Opinion of the Scientific Committee on Plants regarding the evaluation of Benomyl, Carbendazim and Thiophanate-Methyl in the context of Council Directive 91/414/EEC concerning the placing of plant protection products on the market (opinion adopted by the Scientific Committee on Plants on 7 March 2001)

1. TITLE

PRELIMINARY OPINION OF THE SCIENTIFIC COMMITTEE ON PLANTS REGARDING THE EVALUATION OF BENOMYL, CARBENDAZIM AND THIOPHANATE-METHYL IN THE CONTEXT OF COUNCIL DIRECTIVE 91/414/EEC CONCERNING THE PLACING OF PLANT PROTECTION PRODUCTS ON THE MARKET.

(Opinion adopted by the Scientific Committee on Plants on 7 March 2001)

2. TERMS OF REFERENCE

The Scientific Committee on Plants (SCP) is requested to respond to the following question in the context of the Commission's work on the implementation of Council Directive 91/414/EEC concerning the placing of plant protection products on the market.

"Can the Committee comment on the advisability of establishing an Acceptable Daily Intake (ADI) and Acceptable Operator Exposure Level (AOEL) having regard particularly to the results of mutagenicity, carcinogenicity and reproductive data for the active substance?"

3. BACKGROUND

Benomyl, carbendazim and thiophanate-methyl are three existing active substances (a.s.) in the context of Council Directive 91/414/EEC [1] , which are covered by the first stage of the work programme established by Commission Regulation (EEC) 3600/92 [2].

For the three a.s., an evaluation report has been prepared by the Rapporteur Member States (RMS), Germany, on the basis of a dossier submitted by the notifiers, namely: Du Pont de Nemours for benomyl, Nisso Chemical Europe for thiophanate-methyl and Agrevo (now Aventis CropSciences), BASF, Agrichem BV, Du Pont de Nemours, B.V. Luxan and Efthymiadis for carbendazim.

Benomyl, carbendazim and thiophanate-methyl are closely related systemic fungicides of the methyl benzimidazole carbamate (MBC) family. Both benomyl and thiophanate-methyl function by the generation of carbendazim. They are used in various crops, for example in cereals, oilseed rape, fruit and vegetable production.

Before the ECCO [3] Peer Review is completed, the European Commission requested the SCP to issue a preliminary opinion related to the genotoxicity profile of the three substances.

The Committee was aware of the Classification Labelling Recommendations (hazard identification) of the Specialised Experts [4] that both benomyl and carbendazim should be classified as Category 2 mutagens and Category 2 for toxicity to reproduction (fertility and developmental effects).

4. OPINION

Question:

"Can the Committee comment on the advisability of establishing an Acceptable Daily Intake (ADI) and Acceptable Operator Exposure Level (AOEL) having regard particularly to the results of mutagenicity, carcinogenicity and reproductive data for the active substance?"

Opinion of the Committee:

The Committee noted that carbendazim is the biologically active substance common to all three of these fungicides. Benomyl in particular, but also thiophanate-methyl, is metabolised to carbendazim and all three substances produce numerical chromosomal aberrations (aneuploidy) in mammalian cells, exposed in vivo. There is no evidence that any other form of damage to genetic material is induced by any of these substances. Carcinogenicity is not a concern. The known effects of these fungicides upon reproduction are explicable by interaction with the microtubules of the spindle apparatus. The mechanism of aneuploidy induction is well understood and consists of inhibition of polymerisation of tubulin, the protein that is essential for the segregation of chromosomes during cell division: it does not involve any interaction with DNA. Since multiple copies of tubulin molecules are present in proliferating cells, in the presence of low concentration of the fungicides a limited number of tubulin molecules will be affected and consequently no toxicological adverse effects will ensue. Consequently, a clear no adverse effect level is recognisable and both an ADI and an AOEL can be established.

Scientific background on which the opinion is based:

Benomyl, carbendazim and thiophanate-methyl belong to the methyl benzimadazole carbamate class of fungicides used in agriculture and anthelmintic agents used in both food producing and companion animals. Both benomyl and thiophanate-methyl are pro-fungicides that generate carbendazim, the biologically active molecule that is also the metabolite of toxicological concern and responsible for the activities discussed here.

4.1 Carcinogenicity

Positive findings in carcinogenicity studies with carbendazim were limited to hepatocellular tumours in certain strains of mice, which were increased in two of three studies. Benomyl and thiophanate-methyl also induced hepatocellular tumours in mice, in single studies only. As data on the mode of action of these particular substances in mouse liver do not indicate a DNA-reactive effect, the Committee concluded that these mouse liver tumours could not be interpreted as predicting a carcinogenic hazard to humans.

4.2 Toxicity to Reproduction

Most dietary studies of benomyl or carbendazim have shown there to be only minor signs of reproductive toxicity at high doses and no effects on development in the absence of maternal and/or paternal toxicity, whereas gavage administration induced both testicular changes that resulted in reduced fertility and teratogenic effects with a predominance of head and eye malformations. In addition, oligospermia, testicular atrophy and degeneration and foetotoxicity were found in a more recent, two-generation dietary study with high doses of benomyl (Du Pont, 1991).

4.3 Genotoxicity

On the basis of the available data the overall genotoxicity profile of the MBCs can be summarised as:

In vitro assays

1. Negative results for induction of point mutation and chromosome structural damage by benomyl, carbendazim and thiophanate-methyl.

2. Positive results for the induction of numerical chromosome changes (aneuploidy) in a variety of cultured mammalian cells by benomyl, carbendazim and thiophanate-methyl.

In vivo assays

1. Positive results in rodent bone marrow for the induction of micronuclei by benomyl, carbendazim and thiophanate-methyl. These micronuclei predominantly contain whole chromosomes.

2. Positive results for the induction of numerical chromosome changes in both male and female germ cells of rodents by benomyl and carbendazim, but thiophanate-methyl has not been adequately tested in this respect.

4.4 Primary mechanism of toxicity of the MBCs

There is an extensive scientific literature which demonstrates that methyl-benzimidazol-2-yl carbamates (MBC) interact with tubulin, disrupting microtubule assembly, preventing the formation of the cell division spindle and thus resulting in a failure of cell division. The inhibition of tubulin polymerisation by carbendazim modifies the formation of the mitotic spindle of cultured mammalian cells. Concentrations of carbendazim below those which completely eliminate mitotic spindle formation in mammalian cells lead to the formation of "imperfect" mitotic spindles and thus to the mal-segregation of chromosomes. The mal-segregation of chromosomes in the presence of carbendazim results in the production of aneuploid progeny cells including those with both reduced and increased chromosome numbers i.e. monosomic and trisomic. The loss of chromosomes in cultured mammalian cells following carbendazim exposure has been assessed using the **in vitro** micronucleus assay (Elhajouji **et al.,** 1995). Mal-segregation leading to the production of monosomic and trisomic cells has been assessed by the measurement of both losses and gains of chromosomes in cytochalasin B induced binucleate human lymphocytes (Bentley **et al.,** 2000). It can be concluded that the genotoxicity of carbendazim is due to the inhibition of tubulin assembly, which results in the induction of aneuploidy.

The reproductive toxicity of MBCs involves the reduction of testicular and epididymal weights together with reduced epididymal sperm counts and reduced fertility (Carter & Laskey 1982, Carter **et al.,** 1984; Barnes **et al.,** 1983; Linder **et al.,** 1988; Hess **et al.,** 1991). Histological examinations indicate that there is seminiferous tubular atrophy, early sloughing of the germ cells and occlusion of the efferent ductules following MBC exposure (Hess **et al.,** 1991).

Evidence strongly indicating that carbendazim is responsible for the testicular toxicity of benomyl has been provided in experiments in which equimolar concentrations of benomyl and carbendazim were administered to rats, either intraperitoneally or by direct injection into the testis (Lim & Miller, 1997). Whereas no significant testicular damage was observed both 1 and 2 hours after benomyl administration by the interperitoneal route, carbendazim administration resulted in sloughing of the seminiferous epithelium after 1 hour, which increased in severity at the 2-hour time point. Intratesticular treatment with benomyl caused little testicular damage after 1 hour whereas an equimolar amount of carbendazim produced severe disruption of the seminiferous epithelium. Testicular levels of carbendazim and benomyl were measured at various times after both routes of administration. The Area Under the (time-concentration) Curve (AUCs) from the concentration in the testis vs time plots for both benomyl and carbendazim showed excellent relationships with the number of tubules which exhibited sloughing. However, when the contribution of carbendazim to the benomyl response was subtracted, no effect of benomyl was discernible. The concentration which reduced microtubular assembly by 50 % was 5 µM (1µg/ml) for carbendazim and 75 µM (15µg/ml) for benomyl. It is noted that following an oral dose of 3 mg/kg bw, an average Maximum Concentration (C_{max}) in blood of about 1 mg/ml is found in both rats and mice, while a dose of 300 mg/kg bw results in an average C_{max} of about 17 mg/ml in rats and 50 mg/ml in mice (Kellner & Eckert, 1983). It can be concluded that the inhibition of microtubular polymerisation is responsible for the toxicity of MBCs in testicular tissue.

The cell division spindle is made up of multiple spindle fibres that present multiple cellular targets which must be damaged by MBCs before chromosome malsegregation occurs and the fidelity of cell division is disturbed. Experiments undertaken with benomyl and carbendazim have demonstrated No Observed Effect Levels (NOELs) for aneuploidy induction using **in vitro** assays for these two chemicals (Marshall **et al.**, 1996, Bentley **et al.**, 2000). It would be difficult to define precise thresholds for activity from these data and the mathematical models that had been used for their analysis, but the dose response curves obtained provide convincing evidence for the **in vitro** NOELs.

In mammalian cells, the cell division spindle is a critical structural component responsible for the accurate segregation and distribution of chromosomes during both mitotic and meiotic cell division. The fundamental differences between mitosis and meiosis are that during the later division homologous chromosomes pair, form chiasma and recombine their genetic material. In the 1^{st} division of meiosis it is the whole chromosomes that are segregated to progeny cells, whereas in mitosis it is the chromatids produced by DNA replication that are segregated. During the 2^{nd} division of meiosis and in mitotic divisions the centromeres separate and segregate to the opposite poles of the dividing cell and thus to each of the progeny cells.

Both mitosis and meiosis involve the polymerisation of tubulin, assembly of microtubules and the formation of a cell division spindle. The cellular target of MBCs interactions are essentially the same for both mitosis and meiosis. However, there is currently available no evidence to prove conclusively that the concentrations of carbendazim which modify mitosis

and meiosis are identical. Data are only available which demonstrate the detailed dose response of carbendazim in cultured somatic cells. The SCP is aware that studies on germ cells are in progress [5]. Even if it can be established that the effects on sperm occur at lower doses than for somatic cells, this would not invalidate the concept of a dose threshold effect in both mitotic and meiotic cells. It should be noted that this conclusion does not conflict with the hazard labelling recommendations of the Specialised Experts that benomyl and carbendazim should be classified as Category 2 mutagens and Category 2 reproductive toxicants.

A wide range of experimental data supports the hypothesis that differences in the binding affinity between fungal and mammalian tubulin is the primary reason for the relatively low mammalian toxicity of the benzimidazole fungicides (Davidse and Flach 1977; Ireland **et al.,** 1979).

4.5 Conclusion

It has been firmly established that direct binding of carbendazim to tubulin is required for the toxic effects of the methylbenzimidazoles. Through this mechanism carbendazim and its precursors provoke toxic effects on reproduction and induce numerical changes in chromosomes (aneuploidy) in mammalian cells **in vitro** and in bone marrow and male and female germ cells of rodents dose **in vivo**. There is no evidence for the induction of gene mutations **in vitro,** for or structural chromosomal damage **in vitro** or **in** vivo or for interaction with DNA of liver cells of rats dosed **in vivo** with carbendazim. Thus, interactions of carbendazim and its precursors with biological material is of a nature that is entirely consistent with a dose level being identifiable as having no toxicological effect.

5. REFERENCES

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6. DOCUMENTATION MADE AVAILABLE TO THE COMMITTEE

- 1. Evaluation of Benomyl in the context of Council Directive 91/414/EEC concerning the placing of plant protection products on the market: Terms of reference (Doc. SCP/BENOMYL/001) submitted by HEALTH AND CONSUMER PROTECTION DG, 12 May 2000.
- 2. Evaluation of Carbendazim in the context of Council Directive 91/414/EEC concerning the placing of plant protection products on the market: Terms of reference (Doc. SCP/CARBEN/001) submitted by HEALTH AND CONSUMER PROTECTION DG, 12 May 2000.
- 3. Evaluation of Thiophanate-methyl in the context of Council Directive 91/414/EEC concerning the placing of plant protection products on the market: Terms of reference (Doc. SCP/THIOPHAN/001) submitted by HEALTH AND CONSUMER PROTECTION DG, 12 May 2000.
- 4. Benomyl: Evaluation table - Doc. 5029/VI/98 rev3. (Doc. SCP/BENOMYL/003) submitted by HEALTH AND CONSUMER PROTECTION DG, 22 May 2000.
- 5. Carbendazim: Evaluation table - Doc. 5029/VI/98 rev3. (Doc. SCP/BENOMYL/003) submitted by HEALTH AND CONSUMER PROTECTION DG, 22 May 2000.
- 6. Thiophanate-methyl: Evaluation table - Doc. 5029/VI/98 rev3. (Doc. SCP/BENOMYL/003) submitted by HEALTH AND CONSUMER PROTECTION DG, 22 May 2000.
- 7. Carbendazim, Benomyl, Thiophanate-methyl: Draft summary report, Commission group of specialised experts in the field of carcinogenicity, mutagenicity and reprotoxicity, Arona Sept. 1999 (Doc. SCP/BENOMYL/004) submitted 22 May 2000.
- 8. Benomyl: Addendum to the Monograph: addendum 2, 3 March 2000, Germany (Doc. SCP/BENOMYL/005) submitted by HEALTH AND CONSUMER PROTECTION DG 22 May 2000.
- 9. Carbendazim: Addendum to the Monograph: addendum 2, 3 March 2000, Germany (Doc. SCP/CARBEN/005) submitted by HEALTH AND CONSUMER PROTECTION DG 22 May 2000.
- 10. Thiophanate-methyl: Addendum to the Monograph: addendum 2, 3 March 2000, Germany (Doc. SCP/THIOPHAN/005) submitted by HEALTH AND CONSUMER PROTECTION DG 22 May 2000.
- 11. EC reviews of benomyl, carbendazim, thiophanate-methyl: Comments from Pesticides Safety Directorate, UK, (Doc. SCP/BENOMYL/006) submitted 18 July 2000.

- 12. Benomyl, carbendazim, thiophanate-methyl: committee on mutagenicity of chemicals in food consumer products and the environment, Statement on thresholds for aneugens: extrapolation of data from somatic cells to germ cells. Consideration of summary record of Commission group of specialised experts in the field of carcinogenicity, mutagenicity and reproductivity. (Doc. SCP/BENOMYL/007) submitted by Pesticides Safety Directorate, 18 July 2000.
- 13. Benomyl/ Carbendazim (Doc. BENOMYL/009, submitted by DuPont, 11 August 2000)
    - Statement for the Scientific Committee on Plants : The Relevance of Benomyl and Carbendazim Mutagenicity to the Establishment of an ADI and AOEL (Dupont-4544);
    - COM statement on Thresholds for aneugens : Extrapolation of data from somatic cells to germ cells;
    - The role of Aneuploidy Data in the Risk Assessment of Agricultural Pesticides
    - Statement for the Specialised Experts Committee : Industry's Position on the EU Classification of Benomyl and Carbendazim for Human Health Effects - Toxicity to Reproduction (Dupont 4342);
    - 14C-Benomyl : Summary of Dermal Bioavailability in Rats and Rabbits (Dupont-4352);
    - Sperm-Fish Assay with Carbendazim (DuPont-4533).
- 14. Review paper on benzimidazole based fungicides. (Doc. SCP/BENOMYL/010) submitted by Prof. Parry, 24 October 2000.
- 15. Background information on mutagenicity, carcinogenicity and reproductive toxicity of benzimidazoles fungicides. (Doc. SCP/BENOMYL/011) submitted by Prof. Savolainen, 26 October 2000.
- 16. Comments relating to EC reviews of benomyl, carbendazim and thiophanate-methyl. (Doc. BENOMYL/012) submitted by Pesticide Safety Directorate, UK, 3 November 2000.
- 17. Comments relating to EC reviews of benomyl, carbendazim and thiophanate-methyl: statement of the COM. (Doc. BENOMYL/013) submitted by Pesticide Safety Directorate, UK, 3 November 2000.
- 18. Comment to the review paper on genotoxicity of benzimidazole based fungicides SCP/BENOMYL/010. (Doc. SCO/BENOMYL/014) submitted by Dr. Crebelli, 3 November 2000.
- 19. Benomyl: Monograph prepared by Germany (Volumes 1 to 4) - 13 November 1997.
- 20. Carbendazim: Monograph prepared by Germany (Volumes 1 to 4) - 13 November 1997.
- 21. Thiophanate-methyl: Monograph prepared by Germany (Volumes 1 to 4) - 13 November 1997.

7. ACKNOWLEDGEMENTS

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Carcinogenicity WG: Prof. Maroni (Chairman) and Committee members: Dr. Delcour-Firquet, Prof Leszkowicz, Dr. Meyer, Dr. Moretto, Prof. Petsinger, Prof. Savolainen, Prof. Silva Fernandes, Dr. Speijers and invited experts Dr. Crebelli, Prof. Galli, Dr. McGregor, Prof. Parry, Dr. Rice, Prof. Schulte-Hermann and Dr. Wester.

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[1] OJ N° L 230 of 19. 8.1991, p. 1.

[2] OJ N° L 366 of 15.12.1992, p. 10.

[3] European Commission Co-ordination.

[4] Commission group of specialised experts in the field of carcinogenicity, mutagenicity and reprotoxicity, established under Directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances.

[5] Assessment of the dose response of carbendazim in the testes of mice currently being performed at GSF Laboratory at Neuherberg, Germany