (1983a)
Chromosome aberration assay	NMRI mice spermatogonia	0, 91, 272 and 816 mg/kg bw orally in PEG 400 per day on 5 consecutive days; at 816 mg/kg all mice died	91.7	negative	Hool & Arni (1983b)
Dominant lethal assay	Male NMRI mice	0, 272 and 816 mg/kg bw orally	91.7%	negative	Hool & Arni (1983c)

^a without metabolic activation^b with metabolic activation^c positive controls yielded positive result(s)

Special studies on skin and eye irritation and skin sensitization

Penconazole (purity 88.4%) produced slight erythema in 3 male and 3 female New Zealand white rabbits when applied under occlusive conditions to the shaven intact and abraded skin for 24 hours, which disappeared within 48 h (Ullmann & Gfeller, 1980b).

Penconazole (0.1 mg) was inserted into the conjunctival sac of the left eye of nine New Zealand white rabbits. At 30 seconds after treatment, the eyes of 3/9 rabbits were washed with physiological saline. In unrinsed eyes slight damage of the cornea and slight conjunctival redness and chemosis were observed up to 7 days after treatment. Rinsed eyes were normal 4 days after exposure. Two rabbits died during the experiment. Bloody exudate in the pleural and abdominal cavities was observed at autopsy (Ullmann & Gfeller, 1980a).

In a similar study, nine New Zealand white albino rabbits were given doses of 100 mg of undiluted penconazole (purity not given) into the conjunctival sac of the left eye. Three of nine eyes were washed. Conjunctival redness, chemosis and discharge was observed in all animals at one hour after application which lasted up to 7 days after treatment. The iris showed swelling but these changes disappeared within 24 h. Corneal opacity and positive fluorescein staining occurred but did not occur in any animal at 48 h (washed eyes) and on day 7 (non-washed eyes) (Kuhn, 1988).

Penconazole (purity 88.4%) was tested for skin sensitization in 10 male and 10 female Pirbright white guinea-pigs in an optimization test. No sensitization was observed when the guinea-pigs received 10 intracutaneous injections (0.1 ml of a 0.1% suspension of penconazole in propylene glycol) followed 14 days later by a single challenge injection (0.1 ml of 0.1% suspension of penconazole in propylene glycol) (Ullmann & Gfeller, 1980c).

COMMENTS

Penconazole administered orally to mice and rats was rapidly absorbed and excreted, predominantly in the urine. Female rats eliminated more in the urine and less in the faeces than male rats. Very low residues were found in organs and tissues in both males and females.

Numerous metabolites were identified in urine and faeces. The major metabolic pathways involved oxidation of the pentyl side chain to alcohols and acids with sequential cleavage of the terminal carbon. As the oxidation products were conjugated, the resulting metabolic patterns were complex. More polar and conjugated products were found in female rats. Cleavage of the alkyl

bridge between the two rings led to the formation of 1,2,4-triazole, which was a major metabolic route in male rats.

Penconazole showed low acute oral toxicity to mice, rats and hamsters, but was slightly more toxic to rabbits. The World Health Organization has classified penconazole as unlikely to present acute hazard in normal use (WHO, 1992).

Short-term studies with mice, rats and dogs indicated that the liver was the primary target organ. In a special study with male rats, induction of microsomal liver enzymes was demonstrated. In a 13-week study in mice, increased liver weight and liver hypertrophy were observed at 500, 1000 and 2400 ppm. The NOAEL was 300 ppm, equivalent to 45 mg/kg bw/day.

In three 90-day studies performed with rats, liver weight and liver histopathology were the main effects, except for the second study. In the first study, increase in relative liver weight was observed at all dietary levels (30, 300 or 3000 ppm), while in the third study (dietary levels of 10, 100, 300, 500, 1000 or 2400 ppm) the NOAEL was 300 ppm, equivalent to 15 mg/kg bw/day. In the second study (dietary levels of 10, 30 or 100) some biochemical parameters were affected at 30 and 100 ppm. The NOAEL was 10 ppm, equal to 0.8 mg/kg bw/day.

In a one-year study in dogs, increased liver weights and histopathological liver effects were observed at dietary concentrations of 500 and 2500/5000 ppm. At the highest dose level reduced testis weight and atrophic changes were also observed. The NOAEL was 100 ppm, equal to 3.0 and 3.3 mg/kg bw/day for males and females, respectively.

In a two-year feeding study in mice (dietary concentrations of 0, 5, 75, 150 or 300 ppm) increased liver weight at interim kill was seen at 300 ppm. The NOAEL in this study was 150 ppm, equal to 19.3 mg/kg bw/day for males and 17.2 mg/kg bw/day for females. In a long-term study in rats (dietary concentrations of 0, 5, 75, 150 or 300 ppm) liver weight was increased at 150 and 300 ppm. The NOAEL was 75 ppm, equal to 3.8 and 4.0 mg/kg bw/day for males and females, respectively. Penconazole was not carcinogenic in mice or rats.

Two two-generation reproduction studies in rats were reviewed. In the first study (dietary concentrations of 0, 80, 400 or 2000 ppm), mortality and delayed parturition were observed, as well as decreased body-weight gain of parents and pups and increased relative liver weights in parents and pups at 2000 ppm. Hypertrophy of liver cells was found at 400 and 2000 ppm. The NOAEL was 80 ppm, equal to 5.5-6.5 mg/kg bw/day for males and 7.5-8.5 mg/kg bw/day for females. In the second study (dietary concentrations of 0, 25, 250 or 2500 ppm), liver weights were not determined. The main effect at 2500

ppm was reduced body-weight gain of parents and pups and mortality of pups during lactation. The NOAEL was 250 ppm, equivalent to 12.5 mg/kg bw/day.

Embryotoxicity/fetotoxicity was observed in three teratogenicity studies with rats. In two studies (gavage doses of 0, 30, 100 or 300 mg/kg bw/day in one study and 0, 300 or 450 mg/kg bw/day in the other), maternal toxicity, an increased number of resorptions, decreased pup weight and delayed ossification were observed at the high doses. Maternal toxicity or embryotoxicity were not observed at 30 mg/kg bw/day. In the third study (gavage doses of 0, 5, 100 or 500 mg/kg bw/day), the NOAEL was 100 mg/kg bw/day. In two teratogenicity studies with rabbits (doses of 0, 25, 75 or 150 mg/kg bw/day in one study and 0, 10, 50 or 200 mg/kg bw/day in the other), maternal body-weight and food consumption were reduced and the number of early resorptions was increased at the highest doses. Overall, the NOAEL was 75 mg/kg bw/day for both maternal toxicity and embryotoxicity.

After reviewing the available *in vitro* and *in vivo* short-term genotoxicity data, the Meeting concluded that penconazole was not genotoxic.

An ADI was allocated on the basis of the NOAEL determined from the one-year study in dogs, which was supported by the NOAEL from the long-term study in rats. A safety factor of 100 was applied.

TOXICOLOGICAL EVALUATION

Level causing no toxicological effect

Mouse:	150 ppm, equal to 17 mg/kg bw/day (two-year study)
Rat:	75 ppm, equal to 3.8 mg/kg bw/day (two-year study)
	80 ppm, equal to 5.5 mg/kg bw/day (two-generation reproduction study)
	30 mg/kg bw/day (teratology study)
Rabbit:	75 mg/kg bw/day (teratology study)
Dog:	100 ppm, equal to 3 mg/kg bw/day (one-year study)

Estimate of acceptable daily intake for humans

0-0.03 mg/kg bw.

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

Observations in humans.

REFERENCES

Arni, P. & Müller, D. (1980) *Salmonella*/mammalian-microsome mutagenicity test with CGA 71818 (test for mutagenic properties in bacteria). Unpublished report experiment No. 800550 dated 29 September 1980 from Ciba-Geigy Protection of Health and Environment, Toxicology, Basle, Switzerland. Submitted to WHO by Ciba-Geigy Ltd., Basle, Switzerland.

Arni, P. & Müller, D. (1983) *Saccharomyces cerevisiae* D7/mammalian-microsome mutagenicity test *in vitro* with CGA 71818. Unpublished report experiment No. 811560 dated 27 June 1983 from Ciba Geigy, Protection of Health and Environment, Toxicology, Basle, Switzerland. Submitted to WHO by Ciba-Geigy Ltd., Basle, Switzerland.

Arni, P. & Müller, D. (1984) Intravascular host-mediated assay with *S. typhimurium*. Unpublished report experiment No. 830749 dated 3 May 1984 from Ciba Geigy, Protection of Health and Environment, GU 2.3, Experimental Pathology, Basle, Switzerland. Submitted to WHO by Ciba-Geigy Ltd., Basle, Switzerland.

Basler, W., Gfeller, W., Zak, F., Zakova, N. & Grieve, A.P. (1982) CGA 71818: 3 months toxicity study in rats. Unpublished final report, GU project No. 801194 dated 24 February 1982 from Ciba-Geigy Basle, Switzerland. Submitted to WHO by Ciba-Geigy Ltd., Basle, Switzerland.

Basler, W., Komarek, J., Zak, F. & Beri, J. (1983) CGA 71818: 3 month toxicity study in rats. Unpublished final report GU project No. 821054 dated 17 August 1983 from Ciba-Geigy Basle, Switzerland. Submitted to WHO by Ciba-Geigy Ltd. Basle, Switzerland.

Basler, W., Komarek, J., Zak, F. & Skorpil, V. (1984) CGA 71818: 28-day oral cumulative toxicity study in rats. Unpublished final report, GU project No. 820822 dated 28 June 1984 from Ciba-Geigy, Basle, Switzerland. Submitted to WHO by Ciba-Geigy Ltd., Basle, Switzerland.

Basler, W., Gretener, P., Zak, F. & Krinke, G. (1985a) CGA 71818: Lifetime carcinogenicity and chronic toxicity study in mice. Unpublished final report GU project No. 811414 dated 1 July 1985 from Ciba-Geigy, Basle, Switzerland. Submitted to WHO by Ciba-Geigy Ltd., Basle, Switzerland.

Basler, W., Gretener, P., Zak, F. & Naylor, D.C. (1985b) CGA 71818: Lifetime carcinogenicity and chronic toxicity study in rats. Unpublished final draft GU project no.: 811415 d.d. 25 June 1985 from Ciba-Geigy, Basle, Switzerland. Submitted to WHO by Ciba-Geigy Ltd., Basle, Switzerland.

Bathe, R. & Gfeller, W. (1980a) Acute oral LD₅₀ in the rat of technical CGA 71818. Unpublished report project No. 800553 dated 28 May 1980 from Ciba-Geigy, Basle, Switzerland. Submitted to WHO by Ciba-Geigy Ltd., Basle, Switzerland.

Bathe, R. & Gfeller, W. (1980b) Acute dermal LD₅₀ in the rat of technical CGA 71818. Unpublished report project No. 800559 dated 19 March 1980 from Ciba-Geigy, Basle, Switzerland. Submitted to WHO by Ciba-Geigy Ltd., Basle, Switzerland.

Bathe, R. & Gfeller, W. (1980c) Acute oral LD₅₀ in the Chinese hamster of technical CGA 71818. Unpublished report project No. 800555 dated 19 March 1980 from Ciba-Geigy, Basle, Switzerland. Submitted to WHO by Ciba-Geigy Ltd., Basle, Switzerland.

Beilstein, P. & Müller, D. (1984a) BALB/3T3 cell transformation assay with CGA 71818. Unpublished report test No. 830755 dated 6 September 1984 from Ciba-Geigy, Protection of Health and Environment, Basle, Switzerland. Submitted to WHO by Ciba-Geigy Ltd., Basle, Switzerland.

Beilstein, P. & Müller, D. (1984b) L5178Y/TK⁺ mouse lymphoma mutagenicity test. CGA 71818 tech. (*in vitro* test for mutagenic properties of chemical substances in mammalian cells). Proj. No.: 811524. Unpublished report dated 9 October 1984 from Ciba-Geigy Ltd., Basle, Switzerland. Submitted to WHO by Ciba-Geigy Ltd., Basle, Switzerland.

Deperade, E. & Arni, P. (1984) *Salmonella*/mammalian-microsome mutagenicity test. Unpublished report project No. 839759 dated 20 February 1984 from Ciba-Geigy Protection of Health and Environment, Basle, Switzerland. Submitted to WHO by Ciba-Geigy Ltd., Basle, Switzerland.

Fritz, H. & Giese, K. (1981) Report on CGA 71818 tech. teratology study (seg.II) in rats. Unpublished report test No. 800549 d.d. 25 August 1981 from Ciba-Geigy, Reproductive Toxicology, Basle, Switzerland. Submitted to WHO by Ciba-Geigy Ltd., Basle, Switzerland.

Fritz, H., Suter, H.P., Zak, F. & Skorpil, V. (1983a) Report on CGA 71818 technical. 2-generation toxicity study in rats. Unpublished report test No. 811416 from Ciba-Geigy, Toxicology GU 2, Switzerland. Submitted to WHO by Ciba-Geigy Ltd., Basle, Switzerland.

Fritz, H., Suter, H.P., Zak, F. & Skorpil, V. (1983b) Two-generation reproduction study in rats with CGA 71818 technical. Additional data submission. Unpublished report test No. 811416 from Ciba-Geigy, Experimental Toxicology, Sisseln, Switzerland. Submitted to WHO by Ciba-Geigy Ltd., Basle, Switzerland.

Gfeller, W., Zak, F. & Naylor, D.C. (1984) CGA 71818 12 month toxicity study in dogs. Unpublished final report GU project No. 801187 dated February 1984 from Ciba-Geigy, GU2 Toxicology, Basle, Switzerland. Submitted to WHO by Ciba-Geigy Ltd., Basle, Switzerland.

Giese, K. & Suter, H.P. (1982) Report on CGA 71818 tech. Teratology study in rabbits. Unpublished report test No. 811354 dated March 1982 from Ciba-Geigy Reproductive Toxicology GU 2.1, Sisseln, Switzerland. Submitted to WHO by Ciba-Geigy Ltd., Basle, Switzerland.

Hamböck, H. (1980) Distribution, degradation and excretion of CGA 71818 in the rat. Unpublished project report 41/80 dated 6 November 1982 from Ciba-Geigy AG 2.52, Basle, Switzerland. Submitted to WHO by Ciba-Geigy Ltd., Basle, Switzerland.

Hamböck, H. (1982) The major urinary metabolites of CGA 71818 in the rat. Unpublished project (status) report 15/82 dated 17 May 1982 from Ciba-Geigy AG 2.52, Basle, Switzerland. Submitted to WHO by Ciba-Geigy Ltd., Basle, Switzerland.

Hamböck, H. (1984) The metabolic fate of CGA 71818 in the rat. Unpublished project report 23/83 dated 10 May 1984 from Ciba-Geigy, AG 2.52, Basle, Switzerland. Submitted to WHO by Ciba-Geigy Ltd., Basle, Switzerland.

Hamböck, H. (1985) Sex dependency of the metabolite pattern of CGA 71818 after oral administration to rats. Addendum to project report 41/80. Unpublished report 1/85 dated 11 January 1985 from Ciba-Geigy AG 2.52 Basle, Switzerland. Submitted to WHO by Ciba-Geigy Ltd., Basle, Switzerland.

Hartmann, H.R. & Gfeller, W. (1987) CGA 71818 tech. Acute aerosol inhalation toxicity in the rat. Unpublished final report GU project No. 871169 d.d. 6 August 1987 from Ciba-Geigy Ltd, GU 2 Toxicology, Basle, Switzerland. Submitted to WHO by Ciba-Geigy Ltd., Basle, Switzerland.

Hiles, R.A. (1987a) CGA 71818 technical. Kinetic study in albino rats with CGA 71818 technical. Unpublished report HLA 6117-122 dated 24-2-1987 from Hazleton Laboratories America, Inc. Madison, Wisconsin 53704. Submitted to WHO by Ciba-Geigy Ltd., Basle, Switzerland.

Hiles, R.A. (1987b) 90-Day subchronic dietary toxicity and kinetic study in albino mice with CGA-71818 technical. Unpublished report HLA 6117-121 dated 4-3-1987 from Hazleton Laboratories America, Inc. Madison, Wisconsin 53704. Submitted to WHO by Ciba-Geigy Ltd., Basle, Switzerland.

Hiles, R.A. (1987c) 90-Day subchronic dietary toxicity and kinetic study in albino rats with CGA-71818 technical. Unpublished report HLA 6117-120 dated 14-04-1987 from Hazleton Laboratories America, Inc. Madison, Wisconsin 53704. Submitted to WHO by Ciba-Geigy Ltd., Basle, Switzerland.

Hool, G. & Arni, P. (1983a) Sister chromatid exchange study CGA 71818 Chinese hamster. Unpublished report dated 2-06-1983 project No. 811523 from Ciba-Geigy Ltd, Protection of Health and Environment, Toxicology, Basle, Switzerland. Submitted to WHO by Ciba-Geigy Ltd., Basle, Switzerland.

Hool, G. & Arni, P. (1983b) Chromosome studies in male germinal epithelium CGA 71818 mouse. Unpublished report dated 17-06-1983 project No. 811520 from Ciba-Geigy Ltd, Protection of Health and Environment, Toxicology, Basle, Switzerland. Submitted to WHO by Ciba-Geigy Ltd., Basle, Switzerland.

Hool, G. & Arni, P. (1983c) Dominant lethal test, mouse 8 weeks CGA 71818. Unpublished report dated 2-12-1983 project No. 811519 from Ciba-Geigy Ltd., Protection of Health and Environment, Experimental Pathology, Basle, Switzerland. Submitted to WHO by Ciba-Geigy Ltd., Basle, Switzerland.

Hool, G. & Langauer, M. (1982) Nucleus anomaly test in somatic interphase nuclei. CGA 71818 Chinese hamster. Unpublished report dated 20-1-1982 experiment No. 800551 from Ciba-Geigy Ltd, Protection of Health and Environment, Toxicology, Basle, Switzerland. Submitted to WHO by Ciba-Geigy Ltd., Basle, Switzerland.

Kobel, W. (1981) Acute oral LD₅₀ in the rabbit of technical CGA 71818. Unpublished report dated 4-3-1981, project No. 800554 from Ciba-Geigy Ltd., Exp. Toxicology Sisseln, Switzerland, Submitted to WHO by Ciba-Geigy Ltd., Basle, Switzerland.

Kuhn, J.O. (1988) Primary eye irritation study in rabbits EPA guidelines No. 81-4. Unpublished report dated 31-03-1988 project no.: 5303-88 from Stillmeadow Inc. Houston, Texas, USA. Submitted to WHO by Ciba-Geigy Ltd., Basle, Switzerland.

LeVan, L.W. (1987) Acute kinetic study with CGA-71818 technical in albino rats. Unpublished report dated 2-03-1987 project No. HLA 6117-123 from Hazleton Laboratories America Inc. Madison, Wisconsin, USA. Submitted to WHO by Ciba-Geigy Ltd., Basle, Switzerland.

Murphy, R.T. & Capps, T.M. (1988a) CGA-71818 Metabolism in hens - a summary. Unpublished report No. ABR-88009 dated 20-05-1988 from Ciba-Geigy Corp. Greensboro, NC, USA. Submitted to WHO by Ciba-Geigy Ltd., Basle, Switzerland.

Murphy, R.T. & Capps, T.M. (1988b) CGA-71818 Metabolism in goats - a summary. Unpublished report No. ABR-88008 d.d.20-05-1988 from Ciba-Geigy Corp. Greensboro, NC, USA. Submitted to WHO by Ciba-Geigy Ltd., Basle, Switzerland.

Nemec, M.D. & Keets, S.A., Leist, P.L. & Mercieca, M.D. (1985) A teratology study (segment II) in albino rabbits with CGA-71818 technical. Unpublished report No. WIL-82004 dated 31-07-1985 from WIL Research Laboratories Inc., Ashland, Ohio, USA. Submitted to WHO by Ciba-Geigy Ltd., Basle, Switzerland.

Puri, E. & Müller, D. (1983) Autoradiographic DNA repair test on human fibroblast CGA 71818 . Unpublished report dated 2-12-1983 project No. 811657 from Ciba-Geigy Ltd., Protection of Health and Environment, Toxicology, Basle, Switzerland. Submitted to WHO by Ciba-Geigy Ltd., Basle, Switzerland.

Puri, E. & Muller, D. (1984) Autoradiographic DNA repair test on rat hepatocytes. CGA 71'818 (*in vitro* test for DNA-damaging properties). Proj. No.: 811522. Unpublished report dated 30 January 1984 from Ciba-Geigy Ltd., Basle, Switzerland. Submitted to WHO by Ciba-Geigy Ltd., Basle, Switzerland.

Salamon, C.M. (1985) CGA-71818 technical teratology study in rats. Unpublished report No. 450-2087 dated 16-09-1985 from American Biogenics Corp., Decatur, Illinois, USA. Submitted to WHO by Ciba-Geigy Ltd., Basle, Switzerland.

Sarasin, G. (1980) Report on acute oral LD₅₀ in the mouse of CGA 71818 technical. Unpublished report No. 800552 dated 20-10-1980 from Ciba-Geigy Ltd., Basle, Switzerland. Submitted to WHO by Ciba-Geigy Ltd., Basle, Switzerland.

Schardein, J.L. (1987) Two-generation reproduction study in albino rats with CGA 71818. Unpublished report No. 382-119 dated 14-08-1987 from International Research and Development Corp., Mattawan, Michigan, USA. Submitted to WHO by Ciba-Geigy Ltd., Basle, Switzerland.

Seiffert, G., Komarek, J., Zak, F., Malik, C. & Zakova, N. (1983) CGA 71818 21 day repeated dose dermal toxicity study in rabbits. Unpublished report dated September 1983, project No. 820206 from Ciba-Geigy Ltd., Basle, Switzerland. Submitted to WHO by Ciba-Geigy Ltd., Basle, Switzerland.

Strasser, F.F. & Müller, D. (1982) Point mutation assay with mouse lymphoma cells. Host-mediated assay with CGA 71818. Unpublished report project No. 811355 dated 5-01-1982 from Ciba-Geigy Ltd., Basle, Switzerland. Submitted to WHO by Ciba-Geigy Ltd., Basle, Switzerland.

Ullmann, L. & Gfeller, W. (1980a) Report on eye irritation in the rabbit after single application of technical CGA 71818. Unpublished report project No. 800557 dated 28-05-1980 from Ciba-Geigy Ltd., Basle, Switzerland. Submitted to WHO by Ciba-Geigy Ltd., Basle, Switzerland.

Ullmann, L. & Gfeller, W. (1980b) Report on skin irritation in the rabbit after single application of technical CGA 71818. Unpublished report project No. 800558 dated 28-05-1980 from Ciba-Geigy Ltd., Basle, Switzerland. Submitted to WHO by Ciba-Geigy Ltd., Basle, Switzerland.

Ullmann, L. & Gfeller, W. (1980c) Report on skin sensitizing (contact allergenic) effect in guinea-pigs of technical CGA 71818. Unpublished report project No. 800560 dated 12-06-1980 from Ciba-Geigy Ltd., Basle, Switzerland. Submitted to WHO by Ciba-Geigy Ltd., Basle, Switzerland.

Van Dijk, A. (1987) ($U-^{14}C$) phenyl CGA 71818: Absorption, distribution, excretion and metabolism after single oral and repeated oral administration to the rat. Unpublished report project No. 075666 dated 11-06-1987 from RCC Umweltchemie AG, Itingen, Switzerland. Submitted to WHO by Ciba-Geigy Ltd., Basle, Switzerland.

Waechter, F., Bentley, P. & Stäubli, W. (1985) The effect of penconazole on drug metabolizing enzymes in the livers of male rats and mice. Unpublished report dated April 1985 from Ciba-Geigy Ltd., Basle, Switzerland. Submitted to WHO by Ciba-Geigy Ltd., Basle, Switzerland.

WHO (1992). The WHO recommended classification of pesticides by hazard and guidelines to classification 1992-1993 (WHO/PCS/92.14). Available from the International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland.

