Withdrawal period for Coxidin® for chickens and turkeys for fattening and re-examination of the provisional Maximum Residue Limit

Scientific Opinion of the Panel on Additives and Products or Substances used in Animal Feed

(Question No EFSA-Q-2007-192)

Adopted on 18 June 2008

PANEL MEMBERS
Georges Bories, Paul Brantom, Joaquim Brufau de Barberà, Andrew Chesson, Pier Sandro Cocconcelli, Bogdan Debski, Noël Dierick, Anders Franklin, Jürgen Gropp, Ingrid Halle, Christer Hogstrand, Joop de Knecht, Lubomir Leng, Anne-Katrine Lundbye Haldorsen, Alberto Mantovani, Miklós Mézes, Carlo Nebbia, Walter Rambeck, Guido Rychen, Atte von Wright and Pieter Wester

SUMMARY
Following a request from the European Commission, the European Food Safety Authority was asked to deliver a scientific opinion on the proposal for reducing the withdrawal period from three days to one day and the setting of a final maximum residue limit (MRL) for the product Coxidin® for chickens and turkeys for fattening.

No data which would allow proposing a final MRL for monensin in poultry tissues was provided.

A number of monensin metabolites (M1, M2, M5, M6) were isolated and tested for their biological activities. All monensin metabolites tested appeared to show lower ionophoric activity than the parent compound. These findings confirm the results of earlier studies. Comparable results on reduced ionophoric activity of metabolites from a related polyether antibiotic support the above findings on monensin.

Non-extractable residues in chicken liver and kidney after a one-day withdrawal period amount to more than 50 % of the total residues. About 90 % of total radioactivity was associated with the abdominal fat in chicken for fattening. In milk, about 25 % of the total residues are attributed to fatty acids. The Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) concludes that a considerable part of the non-extractable residues is not drug-related.

The FEEDAP Panel, following a weight of evidence approach, concludes that monensin derived residues of toxicological relevance probably represent, as a conservative estimate, not more than 50 % of the total residues.

1 For citation purposes: Scientific Opinion of the Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) on a request from the European Commission on the withdrawal period for Coxidin® for chickens and turkeys for fattening and the re-examination of the provisional Maximum Residue Limit. The EFSA Journal (2008) 731, 1-14
After applying a 50 % reduction of the toxicological relevance of total residues, the human exposure would amount to 0.103 mg day\(^{-1}\) (57 % of the ADI). Based on the existing MRL values, the consumption of chicken edible tissues would contribute to 51 % of the ADI.

Recent marker residue data obtained after one-day withdrawal in chicken for fattening were below the MRLs. Therefore, a one-day withdrawal time for Coxidin\textsuperscript{®} for chickens and turkeys for fattening could be set.

**Key words:** coccidiostats, monensin sodium, Coxidin\textsuperscript{®}, total residues, marker residues, MRL, withdrawal period, monensin metabolites, ionophoric activity, metabolites, chickens for fattening, turkeys for fattening
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BACKGROUND

Regulation (EC) No 1831/2003\(^2\) establishes the rules governing the Community authorisation of additives for use in animal nutrition. In particular, Article 13(3) of that Regulation lays down that if the holder of an authorisation proposes changing the terms of the authorisation by submitting an application to the Commission, accompanied by the relevant data supporting the request for the change, the Authority shall transmit its opinion on the proposal to the Commission and the Member States.

The European Commission received a request from the company Huvepharma NV\(^3\) to modify the withdrawal period from three days to one day and to set the final MRL for the product Coxidin® (monensin sodium), to be used as a feed additive for chickens and turkeys for fattening (category: coccidiostats) under the conditions mentioned in Table 1.

The product Coxidin® is a preparation of monensin sodium which has been initially authorised at Community level under Regulation (EC) No 109/2007\(^4\) and than under Regulation (EC) No 156/2008\(^5\) for use in chickens and turkeys for fattening, until 6 February 2017.

According to Article 7(1) of Regulation (EC) No 1831/2003, the Commission forwarded the application to the European Food Safety Authority (EFSA) as an application under Article 13(3) (modification of the authorisation of a feed additive). EFSA received directly from the applicant the technical dossier in support of this application. According to Article 8 of that Regulation, EFSA, after verifying the particulars and documents submitted by the applicant, shall undertake an assessment on the proposals for change made by the applicant. The particulars and documents in support of the application were considered valid by EFSA as of 10 March 2008.

The Scientific Committee on Animal Nutrition (SCAN) has issued three opinions in which monensin sodium was assessed. The first one was issued in 1979 on specific questions about the safety for consumer and the environment of the combined use of the active substance with flavophospholipol (EC, 1979). The second, issued in 1981, dealt with specific questions about the safety for the consumer and the environment of monensin sodium when used as a coccidiostat in feedingstuff for poultry (EC, 1981). The third opinion was issued in 1983 and concerned the use of monensin sodium in feedingstuffs for turkeys (EC, 1983).

The Scientific Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) issued an opinion on the evaluation of the coccidiostat COXIDIN® (Monensin Sodium) (EFSA, 2005), following by the opinion on the safety of Coxidin® (monensin sodium) (EFSA, 2006a). Than, in the same year, the Panel adopted an opinion on the Maximum Residue Limit for monensin sodium for chickens and turkeys for fattening (EFSA, 2006b). Finally, in 2007, an opinion on Efficacy of Coxidin® 25 % (monensin sodium) as a feed additive for turkeys (EFSA, 2007) was adopted.

TERMS OF REFERENCE

According to Article 8 of Regulation (EC) No 1831/2003, EFSA shall determine whether the feed additive complies with the conditions laid down in Article 5. EFSA shall deliver an opinion on the proposal for changing the withdrawal period from three days to one day for the product Coxidin®, a coccidiostat for chickens and turkeys for fattening with monensin sodium.

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\(^2\) OJ L 268, 18.10.2003, p. 29  
\(^3\) Huvepharma NV, Uitbreidingstraat 80, 2600 Antwerpen, Belgium  
\(^4\) OJ L 31, 06.02.2007, p. 6  
\(^5\) OJ L 48, 22.2.2008, p. 14
as active substance, when used under the conditions described in Table 1, and setting a final MRL for monensin.

ACKNOWLEDGEMENTS
The European Food Safety Authority wishes to thank the members of the Working Group on Coccidiostats for the preparation of this opinion.
### Table 1. Register entry as proposed by the applicant

<table>
<thead>
<tr>
<th>Additive</th>
<th>Coxidin®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Registration number/EC No/No (if appropriate)</td>
<td>5 1701</td>
</tr>
<tr>
<td>Category of additive</td>
<td>(e) coccidiostat</td>
</tr>
<tr>
<td>Functional group of additive</td>
<td>-</td>
</tr>
</tbody>
</table>

#### Description

<table>
<thead>
<tr>
<th>Composition, description</th>
<th>Chemical formula</th>
<th>Purity criteria (if appropriate)</th>
<th>Method of analysis (if appropriate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active substance: Sodium salt of polyether monocarboxylic acid produced by Streptomyces cinnamonensis, 28682, LMG S-19095 in powder form. Additive composition: monensin sodium technical substance equivalent to monensin activity: 25%. Perlite: 15-20% and wheat bran: 55-60%.</td>
<td>C₃₆H₆₁O₁₁Na</td>
<td>(short description) Factor composition: Monensin A: not less than 90% Monensin A + B: not less than 95% Monensin C: 0.2 – 0.3%</td>
<td>(short description) HPLC (details are available at the Community Reference Laboratory)</td>
</tr>
</tbody>
</table>

#### Trade name (if appropriate)

Coxidin®

#### Name of the holder of authorisation (if appropriate)

Huvepharma NV

#### Conditions of use

<table>
<thead>
<tr>
<th>Species or category of animal</th>
<th>Maximum Age</th>
<th>Minimum content</th>
<th>Maximum content</th>
<th>Withdrawal period (if appropriate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chickens for fattening</td>
<td>-</td>
<td>100</td>
<td>125</td>
<td>1 day before slaughter</td>
</tr>
<tr>
<td>Turkeys</td>
<td>16 weeks</td>
<td>60</td>
<td>100</td>
<td>1 day before slaughter</td>
</tr>
</tbody>
</table>

#### Other provisions and additional requirements for the labelling

- Specific conditions or restrictions for use (if appropriate): The additive shall be incorporated in compound feedingstuffs in form of a premixture. Monensin sodium shall not be mixed with other coccidiostats. Dangerous for equines. This feedingstuff contains an ionophore: avoid simultaneous administration with tiamulin and monitor for possible adverse reactions when used concurrently with other medicinal substances.

- Specific conditions or restrictions for handling (if appropriate): Wear suitable protective clothing, gloves and eye/face protection. In case of insufficient ventilation in the premises, wear suitable respiratory equipment.

- Post market monitoring (if appropriate): Sensitivity testing will be performed on a yearly base in the EU.
### Specific conditions for use in complementary feedingstuffs (if appropriate)

The maximum permitted dose of monensin sodium in complementary feedingstuffs:
- 625 mg/kg for chickens for fattening
- 500 mg/kg for turkeys

### Maximum Residue Limit (MRL) (if appropriate)

<table>
<thead>
<tr>
<th>Marker residue</th>
<th>Species or category of animal</th>
<th>Target tissue(s) or food products</th>
<th>Maximum content in tissues</th>
</tr>
</thead>
</table>
| Monensin sodium| Chickens for fattening and turkeys | Skin/fat | 25 µg monensin sodium/kg of wet skin + fat  
|                 |                               |                                 | 8 µg monensin sodium/kg of wet liver, kidney and muscle. |
ASSESSMENT

1. Introduction

Coxidin® is a feed additive authorised to control coccidiosis at the dose of 100-125 mg kg⁻¹ complete feed in chickens for fattening and 60-100 mg kg⁻¹ in turkeys for fattening, according to Regulations (EC) No 109/2007 and (EC) No 156/2008. The second regulation establishes a withdrawal period of three days for the target species and provisional maximum residue limits (MRLs) of 25 μg monensin sodium kg⁻¹ skin/fat, and 8 μg kg⁻¹ liver, kidney and muscle.

The applicant proposes a reduction of the withdrawal period to one day for the above-mentioned target species and a modification of the MRLs status from provisional to final. The dossier supporting this application does not contain new studies.

EFSA also received a cross-reference letter from Elanco Animal Health concerning the reduced biological activity of some monensin metabolites and one study on the ¹⁴C-monensin residue decline and metabolism in broiler chickens. These data and study can be shared in the context of setting harmonised MRLs.

2. Maximum Residue Limits (MRLs)

In its previous opinion on MRLs for monensin sodium for chickens and turkeys (EFSA, 2006b), the FEEDAP Panel proposed 8 μg kg⁻¹ liver, kidney and muscle and 25 μg kg⁻¹ skin/fat as provisional MRLs. Those values were put into force for monensin sodium from Coxidin® by Regulation (EC) No 109/2007 and Regulation (EC) No 156/2008. These MRLs are already harmonised for the products Elancoban (Regulation (EC) No 108/2007) and Coxidin® (Regulation (EC) No 109/2007).

Those MRLs are also consistent with the analytical methods available. The most sensitive method showed a LOQ of 2.5 μg kg⁻¹ tissues (Chéneau et al., 2007). The lowest MRLs were about three times this LOQ, allowing the operational MRL to be at the level of the MRL.

The FEEDAP Panel does not see a possibility for further reduction of those MRLs and/or a change of their provisional character to a definitive status, until an improved analytical method (lower LOQ) is applied and consequently ratios of marker/total residue for the different withdrawal times and tissues could be established.

3. Toxicological relevance of total monensin residues in tissues

3.1. Pharmacological activity of monensin metabolites

Four (Donoho et al., 1982; Davison, 1984) and five monensin metabolites have been identified in chicken excreta and tissues. In chicken trials with labelled monensin only the parent molecule, and possibly the metabolite M2, exceeded 10 % of the total recovered radioactivity in liver. Chemically, the metabolites represent primarily O-demethylated and mono-, di- and tri-hydroxylated derivatives of the parent molecule. Decarboxylated and ketone derivatives are also found.

Donoho (1984) summarised the data on the biological properties of the metabolite M1, one of the six O-demethylated metabolites of monensin. It appeared that in a variety of biological

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6OJ L 31, 06.02.2007, p .6
7 OJ L 48, 22.2.2008, p. 14
8 Letter from Elanco Animal Health, 17 December 2007
The biological activity of the monensin metabolites M1, M2, M5 and M6 (generated by incubation of monensin in the presence of rat liver microsomes, then isolated and purified) were provided and are considered below.\(^{10}\)

### 3.1.1. Ionophoric properties

Monensin functions as mobile carrier for the metal cations in exchange for protons. This is the basis for establishing the ionophoric properties of monensin (Pressman, 1968) and other polyether antibiotics (Wong et al., 1971). Monensin inhibits by its ionophoric properties ATP hydrolysis in rat liver mitochondria, which can be measured by the reduction of the phosphate release from ATP (Estrada et al., 1968).

Using a modified assay of Estrada et al., the ionophoric activity of the metabolites M1, M2, M5 and M6 has been measured semi-quantitatively.\(^{10}\) All metabolites tested appeared to show lower ionophoric activity than the parent compound. However, the data varied widely. Triplicate determinations were available only for the various concentrations of monensin and M1. The results did not show clear dose-dependent effects of monensin and M1. As only single tests were provided for M2, M5, M6, a statistical evaluation could not be performed. M6 appeared to be the most active metabolite. Nevertheless, the authors of the study concluded that the ionophoric activity of the metabolites M1, M2, M5 and M6 could be estimated at < 5 %, < 10 %, < 10 %, and 10 % of that of monensin, respectively.

O-demethylation, decarboxylation and hydroxylation are common metabolic pathways for all polyether ionophoric compounds. Therefore, comparable results on reduced ionophoric activity of metabolites from related polyether antibiotic may support the above findings on monensin. The ionophoric activity of salinomycin metabolites (extracted from the liver of chickens) could be estimated to be approximately 20 % that of salinomycin, when using a \(^{86}\)Rb radiolabeled binding assay (Dimenna et al., 1989).

### 3.1.2. Non-extractable monensin related residues

Donoho et al. (1982) showed that the percentage of extractable monensin related residues in chicken liver decreased from approximately two-thirds (zero-day withdrawal) to less than one-third after a three-day withdrawal. The authors concluded also that the non-extractable radioactivity likely originates from monensin-derived \(^{14}\)C that has been extensively metabolised and incorporated into natural tissue components and is therefore not drug-related.

In a more recent study\(^{11}\) it could be shown that the non-extractable residues increase with the withdrawal time: in liver of male and female chicken from 37 and 39 % without withdrawal to 51 and 56 % after one-day withdrawal, in kidney from 52 and 40 % to 62 and 51 %, respectively. In the same study it could be shown that about 92 % of a radioactivity in the abdominal fat appeared to be associated to fatty acids.

In a recent opinion, EMEA concluded that ‘monensin represented approximately 2 % of the total radioactivity in milk. Approximately 26.5 % of the total radioactivity in milk was determined to be incorporated into endogenous fatty acids.’ (EMEA, 2007).

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Taken together, these findings constitute an additional safety factor when assessing consumer safety.

3.2. Conclusions

Given the present data on the ionophoric and other biological activities of monensin residues (metabolites), and considering the significant amount of structurally not drug-related (endogenous) residues, the former assessment of the FEEDAP Panel that ‘all the metabolites represent a risk which is at most equal to an equivalent quantity of monensin’ (EFSA, 2006a) should be re-evaluated.

Considering that

- monensin is only a minor part of the monensin residues,
- selected monensin metabolites show reduced biological activity compared to monensin,

and that after a one-day withdrawal period

- monensin structurally related metabolites represent only a fraction of the total residues,

the FEEDAP Panel concludes that, taking a weight of evidence approach, monensin-derived residues of toxicological relevance probably represent, as a conservative estimate, not more than 50 % of the total residues. This is in agreement with EMEA/CVMP opinion (EMEA, 2007).

4. Consumer safety

4.1. Re-assessment of human exposure

Based on the most recent total residue study for Coxidin® (EFSA, 2006b), human exposure after consumption of edible chicken tissues (according to Directive 2001/79/EC) was 0.206 mg day\(^{-1}\), based on the mean values plus the double standard deviation after a one-day withdrawal. After applying a 50 % reduction of the toxicological relevance of total residues, human exposure would be reduced to 0.103 mg day\(^{-1}\) (57 % of the ADI).

In its former opinion on MRLs for monensin in chickens and turkeys (EFSA, 2006b), the FEEDAP Panel showed that the proposed provisional MRLs for liver, kidney, muscle and skin/fat were in the range of the ADI (101 % of 0.18 mg per person). Table 2 shows the data given in the former opinion and introduces as a new element ‘the daily intake of total residues of toxicological relevance (modified DITR)’. Based on this new parameter, consumption of chicken edible tissues would now contribute to 51 % of the ADI. Similar conclusions apply for turkeys for fattening (EFSA, 2006b).

Table 2. Safety of the proposed MRLs for edible tissues from chickens fed Coxidin®

<table>
<thead>
<tr>
<th>Marker : Total residue</th>
<th>Liver (mg kg(^{-1}) tissue)</th>
<th>Kidney (mg kg(^{-1}) tissue)</th>
<th>Muscle (mg kg(^{-1}) tissue)</th>
<th>Skin/fat (mg kg(^{-1}) tissue)</th>
<th>Sum (mg day(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proposed MRL</td>
<td>0.008</td>
<td>0.008</td>
<td>0.008</td>
<td>0.025</td>
<td>0.050</td>
</tr>
<tr>
<td>Consumption (kg day(^{-1}))</td>
<td>0.100</td>
<td>0.010</td>
<td>0.300</td>
<td>0.090</td>
<td></td>
</tr>
<tr>
<td>DITR (mg day(^{-1}))</td>
<td>0.041</td>
<td>0.004</td>
<td>0.124</td>
<td>0.012</td>
<td>0.182</td>
</tr>
<tr>
<td>Consumption (% ADI)</td>
<td>23</td>
<td>2</td>
<td>69</td>
<td>7</td>
<td>101</td>
</tr>
<tr>
<td>Modified DITR (mg day(^{-1}))</td>
<td>0.021</td>
<td>0.002</td>
<td>0.062</td>
<td>0.006</td>
<td>0.091</td>
</tr>
<tr>
<td>Consumption (% ADI)</td>
<td>12</td>
<td>1</td>
<td>34</td>
<td>3</td>
<td>51</td>
</tr>
</tbody>
</table>

* the figures in both lines are calculated considering 50 % toxicological relevance of the total residues
4.2. Withdrawal time

Due to the lack of further data, the ratio marker to total residue used in Table 2 was derived from data at zero-day withdrawal (EFSA, 2006b). Monensin concentration in edible tissues at zero withdrawal time clearly exceeds the MRLs (Appendix). Therefore, a zero-day withdrawal time cannot be retained.

But the data obtained after one-day withdrawal (Appendix) were all below the MRLs. Therefore a one-day withdrawal time for Coxidin® for chickens and turkeys for fattening could be set.

CONCLUSIONS

No new data which would allow proposing a final instead of a provisional MRL for monensin in poultry tissue was provided.

All monensin metabolites tested (M1, M2, M5, M6) appeared to show lower ionophoric activity than the parent compound. These findings confirm the results of earlier studies. Comparable results on reduced ionophoric activity of the metabolites from a related polyether antibiotic support the above findings on monensin.

Non-extractable residues in chicken liver and kidney after a one-day withdrawal period amount to more than 50 % of the total residues. About 90 % of total radioactivity was associated with the abdominal fat in chicken for fattening. Data from dairy cows, taken for comparison because metabolic decarboxylation is a common pathway, indicate that about 25 % of the total residues in milk are attributed to fatty acids. The FEEDAP Panel concludes that a considerable part of the non-extractable residues is not drug-related.

The FEEDAP Panel, following a weight of evidence approach, concludes that monensin derived residues of toxicological relevance probably represent, as a conservative estimate, not more than 50 % of the total residues.

After applying a 50 % reduction of the toxicological relevance of total residue, the human exposure would amount to 0.103 mg day⁻¹ (57 % of the ADI). Based on the MRL values retained, the consumption of chicken edible tissues would contribute to 51 % of the ADI.

Recent marker residue data obtained after one-day withdrawal in chicken for fattening were below the MRLs. Therefore, a one-day withdrawal time for Coxidin® for chickens and turkeys for fattening could be set.

REMARK

Although a one-day withdrawal period is scientifically justified in terms of consumer safety, the FEEDAP Panel does not consider that the one-day withdrawal is a realistic option under feeding conditions applied to poultry in field.

DOCUMENTATION PROVIDED TO EFSA


REFERENCES


## APPENDIX

### Table I. Recent monensin residue values in chickens for fattening

<table>
<thead>
<tr>
<th>Withdrawal days</th>
<th>Liver</th>
<th>Kidney</th>
<th>Muscle</th>
<th>Skin/fat</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mg monensin kg⁻¹ tissue</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0.020</td>
<td>&lt;0.006</td>
<td>&lt;0.006</td>
<td>0.010</td>
<td>Coxidin®/Table 1 of EFSA 2006 – p5</td>
</tr>
<tr>
<td>0</td>
<td>0.015</td>
<td>&lt;0.006</td>
<td>&lt;0.006</td>
<td>0.012</td>
<td>Coxidin®/suppl info - OCT06</td>
</tr>
<tr>
<td>0</td>
<td>0.017</td>
<td>ND</td>
<td>0.006</td>
<td>0.049&lt;sup&gt;(a)&lt;/sup&gt;</td>
<td>Henri et al. 2006</td>
</tr>
<tr>
<td>0</td>
<td>0.015</td>
<td>0.019</td>
<td>0.026</td>
<td>0.033</td>
<td>Godfrey et al. 1997</td>
</tr>
<tr>
<td>1</td>
<td>&lt;0.006</td>
<td>&lt;0.006</td>
<td>&lt;0.006</td>
<td>&lt;0.006</td>
<td>Coxidin®/Table 1 of EFSA 2006 – p5</td>
</tr>
<tr>
<td>1&lt;sup&gt;(b)&lt;/sup&gt;</td>
<td>ND</td>
<td>ND</td>
<td>0.001&lt;sup&gt;(c)&lt;/sup&gt;</td>
<td>0.0018&lt;sup&gt;(d)&lt;/sup&gt;</td>
<td>Henri et al. 2006</td>
</tr>
<tr>
<td>3</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>Coxidin®/Table 1 of EFSA 2006 – p5</td>
</tr>
<tr>
<td>3&lt;sup&gt;(e)&lt;/sup&gt;</td>
<td>&lt;0.006</td>
<td>&lt;0.006</td>
<td>&lt;0.006</td>
<td>&lt;0.006</td>
<td>Coxidin®/suppl info - OCT06</td>
</tr>
<tr>
<td>3&lt;sup&gt;(f)&lt;/sup&gt;</td>
<td>ND</td>
<td>ND</td>
<td>&lt;0.003&lt;sup&gt;(c)&lt;/sup&gt;</td>
<td>&lt;0.003</td>
<td>Henri et al. 2006</td>
</tr>
</tbody>
</table>

(a) Fat  
(b) 23 hours  
(c) Average from five of six values  
(d) After one day withdrawal <0.006 mg kg⁻¹ for all tissues  
(e) Two days  
(f) 71 hours