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.

Data on residues including and excluding wrapper leaves were provided in the US trials on head cabbage recorded in the JMPR Evaluations of 2005. The cabbages including wrapper leaves are intended to represent the commodity in trade, so data on cabbages including wrapper leaves are used to support the MRL. The Meeting was informed that, in the USA, cabbages excluding wrapper leaves are intended to represent the edible portion.

In the four US trials at the GAP PHI of 3 days, mean residues of indoxacarb + R enantiomer in cabbages including wrapper leaves were: 0.21, 0.34, 0.38 and 2.7 mg/kg; and without wrapper leaves were: 0.020, 0.034, 0.025 and 0.054 mg/kg respectively. The highest residue in edible portion from the US trials was 0.054 mg/kg.

In the four South African trials at PHI 3 days (GAP PHI of 3 days), mean residues of indoxacarb + R enantiomer in cabbages were: 0.40, 0.47, 0.83 and 2.0 mg/kg. The commodity analysed was described as "whole heads".

A letter from SABS Commercial[42], where the cabbage samples were analysed, explained that the laboratory policy is to remove obviously damaged, decomposed or withered leaves before shredding and mixing. The laboratory does not automatically remove the outer leaves of a fresh head of cabbage as the heads are picked in such a way that damaged and non-edible parts will remain on the fields.

This information suggests that the intention in the South African trials was to analyse edible portion. The highest residue in edible portion from the South African trials was 2.0 mg/kg.

The Meeting estimated an HR for head cabbage of 2.0 mg/kg.

DIETARY RISK ASSESSMENT

Short-term intake

The IESTI of indoxacarb calculated on the basis of the recommendations for cabbage made by the JMPR represented 90% of the ARfD (0.1 mg/kg bw) for children and 40% for the general population.

The Meeting concluded that the short-term intake of residues of indoxacarb resulting from uses that have been considered by the JMPR is unlikely to present a public health concern.

5.17 PHOSMET (103) – ALTERNATIVE GAP

Phosmet has been evaluated several times for residues by the JMPR from 1976 to 1997. Additional residue information on citrus fruits, pears, nectarines and blueberries was evaluated by the JMPR in 2002. The 2002 JMPR estimated short-term intakes that exceeded the ARfD of 0.02 mg/kg bw for apple, blueberry, citrus fruits, nectarine and pear. The Meeting noted that the ARfD of 0.02 mg/kg bw was conservative and might be refined.

A new ARfD of 0.2 mg/kg bw was established in 2003. The Meeting estimated short-term intakes that exceeded the ARfD for apple (230% children) and pear (150% children). No acute intake concern was estimated for the other commodities (JMPR Report 2003, p. 20 and p. 173).

At the 38th Session of the CCPR in 2006, the Committee noted the acute intake concerns expressed by Australia, the European Union and the USA. The Committee decided to return the draft MRLs for apricot, blueberries, citrus fruit, nectarine and pome fruits to Step 6 and decided to request JMPR to consider using alternative GAP to recommend lower MRLs for these commodities.

New data for GAP and new supervised residue trials were submitted to the 2007 JMPR for pome fruits. New supervised residue trials data were also submitted for oranges and peaches.

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[42] Garbers HV. 8-Jan-2007. Indoxacarb residues in cabbage. Letter. Reference 17/36/8. SABS Commercial (Pty) Ltd, Pretoria, South Africa.