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**SCIENTIFIC COMMITTEE ON FOOD**

**SCF/CS/ADD/MsAd/179 final**  
**6/12/99**

Annex II to the minutes of  
the 119<sup>th</sup> Plenary meeting

**OPINION**  
**ON IMAZALIL FOR INCORPORATION IN CHEESE COATINGS**

(expressed on 2 December 1999)

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## SCIENTIFIC COMMITTEE ON FOOD

SCF/CS/ADD/MsAd/179 final

### **Opinion on imazalil for incorporation in cheese coatings**

(expressed on 2 December 1999)

#### **Terms of Reference**

To give an opinion on the safety in use of imazalil as a food additive for use in coatings for hard and semi-hard cheeses.

#### **Background**

Imazalil is an antifungal agent of the chemical group of imidazole derivatives.

In food production today, Good Manufacturing Practice (GMP) and implementation of the Hazard Analysis Critical Control Point (HACCP) system to ensure hygienic conditions and food safety are general practice. However some food products like cheese, require a certain ripening time after production and are therefore stored for a relative long time before sale. Given temperature and humidity conditions during this storage period, they are very susceptible to mould growth.

To prevent mould growth on the surface of cheese and the possible formation of mycotoxins, cheese coatings containing fungicidal compounds are applied. Imazalil is added as the active ingredient. The coatings are an emulsion of synthetic materials which dry to a film when applied to the cheese surface. They are composed of a co-polymer (vinyl acetate – maleic acid-di-n-butylester), annatto and water.

The permitted constituents of cheese coatings used on hard- and semi-hard cheeses types are described by national laws in many countries.

The approval is requested for the incorporation of imazalil in cheese coatings at a level of 250 mg/kg coating.

The Committee has been asked to evaluate the safety in use of the active ingredient (imazalil) in the coatings and not its carriers.

#### **Present legislation regarding the use of imazalil**

The use of imazalil to prevent growth of undesirable moulds on fresh fruit during storage and other agricultural products has been reviewed by all EU Member States and their respective competent authorities have all allowed its use. The European Commission has adopted directives for Maximum Residue Levels (MRL's) of imazalil in and on cereals and foodstuffs of animal origin (Directive 93/57/EEC)<sup>(1)</sup> and Maximum Residue Levels of imazalil in and on certain products of plant origin (Directive 93/58/EEC)<sup>(2)</sup>. The European Commission also included imazalil as an active substance in Annex I to council Directive 91/414/EEC concerning the placing of plant protection products on the market<sup>(3)</sup>.

#### **Technical data**

The Committee has been fully informed about the product description, the manufacturing process, the product specifications and the methods of analysis<sup>(4)</sup>. The detection limit for imazalil in cheese was found to be 0.05 mg/kg.

## Technical studies

### Studies on the inhibitory activity of imazalil

The Committee has also been fully informed about the inhibitory activity of imazalil in, *in vitro*, model systems and in hard and semi-hard cheeses. The effectiveness of the compound against mould growth at the proposed level of use has been demonstrated<sup>(5)(6)(7)</sup>.

### Study on the chemical stability of imazalil in coatings during storage

Data supplied to the Committee<sup>(8)</sup> show that imazalil is chemically stable and can be quantitatively recovered from cheese coatings, spiked with imazalil in a concentration range between 100-500 ppm, after a storage period of respectively 0, 1 and 3 months at 30°C.

Similar experiments on prolonged storage of citrus and pome fruits, surface treated with radiolabelled imazalil, demonstrated a very slow transformation of the substance to 1-[2-(2,4-dichlorophenyl)-2-hydroxyethyl]-1H-imidazole (R014821). This transformation product is an intermediate in animal and plant metabolism of imazalil. Therefore, in the toxicological studies, this compound is evaluated together with the parent substance.

### Studies on the migration of imazalil into cheese

Migration studies<sup>(9)(10)</sup> demonstrate that imazalil present in cheese coatings at levels up to 250 mg/kg of coating, can migrate into the cheese. However, even after a storage period of 3 months, under conditions as in commercial practice, the bulk of imazalil (i.e. >90%) is found to be present in the surface layer (the first 1 mm depth). This part of the cheese contains the plastic layer and the rind. In none of the cheeses analysed, even after 3 months of ripening, were detectable amounts (i.e. >0.05 mg/kg) found at a depth of 8 to 10 mm; the concentration level of imazalil was already reduced to below the detection limit, between a depth of 6.7 and 7.4 mm.

## Biological studies

The Committee has not undertaken its own review of the biological studies on absorption, distribution, metabolism, excretion and toxicity of imazalil. The original reports of these studies have been thoroughly examined and evaluated by EU Member States under the programme referred to in Council Directive 91/414/EEC<sup>(3)</sup>, for the re-evaluation of existing active substances. Their review report, which was adopted in the Standing Committee on Plants Health on July 11 1997, was made available to the Scientific Committee on Food<sup>(11)</sup>. The biological studies have also been evaluated by the FAO/WHO Joint Meeting on Pesticide Residues (JMPR) in 1995<sup>(12)</sup>. The EU and JMPR reviews both recommended the same Acceptable Daily Intake (ADI) of 0 - 0.03 mg/kg bw/day, based on the lowest no-adverse effect level (NOAEL) of 2.5 mg/kg b.w., identified in a 1-year feeding study in the dog. The same NOAEL was found for maternal toxicity in a rabbit teratogenicity study.

The Committee is content that the range of studies available is comprehensive and covers all the appropriate toxicological end-points which would be required for a food additive. The Committee has no reason to deviate from the ADI recommended by the above cited bodies. Accordingly it is used in the section below, which discusses overall intakes of imazalil from cheese and other sources in relation to the ADI.

## **Human exposure to imazalil from cheese consumption and additional contribution to daily intakes**

The use of imazalil as a pesticide is allowed in a number of agricultural commodities. Given the MRL's for each of these commodities it can be calculated that the Theoretical Maximum Residue Contribution (TMRC) could amount to 0.15 mg/day<sup>(13)</sup>.

Given the ADI of 0.03 mg/kg bw/day, the daily acceptable intake for a person of 60 kg is 1.8 mg/day/person. A TMRC of 0.15 mg is equivalent to just over 8% of the ADI.

In a Scientific Co-operation Programme (SCOOP) of the EU<sup>(14)</sup> the estimated total mean cheese intake (sum of hard cheese, semi-hard cheese and all other types of cheese) ranges from 59 g/person/day (Greece) to 8 g/person/day (Ireland).

On the basis of the fact that cheeses with a normal weight of 12 kg and 80 g of coating, are treated twice with coatings containing 250 mg imazalil/kg coating, the residue level will be not more than 3 mg/kg.

Taking the highest total mean cheese intake in the EU<sup>(14)</sup> of 59 g/person/day and the worst case assumption that this is all hard and semi-hard cheese, the use of imazalil would increase the TMRC by a value of 0.18 mg, equivalent to 10% of the ADI.

If cheese is consumed without the rind much less than 0.18 mg is likely to be consumed. Indeed, as demonstrated by the experimental data, >90% of the fungicide is present in the first mm of the cheese only. Thus a theoretical residue level of only 0.3 mg/kg will be present in the rest of the cheese and the TMRC would be increased by a value equivalent to 1% of the ADI.

For a child of 15 kg, the intake from the 59 g of cheese would be equivalent to 40% of the ADI, assuming the rind is eaten, and 4% if the rind is not consumed.

## **Conclusion**

A residue level of imazalil in whole cheese (with coating) of 3 mg/kg and a mean daily intake of cheese, with coating, of 59 g/person/day, leads to an additional Theoretical Maximum Residue Contribution (TMRC) of 0.18 mg for an adult. Given an ADI of 0.03 mg/kg bw/day this value accounts only for an additional uptake equivalent to 10% of the ADI such that maximum theoretical intakes of imazalil from all sources by adults would not exceed 20% of the ADI.

For a child, assuming the child consumes daily 59 g of cheese, with coating, the Theoretical Maximum Residue Contribution (TMRC) value of 0.15 mg is increased by 0.18 mg. This value accounts for 40% of the ADI. The maximum theoretical intakes of imazalil from all sources by a child would comprise 73% of the ADI. If the rind is not consumed the maximum theoretical intakes of imazalil from all sources would not exceed 37% of the ADI.

Given these data, and the conservative assumption used in deriving these, the Committee is of the opinion that no additional safety issues are raised by the use of imazalil as an antifungal agent in coatings for the production of hard and semi-hard cheeses, given that the residue levels will not exceed 3 mg/kg of cheese.

## REFERENCES

1. Council Directive 93/57/EEC of 29 June 1993 amending the Annexes to Directives 86/362/EEC and 86/363/EEC on the fixing of maximum levels for pesticide residues in and on cereals and foodstuffs of animal origin respectively, Official Journal N° L 211/2 of 23.8.93.
2. Council Directive 93/58/EEC of June 29 1993 amending Annex II to Directive 76/895/EEC relating to the fixing of maximum levels for pesticide residues in and on fruit and vegetables and the Annex to Directive 90/642/EEC relating to the fixing of maximum levels for pesticide residues in and on certain products of plant origin, including fruit and vegetables, providing for the establishment of a first list of maximum levels. Official Journal N°L 211/6 of 23.8.93.
3. Council Directive 97/73/EC of 15 December 1997 including an active substance (imazalil) in Annex I to Council Directive 91/414/EEC concerning the placing of plant protection products on the market. Official Journal N°L353/26 of 24.12.9
4. Woestenborghs, R., Michielsen, L., Pauwels, C., Van Leemput, L. and Heykants, J.,  
A Review of the Methods for the Residue Analysis of the Fungicide Imazalil, Med. Fac. Landbouww. Rijksuniv. Gent, 53/3b, 1988
5. Efficacy of imazalil, pimaricine and their combination against *Penicillium echinulatum* var. *discolore*. Test no.: 920903. October 1992. Data submitted by Petitioner.
6. Efficacy of imazalil and Natamycin against fungi causing spoilage in the dairy industry. Test no.: 871117. November 1992. Data submitted by Petitioner.
7. Sensitivity of *Penicillium echinulatum* to Natamycine and/or imazalil when growing on Cheese. Dutch Institute for Dairy research (NIZO), NOV-1874v, 1992.
8. Quantitative determination and stability of imazalil (R23979) in CESA cheese coatings. Project Number: JPH-CSK 92. Report by W. Steurbaut, University of Ghent, 1993.
9. Migration studies of imazalil in cheese. Dutch Institute for Dairy Research (NIZO). Report by G. Ellen, November 1993.
10. Determination of imazalil in cheese and plastic samples. NOTOX Project 094185. NOTOX B.V. (NI), Report by T. Melkebeke and M.M. Gladines. August 1993
11. Summary on toxicological and metabolism studies on the active substance (imazalil). Update August 1996, EEC Directive 91/414, Annex II/Tier III.
12. Joint FAO/WHO Food Standards Programme Codex Committee on Pesticides Residues, Twenty-seventh Session, The Hague, The Netherlands, 24-29 April, 1995
13. Jansen Pharmaceutica, Imazalil, Submission for acceptance of imazalil as a fungicide for incorporation in cheese coatings, Annex 16, "Human Exposure". ADI of Imazalil, October 1997
14. Scientific Co-operation Programme (SCOOP, Council Directive 93/5/EEC on assistance and cooperation to the Commission by the Member States in the scientific examination of questions relating to food)-Task 4.1., Improvement of the knowledge of food consumption with a view to protection of public health by means of exchange and collaboration between database managers. Final Report, June 1996.