

On the fat basis, the Meeting estimated a maximum residue level of 0.2 mg/kg for poultry meat (fat), an STMR value of 0.05 mg/kg and an HR value of 0.13 mg/kg. Based on the liver results, the Meeting estimated a maximum residue level of 0.2 mg/kg for poultry edible offal, an STMR value of 0.02 mg/kg and an HR value of 0.09 mg/kg. The Meeting estimated a maximum residue level of 0.1 mg/kg for eggs, an STMR value of 0.02 and HR value of 0.07 mg/kg.

The Meeting agreed to withdraw its previous recommendations of maximum residue levels of 0.01* mg/kg for cattle fat, cattle meat, cattle milk, chicken meat, chicken eggs, and chicken edible offal; and 0.02* mg/kg for cattle edible offal.

DIETARY RISK ASSESSMENT

Long-term intake

The International Estimated Daily Intakes (IEDIs) of flusilazole based on STMR and STMR-P values estimated for 22 commodities for the thirteen GEMS/Food regional diets were 2–10% of the maximum ADI (0.007 mg/kg bw). The results are shown in Annex 3 of the Report. The Meeting concluded that the long-term dietary intake of flusilazole residues is unlikely to present a public health concern.

Short-term intake

The International Estimated Short Term Intake (IESTI) of flusilazole calculated on the basis of the recommendations made by the JMPR represented for the general population 0–40% and for children 0–100% of the ARfD (0.02 mg/kg bw). The results are shown in Annex 4 of the Report. The Meeting concluded that the short-term intake of residues of flusilazole resulting from uses that have been considered by the JMPR is unlikely to present a public health concern.

5.15 FOLPET (041)

TOXICOLOGY

Evaluation for an acute reference dose

Folpet, the ISO approved name for *N*-(trichloromethylthio)phthalimide, is registered for the control of fungal diseases in crops (CAS No. 133-07-3). The toxicology of folpet was evaluated by the JMPR in 1969 and 1995 and addenda to the monograph were prepared in 1973, 1984, 1986, 1990 and 2004. In 1995, an ADI of 0–0.1 mg/kg bw was established based on a NOAEL of 10 mg/kg bw per day in a 2-year study of toxicity and carcinogenicity in rats, a 1-year study of toxicity in dogs, and studies of reproductive toxicity in rats and rabbits, and using a safety factor of 100. In 2004, the Meeting established an ARfD for folpet of 0.2 mg/kg bw for women of childbearing age only, based on a NOAEL of 20 mg/kg bw per day for increased incidences of hydrocephalus at 60 mg/kg bw per day in rabbits and using a safety factor of 100.

The Meeting concluded that the database was insufficient (particularly with regard to information about the possible developmental effects of the metabolite phthalimide) to establish the mode of action by which the increased incidence of hydrocephalus was induced.

The sponsor conducted a study of developmental toxicity with phthalimide, and studies to evaluate the potential effects of folpet and phthalimide on the intestinal flora of the rabbit. It is known that the rabbit is dependent on the presence of caecotrophs for adequate nutrition. The sponsor suggested that disruption of the intestinal flora might result in maternal malnutrition, with possible consequent adverse effects on foetal development.

At the request of the CCPR at its 39th Session,³⁷ the present Meeting reconsidered the ARfD for folpet on the basis of new data.

All pivotal studies with folpet and phthalimide were certified as being compliant with GLP.

Toxicological data

Data evaluated by JMPR 2004

With respect to the kinetics and metabolism of folpet, the following description is quoted from JMPR 2004:

In rodents treated orally, folpet is rapidly degraded to phthalimide and thiophosgene (via thiocarbonyl chloride). Studies of metabolism in vitro with human blood revealed that folpet is rapidly degraded to phthalimide, with a calculated half-life of 4.9 s. Thiophosgene is rapidly detoxified by reaction with cysteine or glutathione, for example, and is ultimately rapidly excreted.

With respect to the developmental toxicity of folpet the following description is quoted from JMPR 2004:

In a study from the published literature, the teratogenic effects of a number of phthalimide derivatives, including folpet, were tested in pregnant golden hamsters. The Meeting noted that this study has major limitations (e.g., small number of animals per dose, limited reporting of the data) and is therefore of limited value. It does, however, suggest that developmental effects may occur after a single exposure to folpet, albeit at maternally toxic doses.

Folpet has been tested in a number of studies of developmental toxicity in rats. In two out of three studies, no foetal developmental anomalies were found at doses of up to 800 mg/kg bw per day. In one study, however, a possible slight increase in developmental anomalies was reported at 150 mg/kg bw per day.

Folpet has been tested in a number of studies of developmental toxicity in rabbits treated by gavage. In a study in which New Zealand white rabbits were given folpet at a dose of 0, 10, 20, or 60 mg/kg bw per day on days 6–28 of gestation, the NOAEL for maternal toxicity was 10 mg/kg bw per day on the basis of reduced body-weight gain and food consumption. The NOAEL for foetal toxicity was 10 mg/kg bw per day on the basis of reduced foetal body weights. The maternal toxicity and the associated reduction in foetal body weight are likely to be caused by high local concentrations of folpet and are not considered to be relevant to dietary exposure. At 60 mg/kg bw per day, there was a significant increase in the incidence of hydrocephaly in four foetuses out of three litters. In these same foetuses, skull, gastric, and pulmonary abnormalities were also observed. As the observation of hydrocephaly and cleft palate in one foetus at the intermediate dose was considered to be within the historical control range, the NOAEL for these effects was 20 mg/kg bw per day.

In a second study, HY/CR New Zealand white rabbits were given folpet at a dose of 0, 10, 40, or 160 mg/kg bw per day on days 7–19 of gestation. The NOAEL for maternal toxicity was 10 mg/kg bw per day on the basis of reductions in body-weight gain and in gravid uterine weight. The NOAEL for foetal toxicity was 10 mg/kg bw per day on the basis of an increased incidence of bilateral lumbar ribs and delayed skeletal maturation.

In a pulse-dose study, pregnant D1A *Hra*: (New Zealand white) rabbits were given folpet at a dose of 60 mg/kg bw per day by gavage on days 7–9, 10–12, 13–15, or 16–18 of gestation. There were occasional occurrences of abortion, but it was not clear whether these abortions were related to treatment with folpet. Maternal body weight and food consumption were significantly reduced in all treated animals. Two foetuses with hydrocephalus were observed, one in the group treated on days 10–12 of gestation and one in the group treated on days 16–18 of gestation. These incidences were considered to be within the historical control range. A significantly increased incidence (12.1%) of foetuses with an irregularly shaped fontanelle was observed in the group treated on days 13–15 of gestation; the incidence in controls was 4.5%. The significance of these effects was not clear.

The results of studies considered by the Meeting in 2004 suggested that folpet was rapidly degraded to phthalimide. The other component of the parent molecule, thiophosgene, is rapidly

³⁷Codex Alimentarius Commission. *Report of the 39th Session of the Codex Committee on Pesticide Residues, 7–12 May 2007, Beijing, China* (ALINORM07/30/24).

detoxified by reaction with cysteine or glutathione, for example, and is ultimately rapidly excreted. During the present Meeting, the sponsor provided a toxicokinetic study in rats, not previously evaluated by JMPR.

Toxicokinetics

In a toxicokinetic study in rats, concentrations of folpet and its metabolites were measured in the faeces and urine. The study was evaluated by the present Meeting, focusing on concentrations of folpet in order to establish the amount of folpet that reaches the distal parts of the gastrointestinal tract.

Rats were given [¹⁴C] labelled folpet at a dose of 10 or 500 mg/kg bw by gavage. Extracts of urine were qualitatively analysed by high-performance liquid chromatography (HPLC) and GC/MS. Phthalamic acid was found only in the urine. Extracts of faeces were qualitatively analysed by TLC by comparison with reference compounds. Quantification of faecal metabolites was performed by linear plate scanner and autoradiography. Several compounds were identified in faeces, including phthalimide, phthalamic acid, phthalic anhydride and parent folpet. Toxicokinetic data are presented in Table 11.

Table 11. Toxicokinetic data for rats given [¹⁴C] labelled folpet by gavage

Dose	Radioactivity excreted, males/females (% of administered dose)		Folpet in urine (% of radioactivity)	Folpet in faeces	
	Urine	Faeces		% of radiolabel (males/females)	% of total dose
10 mg/kg bw, single dose	91.7/92.7	6.4/5.1	ND	15/27	0.5–1.5
10 mg/kg bw, repeated doses	88.3/84.0	7.6/7.8	ND	18/17	1.3–1.4
500 mg/kg bw	56.5/60.5	41.3/39.6	ND	93/92	36.8–38.4

ND, not detected.

After a single dose at 10 mg/kg bw, about 92% and 6% of the radiolabel administered was recovered from the urine and faeces, respectively. At this single dose, no folpet was detected in the urine. Of the radiolabel recovered from the faeces, 0.5–1.5% was associated with folpet. After 14 consecutive doses at 10 mg/kg bw per day, the proportions of folpet in faeces were similar to those found after a single dose at 10 mg/kg bw; folpet was not detected in the urine. At 500 mg/kg bw, 56–60% and 39–41% of the radiolabel administered was recovered from the urine and faeces, respectively. No folpet was detected in the urine. Of the radiolabel recovered from the faeces, 36.8–38.4% was identified as folpet.³⁸

Developmental toxicity

In a study of developmental toxicity, groups of 25 time-mated female New Zealand White rabbits received daily administrations of phthalimide (purity, 100%) at a dose of 0, 5, 15 or 30 mg/kg bw per day by gavage from days 6 to 28 after mating. The vehicle was water containing 0.5% w/v Tween 80 and 0.7% w/v carboxymethylcellulose. In view of the relative molecular masses of folpet (296.6) and phthalimide (147.1), the dose of phthalimide of 30 mg/kg bw per day would be equimolar to a dose of folpet of about 60 mg/kg bw per day. All animals were examined twice per day for clinical signs. Body weight was recorded daily from the day of mating until day 29 of gestation, when they were

³⁸ Wood, S.G., Chasseaud, L.F., Cheng, K., Hall, M., Fitzpatrick, K., Iqbal, S., Barlett, A. (1991) Metabolic fate of ¹⁴C-folpet in Sprague-Dawley rats. Unpublished report No HRC/MBS 41/91499 from Huntingdon Life Sciences Limited, Woolley Road, Alconbury, Huntingdon, Cambridgeshire. Submitted to WHO by Makhteshim Chemical Works, Beer-Sheva, Israel.

killed. Food intake was recorded daily from the first day after mating until day 29 of gestation. On day 29, the animals were killed and examined macroscopically. In females in the control group and in the group receiving the highest dose, the duodenum and sphincter of Oddi (hepatopancreatic sphincter) were examined microscopically. The ovaries and uterus were removed and the foetuses were weighed and examined for visceral and skeletal abnormalities.

There were no mortalities. At necropsy, in the control group, and the groups at 5 and 15 mg/kg bw per day, three, five and two females, respectively, did not appear to be pregnant. One female in the control group aborted on day 21 and one female in the group at 15 mg/kg bw per day appeared to have total litter resorption. In the dams, no treatment-related clinical signs or effects on body weight and food consumption, and no macroscopic or microscopic abnormalities were observed. Increases in implantation losses were observed in the treated groups (19.3%, 24.0%, 26.8% and 36.0% in the control group and the groups receiving the lowest, intermediate and highest dose, respectively), reaching statistical significance for pre-implantation loss in the group receiving the highest dose. Since implantation in rabbits occurs at around days 7–8 after mating, the effects on pre-implantation loss may have been treatment-related. Increases in pre-implantation losses were observed in the treated groups (13.4%, 16.9%, 19.5% and 25.7% in the control group and in the groups receiving the lowest, intermediate and highest dose, respectively), reaching statistical significance in the group receiving the highest dose. In the group at the highest dose, reductions in the mean number of implantations and number of live foetuses were considered to be the result of increased implantation loss. The slightly lower mean litter weights and slightly increased foetal weights in the group at the highest dose were considered to reflect the decreased number of implantations in this group. In the foetuses, no treatment-related effects on visceral and skeletal parameters were observed.

The NOAEL for maternal toxicity was 30 mg/kg bw per day i.e., the highest dose tested. The NOAEL for embryo/fetotoxicity was 15 mg/kg bw per day on the basis of increased pre-implantation loss at the highest dose.³⁹

Inhibition of microbial activity in vitro

A study was performed to determine minimum inhibitory concentrations (MIC) of folpet (purity, 95.8%) against two bacterial species (*Bacteroides* sp. and *Enterococcus faecalis*) and one species of yeast (*Candida albicans*). These bacteria were considered to be representative of anaerobic bacteria in the rabbit gut. *Candida albicans* was considered to be representative of yeast that may occur in the rabbit gut. The MIC values for *Bacteroides* sp., *Enterococcus faecalis* and *Candida albicans* were 20–50, 50–200 and 5 µg/mL, respectively. The Meeting concluded that folpet demonstrates antimicrobial activity against organisms considered representative of rabbit gut flora.⁴⁰

In a study to determine MIC of phthalimide (purity, 100%), the MIC values for *Bacteroides* sp., *Enterococcus faecalis* and *Candida albicans* were all > 1000 µg/mL, except for one strain of *C. albicans* strain for which the MIC value was 1000 µg/mL. The Meeting concluded that phthalimide demonstrates no significant antimicrobial activity against organisms considered representative of rabbit gut flora.⁴¹

The Meeting concluded that the existing database, i.e., the new studies conducted after 2004 and the previously evaluated studies, was adequate to characterize the potential hazards of folpet to foetuses, infants and children.

³⁹ Blee, M.A.B. (2006) Tetrahydrophthalimide. Prenatal toxicity study in the rabbit by oral gavage administration. Unpublished report No R-18202, MAK 864/053232 from Huntingdon Life Sciences Limited, Woolley Road, Alconbury, Huntingdon, Cambridgeshire. Submitted to WHO by Makhteshim Chemical Works, Beer-Sheva, Israel.

⁴⁰ Akhurst, L.C (2005a) Captan: determination of minimum inhibitory concentration against selected micro-organisms representative of rabbit gut microflora. Unpublished report No. R-18666, MAK 0888/052848 from Huntingdon Life Sciences Ltd, Huntingdon, Cambridgeshire, England. Submitted to WHO by Makhteshim Chemical Works, Beer-Sheva, Israel.

⁴¹ Akhurst, L.C (2005b) THPI: determination of minimum inhibitory concentration against selected micro-organisms representative of rabbit gut microflora. Unpublished report No. R-18735, MAK 0890/053252 from Huntingdon Life Sciences Limited, Huntingdon, Cambridgeshire, England. Submitted to WHO by Makhteshim Chemical Works, Beer-Sheva, Israel.

Toxicological evaluation

In 2004 JMPR established an ARfD of 0.2 mg/kg bw for women of childbearing age only based on a NOAEL of 20 mg/kg bw per day identified on the basis of an increased incidence of hydrocephalus at 60 mg/kg bw per day in the study in rabbits and using a safety factor of 100.

On the basis of the study of developmental study with phthalimide in rabbits, the Meeting considered that it is unlikely that phthalimide (or its metabolites, including phthalamic acid) is a teratogenic agent.

In view of the results of studies of microflora inhibition, the hypothesis that the inhibition of caecal microflora in the rabbit by folpet causes malnutrition was plausible. However, although unchanged folpet was not detected in the urine of rats given single low or high doses, this does not necessarily imply a lack of systemic absorption of the parent compound, as folpet is rapidly metabolized. Certainly, toxicokinetic studies with structurally-related captan suggested that this compound is systemically available after oral administration. Thus it could not be excluded that the embryo/fetotoxic effects observed in a study of developmental toxicity with folpet in rabbits could be a result of a direct action of folpet or one of its metabolites. Furthermore, equivalent toxicokinetic and metabolism studies in rabbits, the species in which the critical developmental effects of concern were seen, did not appear to have been performed.

In view of these considerations, the Meeting concluded that there was no sound basis on which to change the ARfD established in 2004. The Meeting reconfirmed the ARfD of 0.2 mg/kg bw based on a NOAEL of 20 mg/kg bw per day identified on the basis of an increased incidence of hydrocephalus at 60 mg/kg bw per day in the study in rabbits and using a safety factor of 100. This ARfD applies to women of childbearing age. The Meeting concluded that it was unnecessary to establish an ARfD for the general population.

An addendum to the toxicological monograph was not prepared.

Estimate of acute reference dose

0.2 mg/kg bw, for women of childbearing age
Unnecessary for the rest of the general population

Information that would be useful for the continued evaluation of the compound

Results from epidemiological, occupational health and other such observational studies of human exposures.

5.16 INDOXACARB (216)

RESIDUE AND ANALYTICAL ASPECTS

Indoxacarb was evaluated for the first time by JMPR in 2005 and an ADI of 0-0.01 mg/kg bw was established. An ARfD of 0.1 mg/kg bw was also established. MRLs were recommended for a number of crop and animal commodities.

An MRL of 3 mg/kg was recommended for head cabbages.

CCPR at its 39th Session (2007) decided to return the MRL for head cabbages to Step 6 because of short-term intake concerns and noted that indoxacarb had been scheduled for evaluation by 2007 JMPR (alternative GAP) (ALINORM 07/30/24 – Rev 1, paragraph 127).

The 2005 JMPR evaluated the supervised residue trials for indoxacarb uses on cabbage. The recommended maximum residue level for cabbage was based on the combined residue data from USA (0.21, 0.34, 0.38 and 2.7 mg/kg) and South Africa (0.40, 0.47, 0.83 and 2.0 mg/kg). The IESTI was based on the estimated HR of 2.7 mg/kg.