ANNEX B

Metconazole

B.6 Toxicology and Metabolism
(Addendum January 2005)

Note: the changes and comments in this addendum were also included in a revised version of the DAR (yellow marked). Moreover, more detailed information was added in the DAR where indicated.

Data requirement –reporting table 2(2)

B.6.12.2 Comparative dermal absorption, in vitro using rat and human skin (Annex IIIA 7.3)

study was submitted, see revised DAR

Open point 2.1 –reporting table 2(7)

B.6.11.3 Acute inhalation toxicity to rats (Annex IIIA 7.1.3)

The product is considered harmful by inhalation and should be labelled Xn;R20. In addition, the formulation contains a solvent (carrying the label Xi, R37) at a concentration >20%.
According to the dangerous preparation directive (DPD), the formulation should be classified accordingly. In addition, at necropsy, most top-dose decedents showed lung/trachea abnormalities, including fluid accumulation. In the animals sacrificed at termination, red lung foci were observed. These findings were considered treatment-related, and indicate that the product was slightly irritant for the respiratory tract. Such findings are not systematically observed in inhalation studies and are indicative of slight irritation. In conclusion, as the DPD dictates the assignment of R37, and the *in-vivo* study seems to confirm this, there is more reason to classify, than to leave the product unclassified (see also medical data).

Open point 2.2 –reporting table 2(8)

for details, see revised DAR

B.6.14.1 Estimation of operator exposure (Annex IIIA 7.2.1.1)

According to the UK POEM operator exposure model, no safe use would be expected to Metconazole, formulated as “BAS 555 00F” (60 g/L soluble liquid), both in the absence and in the presence of gloves during any task. When operator exposure was estimated using the German model it was observed that no safe use was expected in the absence of PPE, but that the use was acceptable when gloves, coveralls and boots would be worn during the operations.
Hence, it is recommended to include the safety phrases S36/37 (use of protective clothing and gloves) on the label.

Open point 2.3 –reporting table 2(9)

B.6.14.3 Estimation of bystander exposure (Annex IIIA 7.2.2)

The bystander theoretical <u>dermal exposure</u> to Metconazole was estimated according to the following relationship:

D = 100% deposition * drift deposition * exposed area,
where:
-the 100% deposition equals the application rate (0.09 kg a.s./ha = 9 mg/m²)
-drift deposition, for a 7.5 m distance in a field crop was estimated 0.13%, and,
-exposed area was estimated 0.4225 m²/person/day (exposed area includes: head, back and front of neck, forearms, 1/2 upperarms and hands; working day about 6h).

Based upon these assumptions, the bystander dermal exposure is maximally 0.00494 mg/person/day. Taking into account the presence of a bystander of 60 kg, and a dermal absorption of 65%, the exposure is estimated 0.000054 mg/kg b.w./d, which represents 0.54% of the AOEL.

The bystander theoretical inhalation exposure was estimated according to the following relationship:

$I = I_A * WR * AR$,
where:
-I_A corresponds to the specific exposure application, estimated 0.001 mg a.i. in field crops,
-WR is the working rate, 20 ha/d
-AR is the application rate, 0.09 kg a.s./ha

According to these values, the bystander maximal theoretical inhalation exposure is 0.0018 mg a.s./person/day. If the value is adapted to a 1 minute exposure (instead of 6h for the operator exposure), the expected absorbed dose by inhalation would be 0.083×10^{-6} mg/kg bw, which represents 0.00083% of the AOEL.
Even if a 6h-exposure was considered, the estimated inhalation exposure would represent only 0.00003 mg a.s./kg bw, corresponding to 0.3% of the AOEL.

Open point 2.4 –reporting table 2(10)

B.6.14.4 Estimation of worker exposure (Annex IIIA 7.2.3.1)

Metconazole formulated as "BAS 555 00F", is used as a fungicide on cereal crops, and thus inspection shortly after spraying is not expected. Therefore, a re-entry period for workers to the crop should not be established. The contact to freshly pulverised crops (i.e. before drying of the product) by workers or public is generally considered unrealistic. However, a calculation was performed.

The worker exposure may be estimated by means of the following equation:

$D = DFR * TF * AR * P$,
where:
-DFR is the dislodgeable foliar residue
-TF is the transfer factor
-WR is the working rate
-AR is the application rate, which is maximally 0.09 kg a.s./ha
-P is the penetration factor, where additionally, a dermal absorption of 65% was taken into account

Assuming a working rate of 1h/d (scouting task), a transfer factor TF=5000 cm²/person/h (low-crop estimation), a DFR=0.001 mg a.s./cm², and a default penetration facor (PPE used)=5%.

Hence, the potential dermal exposure was about 0.0242 mg/kg b.w./d, consuming 2.44% of the AOEL.

Open point 2.5 and 2.6 –reporting table 2(11)

In only one out of 5 full studies conducted on the rabbit (Masters 1991b, additional study), the developmental NOAEL (4 mg/kg b.w./d) was established at a dose lower than that causing maternal toxicity (NOAEL=10 mg/kg b.w./d). In three other studies, developmental effects were observed at a dose which was also maternotoxic. In one study, no developmental effects was present. Whereas the incriminated study could, considered on itself, be sufficient to consider the compound as a Class 2 teratogen: Category 2 with the risk phrase R61 ("May cause harm to the unborn child"), the other equivalent studies did not confirm this classification.
In the rat, the cis/trans enantiomeric mixture induced developmental effects at the same maternotoxic dose. When testing the cis-enantiomer, developmental effects were demonstrated at 24 mg/kg b.w./d (bilateral hydroureter), while maternotoxicity occurred at 60 mg/kg b.w./d. However, the observed effect is not of sufficient severity to be considered really teratogenic, unlike hydrocephalus which was observed at a higher dose.

In conclusion, the weight of evidence demonstrates that, classifying the substance as a class 3 teratogen (R63) sufficiently reflects the developmental hazard.

The relevant data were transmitted to the expert group Classification and Labelling of Pesticides (ECB-Ispra), which will discuss the topic in due time (proposal for the next ATP).

Data requirement –reporting table 2(31)

Table B.6.6.2.2-7c: In-house historical control data from contemporary NZW rabbit teratogenicity studies in HRC, in the period 1988-1993 (N=37), for the observed incidence of hydrocephaly/cebocephaly.

In view of the very low incidence of hydrocephaly/cebocephaly within the control animals (Gp1), results of treated groups (Gp2: low dose, Gp3: middle dose and Gp4/5: high dose(s)) were also compiled and used to expand the database.

	foetuses				**Litters**			
	Gp1	**Gp2**	**Gp3**	**Gp4/5**	**Gp1**	**Gp2**	**Gp3**	**Gp4/5**
N° examined	4640	4720	4384	3702	558	299	281	466
N° observed	6	4	5	7	6	4	5	6
% observed	0.129	0.085	0.114	0.189	1.08	1.34	1.78	1.29

Table B.6.6.2.2-7d: Cumulative table of the observed incidence of hydrocephaly/cebocephaly for all early NZW rabbit teratogenicity studies with Metconazole.

		Dose-level (mg/kg b.w./d)					
		0	**0.5-2**	**4**	**10**	**20-30**	**40-90**
Fetuses	N° examined	627	775	441	750	296	338
	N° (%) hydrocephaly	1 (0.16)	1 (0.13)	1 (0.23)	5 (0.67)	8 (2.70)	4 (1.18)
	N° (%) cebocephaly	2 (0.32)	1 (0.13)	1 (0.23)	2 (0.27)	1 (0.34)	0 (0.0)
Litters	N° examined	79	91	52	86	39	57
	N° (%) hydrocephaly	1 (1.27)	1 (1.10)	1 (1.92)	5 (5.81)	7 (17.95)	4 (7.02)
	N° (%) cebocephaly	2 (2.53)	1 (1.10)	1 (1.92)	2 (2.33)	1 (2.56)	0 (0.0)

Conclusion from the historical data:
Hydrocephaly/cebocephaly were extremely rare malformations within the Interfauna strain of NZW rabbit at the time. Even taking into account the treated groups, average incidences were not higher than 0.189% (foetal incidence) and 1.78% (litter incidence). In the historical control group (Gp1) there was only one study on 37 with an incidence of 2/94 (2.13%) in foetuses, and 2/14 (14.3%) in litters (referred to as the maximal value in the individual study table legends). During the sequence of studies performed with Metconazole, one case of hydrocephaly was observed in the study control, which was also well in line with the in-house historical control rate.
Treatment with Metconazole resulted in a clear increase in incidence at dosages of 10 mg/kg b.w./d and above. The highest dosages lead to increased incidence of late fetal deaths, which was considered to censure the appearance of the abnormalities.
When comparing the figures with the originally submitted published historical control rates (MARTA-MTA), the statement that the Interfauna Rabbit strain in the HRC study facility was more sensitive than other strains was not supported by the facts.

Data requirement –reporting table 2(32)

B.6.9 Medical data (Annex IIA 5.9)

From the statements of the medical doctors from the various factories producing Metconazole (Ibaraki, Rallis and Genay), who had examined the manufacturing plant personnel regularly, it was inferred that no health-related adverse effects are caused by Metconazole.
Clinical signs or poisoning incidents in the manufacturing sites were not reported.
Eleven poison centres in Germany, Austria and Switserland have been contacted by the notifier in October/November 2004. A total number of 8 cases of exposure to Metconazole have been observed. In four cases a potential relationship with Metconazole exposure (slight skin or bronchial irritation) was established.

Open point 2.8 –reporting table 2(33)

B.6.3.3.5 Summary of short-term toxicity studies on Metconazole.

An overall short-term NOAEL of 4.6 mg/kg b.w./d was proposed, based on the effects observed in the 90d mouse study (clinical chemistry modifications, liver histopathology).
RMS considers that the establishment of this NOAEL should remain unchanged for the following reasons:

(i) this value is comparable to the NOAEL established in the rat (6.4 mg/kg b.w./d, based on approximately the same adverse effects)
(ii) in the chronic mouse toxicity study, a comparable long-term NOAEL (4.4 mg/kg b.w./d was established on the same endpoints; it is aknowledged that the NOAEL's may have been higher if the dose-spacing between NOAEL and LOAEL had been chosen tighter, but unfortunately no other data in this species are present to confirm this.
(iii) the reference doses (ADI, AOEL, ARfD) were based upon the teratogenic endpoints, leading to even a lower value (0.01 mg/kg b.w./d).

In conclusion, it is not deemed necessary to dismiss the study data from the 90d mouse subchronic study from both global summary or endpoint list, as in addition, this would not alter the overall hazard assessment of the a.s..