



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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EMA/CVMP/60621/2018
Committee for Medicinal Products for Veterinary Use

European public MRL assessment report (EPMAR)

Isoflurane (porcine species)

On 30 July 2018 the European Commission adopted a Regulation¹ establishing maximum residue limits for isoflurane in porcine species, valid throughout the European Union. These maximum residue limits were based on the favourable opinion and the assessment report adopted by the Committee for Medicinal Products for Veterinary Use.

Isoflurane is intended for use in porcine species as a general anaesthetic when vaporized and administered by inhalation.

Maximum residue limits had previously been established for *Equidae*² (no MRL required classification). Baxter Deutschland GmbH submitted to the European Medicines Agency an application for the extension of maximum residue limits on 19 April 2017.

Based on the original and complementary data in the dossier, the Committee for Medicinal Products for Veterinary Use recommended on 15 March 2018 the extension of maximum residue limits for isoflurane to porcine species.

Subsequently the Commission recommended on 13 June 2018 that maximum residue limits in porcine species are established. This recommendation was confirmed on 4 July 2018 by the Standing Committee on Veterinary Medicinal Products and adopted by the European Commission on 30 July 2018.

¹ Commission Implementing Regulation (EU) No 2018/1076, O.J. L 194, of 31 July 2018

² Commission Regulation (EU) No 37/2010



Summary of the scientific discussion for the establishment of MRLs

Substance name: Isoflurane
Therapeutic class: Anaesthetic
Procedure number: EMEA/V/MRL/003647/EXTN/0002
Applicant: Baxter Deutschland GmbH
Target species: Porcine
Intended therapeutic indication: General anaesthesia of piglets during castration
Route(s) of administration: Inhalation

1. Introduction

Isoflurane is a liquid halogenated hydrocarbon used as a general anaesthetic when vaporized and administered by inhalation. In veterinary medicine, isoflurane is authorised for dogs, cats, ornamental birds, reptiles, rats, mice, hamsters, chinchillas, gerbils, guinea pigs, ferrets, rabbits, pigeons and horses in several member states of the EU. Isoflurane is also authorised for human use. In Switzerland, isoflurane is authorized for anaesthesia of piglets for early castration.

Isoflurane was previously assessed by the CVMP (see published MRL summary report EMEA/MRL/222/97-FINAL) and no ADI was established.

Currently isoflurane is included in Table 1 of the Annex to Commission Regulation (EU) No. 37/2010 of 22 December 2009 in accordance with the following table:

Pharmacologically active substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions	Therapeutic classification
Isoflurane	NOT APPLICABLE	<i>Equidae</i>	No MRL required	NOT APPLICABLE	For anaesthetic use only	NO ENTRY

An application has been submitted for the extension of isoflurane to porcine species. The proposed indication is anaesthesia of piglets during castration. The proposed minimum alveolar concentration (MAC) in oxygen for the target species is 1.2% to 2.0%. The MAC is the concentration of a volatile anaesthetic in the lungs that is needed to prevent movement in 50% of subjects in response to a surgical stimulus. The actual concentrations required depend on many variables including the simultaneous administration of other medicinal products and the clinical condition of the patient. For early castration in piglets, the highest intended dose is 5% in inspired gas. This equals the highest concentration currently authorized in Switzerland for anaesthesia of piglets for early castration. Treatment duration for purpose of early castration is not expected to exceed 2 minutes in the majority of cases.

2. Scientific risk assessment

2.1. Safety assessment

The CVMP previously considered the consumer safety of isoflurane as part of its evaluation of the application to establish MRLs in horses. The data available at that time did not allow establishment of

an ADI and, in making its recommendation, the CVMP took account of the fact that the proposed use in horses related to a small number of individual animals for infrequent and non-regular treatment. This contrasts with the use proposed in pigs, which is a major species and where regular use can be foreseen. Consequently, a reconsideration of the available safety data was considered necessary for the evaluation of the current extension application.

The current safety assessment used the published CVMP Summary report for isoflurane in horses as a starting point and updated this where additional information has become available since the CVMP's previous assessment of the substance.

2.1.1. Overview of pharmacological properties

Isoflurane acts as a central nervous system depressant, and depresses respiration as evidenced by an elevated blood CO₂ pressure.

In a non-GLP experiment in rats, isoflurane administered via the inhalation route at a dose level of 2% for 4 and 10 hours, induced no changes in urinary volume or osmolarity, but there was a slight increase in the mean peak serum inorganic fluoride levels. Mean peak serum inorganic fluoride levels were 6.5 µmole/l following 4 hours exposure and 7.3 µmole/l following a 10 hour isoflurane exposure. In a similar study, Fischer 344 male rats were anaesthetised with isoflurane (2%) for 4 hours. Maximum excretion of ionic fluoride in urine occurred in the first 24 hours post-anaesthesia whilst non-ionic fluoride peaked during the second 24 hours post-anaesthesia. Values returned to pre-anaesthetic levels on day 3 post-anaesthesia except for ionic fluoride which remained slightly elevated for a further period of two days. Thin layer Chromatography (TLC) examination of urine samples indicated that the non-ionic fluoride metabolite was trifluoroacetic acid. No pharmacokinetic parameters were presented in any of the studies.

A non-GLP metabolism study was carried out in 3 Hormel miniature pigs. Animals were exposed by inhalation to isoflurane concentrations ranging from 0.005% to 0.096% for either 20 or 24 hours. Results indicate non hepatic clearance.

Published data showed that isoflurane is defluorinated in adult horses after inhalation. In neonatal horses, isoflurane is not significantly metabolized after inhalation. In this study, isoflurane metabolism was measured in 8 adult and 13 neonatal horses. Adult horses exposed to isoflurane for 8.4 MAC*hours (MAC=1.31% in horses) had significantly elevated serum fluoride levels ($p < 0.0001$) with a mean peak level of 3.8 µmole observed 5 hours post-anesthesia. In these animals, serum fluoride levels returned to the normal values by 24 hours following the end of the exposure. Neonates exposed to 2.1 MAC*hours showed no significant change of serum fluoride levels.

Published data showed a similar pharmacokinetic behaviour for the volatile anaesthetics sevoflurane, halothane and isoflurane in pigs. The tissues/gas partition coefficients were similar and indicated a fat tissue affinity (fat/blood partition coefficient was 64 ± 9 , 51 ± 6 and 57 ± 9 respectively). Furthermore, elimination kinetics of sevoflurane and halothane were studied in rats. Data obtained showed an anaesthetic elimination (β -elimination) time constant for adipose tissue of 241 ± 53 and 246 ± 51 minutes for sevoflurane and halothane respectively. In horses serum fluoride levels returned to normal by 24 hours following the end of the exposure to isoflurane; this indicates that isoflurane behaves similarly to sevoflurane and halothane and it is rapidly eliminated.

Published human observations showed that systemic isoflurane is widely distributed in the tissue depending on perfusion and respective blood:tissue coefficients. For humans exposed to 1.65% (1.3*MAC) isoflurane for 130 minutes on average, the amount of absorbed isoflurane was reported to be 18.1 g, which represents approximately 16.2% of the estimated total amount of 112 g of inspired

isoflurane during treatment. Isoflurane is barely metabolized (0.2%) and 95% is exhaled unchanged. The main potentially hazardous metabolites are fluoride and trifluoroacetic acid. The pharmacokinetic characteristics in humans can be divided in three phases with average elimination half-lives of isoflurane as follows: 2.1 minutes (alveolar space), 19 minutes (well perfused organs like brain, liver, heart and kidney), and 233 minutes (muscle and adipose tissue).

The oral absorption of the metabolite trifluoroacetic acid is poor. Fluoride can be orally absorbed and accumulate in bone, teeth and the kidney, however, no accumulation in bone was observed after intraperitoneal administration of 2.8 g/kg isoflurane every three days over a period of 15 days in mice.

No oral or inhalation pharmacological studies in laboratory animals have been provided.

2.1.2. Calculation of pharmacological ADI , if relevant

No oral NOELs were available. A pharmacological LOEL was derived from inhalation studies with human volunteers by converting inhaled doses to systemic exposure in mg/kg bw per day (see section 2.1.7, below). It was conservatively assumed that systemic exposure via inhalation equated to potential exposure from an oral dose, as no information on oral bioavailability of isoflurane was available. Based on these estimates the inhalation LOEL identified (0.06%) would correspond to a systemic (oral) dose of 2.4 mg/kg bw. The resulting ADI is 0.048 mg/kg bw using a safety factor of 50 (a factor of 5 was used to take account of the fact that the starting point for the calculation was a LOEL and a factor of 10 was used to account for intraspecies variability). A higher safety factor was deemed unnecessary as the adverse effect was only slight at the LOEL (slight decrease of saccadic peak velocity). A slightly higher pharmacological NOEL (4.7 mg/kg bw) was observed in human volunteers following intravenous injection of isoflurane.

2.1.3. Overview of toxicology

The acute inhalation toxicity of isoflurane was determined in mice, rats and dogs in non-GLP studies. LC₅₀ values in mice after inhalation exposure (3 hours at isoflurane concentrations ranging from 0.83% to 1.89%) were 1.69% for males and 1.68% for females (at a temperature of 35°C). In rats, a similar study (3 hour period at an isoflurane concentration from 1.11% to 1.92%) was performed and LC₅₀ values for males were determined to be 1.88% and for females 1.53% at 23°C. At 35°C all tested animals (male or female) died at 1.72% isoflurane. A study was carried out in dogs after inhalation exposure of 2.25% alveolar concentration of isoflurane for a period of 4 hours. No significant adverse effects were observed. In mice (strain, age and weight not specified) the LD₅₀ value after intraperitoneal injection was 6.74 g/kg bw. No data on acute oral toxicity have been provided.

Toxicity after repeated inhalation exposure was investigated in mice, guinea pigs, rabbits, rats, dogs and monkeys. During a 9-week exposure period in mice (isoflurane concentration was 0.02, 0.1 and 0.5% for 4 hours per day), no significant effects on body weight, organ weight or histology (including the testis) were observed. In rats, no alterations were found in body, liver and kidney weights, serum glutamate oxaloacetate transaminase (GOT) and hematocrit, liver and kidney histological examination nor hepatic cytochromes (b₅ and P₄₅₀) after repeated administration of sub-anaesthetic dosages (less than 0.5%) for up to 30 weeks. A NOEL of 0.13% was established which corresponds to a converted oral (equals systemic) NOEL of 223 mg/kg bw per day. No significant effects were observed in guinea-pigs, dogs or monkeys after repeated inhalation administration (at dosages of 0.15%, 1-1.5% and 1-1.5%, respectively). No repeated dose oral toxicity studies have been provided.

Isoflurane did not show any significant adverse effects on female fertility or on foetal development when administered via the inhalation route in sub-anaesthetic dosage (up to 0.4% in mice and 1.6% in

rats). In the same studies, no significant adverse effects on male fertility in relation to female pregnancy rate and number of offspring were observed. However, a study administering low doses of isoflurane repeatedly via inhalation to rats (0.005%, 0.03%, 0.18% or 1.08% for 2 hours daily for 15 days) had effects on other male fertility parameters. A NOEL of 0.005% for 2 hours daily for 15 days can be retained based on decreased serum testosterone, decreased sperm count and changes in histopathology in the testes at higher doses. This corresponds to a converted oral (equals systemic) NOEL of 5.7 mg/kg bw per day. A male fertility study utilizing 0.0002% isoflurane (1 hour daily for 25 days in rats) is considered insufficient because of the inadequate study design. No reproductive oral toxicology studies have been submitted.

In a developmental toxicity study pregnant female mice were exposed to isoflurane by inhalation at doses of 0.006%, 0.06% and 0.6% for 4 hours per day on days 6 to 15 of pregnancy. Only the highest dose level reduced bodyweight in the dams, decreased skeletal ossification and increased the incidence of hydronephrosis. The higher concentration (0.6%) was also foetotoxic and maternotoxic. A NOEL of 0.06% was established which corresponds to a converted oral (equals systemic) NOEL of 199 mg/kg bw per day. Studies carried out in rats (not in GLP compliance) give reassurance that isoflurane is not teratogenic in this species. The NOEL for foetotoxicity was greater than 0.4% isoflurane. Teratology studies carried out in pregnant rabbits (2.28% to 2.34% isoflurane) did not show treatment-related effects. No data on the possible teratogenic effect of isoflurane by the oral route have been submitted.

Several series of Ames tests carried out with isoflurane (0.01-30%) indicated the lack of mutagenic activity. Negative results were also obtained in two more *in vitro* tests; a UDS assay in rat isolated hepatocytes, where isoflurane (0.005-0.500 mg/ml) did not produce any DNA damage and in a Syrian hamster embryo test where no cell transformation occurred using isoflurane (0.005 to 1 mg/ml).

Isoflurane (0.005 to 0.05% for 8 hours) was not mutagenic in two *in vivo* mutagenicity tests (chromosomal aberration in a Chinese hamster bone marrow test and mammalian spot test carried out in pregnant mice).

Furthermore, there are reports in the literature of several tests performed with isoflurane in Chinese hamster ovary and lung cells, and in human lymphocytes, where this compound did not increase the frequency of sister chromatid exchanges.

Recently conducted *in vitro* and *in vivo* COMET assay studies demonstrated positive results, indicating the possibility of transient DNA damage. An oral non-validated and non-standard *in vivo* micronucleus assay was available but the results were considered inconclusive and are therefore of limited relevance.

Considering the totality of available data from earlier and more recently conducted genotoxicity studies, based on a weight of evidence it can be concluded that isoflurane has no potential to cause lasting mutagenic effects.

A carcinogenicity study in mice was inadequate because the treated and control mice were treated differently, control animals were from different experiments and the feed was contaminated. In a second study, groups of 82-90/sex/dose Swiss Webster mice were used. They were exposed (inhalation) 4 hours per day, 5 days per week for 78 weeks with 0-0.4% isoflurane. The highest concentration corresponds to a converted oral (equals systemic) NOEL of 1343 mg/kg bw per day. No dose-related trend in the incidence of any tumor type was detected. A third carcinogenicity study in rats was well conducted and reported. The exposure schedule was 6 hours per day, 5 days per week with isoflurane concentrations up to 0.1% for a minimum of 104 consecutive weeks. The highest concentration corresponds to a converted oral (equals systemic) NOEL of 343 mg/kg bw per day. There was no evidence to suggest any influence of isoflurane on the incidence of any tumor type at inhaled

concentrations less than or equal to 0.1%. The negative data in a carcinogenicity study in mice and in the study in rats indicate that isoflurane does not have carcinogenic potential.

No studies have been carried out with isoflurane to show potential immunotoxicity. However, in the case of this compound, these studies are not necessary because no evidence of immune system damage has been reported in the literature.

2.1.4. Calculation of the toxicological ADI or alternative limit

An overall toxicological NOEL was derived from inhalation studies via systemic dose extrapolation. A toxicological ADI of 0.057 mg/kg bw was established by applying a safety factor of 100 to the NOEL on male fertility of 5.7 mg/kg bw in adult rats (0.005% inhalation for 2 hours daily). An additional safety factor to take account of the fact that the study was sub-acute rather than chronic was deemed not necessary due to the fact that histopathological changes in testes were not observed in mice after exposure to higher doses for 9 weeks and no adverse histopathology of the testes was observed in a GLP carcinogenicity study in rats, treated for 104 weeks.

2.1.5. Overview of microbiological properties of residues

No studies have been carried out with isoflurane to show any potential alteration in the human gut flora. However, isoflurane is not expected to possess antimicrobial properties and consequently these studies are not necessary.

2.1.6. Calculation of microbiological ADI

As the substance is not expected to possess antimicrobial activity the establishment of a microbiological ADI is not considered necessary.

2.1.7. Observations in humans

In human medicine, isoflurane has been extensively used as a general inhalation anaesthetic agent for more than 15 years. During the use of isoflurane no significant toxic effects have been reported in patients or operating theatre personnel. There was no evidence of association between exposure to isoflurane and liver damage or other organ damage in humans. The duration of the pharmacological activity in humans after the end of isoflurane exposure is very short (15-25 minutes).

Studies have suggested a relationship between isoflurane anaesthesia and Alzheimer's disease, however, there was no evidence for any adverse effects at doses without pharmacological effect.

In a volunteer study healthy volunteers were exposed to 0.1, 0.2 and 0.4 MAC (1 MAC = 1.15%) isoflurane for 10 minutes. Even at the lowest concentration of 0.1 MAC, the volunteers' reactions to commands were impaired in the submitted study. The corresponding extrapolated oral NOEL is 3 mg/kg bw. In another volunteer study a LOEC of 0.06% after 15 minutes of isoflurane exposure was retained in volunteers, who had a decreased saccadic peak velocity. The corresponding extrapolated oral LOEL is 2.4 mg/kg bw. Furthermore, a clinical study using emulsified isoflurane administered intravenously was submitted showing an apparent NOEL of 4.7 mg/kg bw, based on neurofunctional effects.

2.1.8. Findings of EU or international scientific bodies

The only relevant evaluation of isoflurane by EU or international scientific bodies are the summary report EMEA/MRL/222/97-FINAL already mentioned and a report from the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals of 2009, which provides an extensive review of available pharmacology and toxicology data for isoflurane, sevoflurane and desflurane to be used by regulatory authorities as scientific basis for setting occupational exposure limits.

In addition, EFSA has set a tentative ADI of 0.05 mg/kg bw for trifluoroacetic acid and an upper intake level of 0.12 mg/kg bw per day for fluoride.

2.1.9. Overall conclusions on the ADI

A pharmacological ADI of 0.048 mg/kg bw (i.e. 2.88 mg/person) was established from a LOEL in humans, where the effect seen was a slight decrease of saccadic peak velocity.

A toxicological ADI of 0.057 mg/kg bw was established based on effects on male fertility.

A microbiological ADI was not established as the substance is not expected to possess antimicrobial activity.

The overall ADI is established as the pharmacological ADI of 0.048 mg/kg bw (i.e. 2.88 mg/person).

2.2. Residues assessment

No original data were provided but literature data covering the metabolism and residue kinetics of isoflurane were available.

2.2.1. Pharmacokinetics in target species

Limited published literature on non-GLP compliant pharmacokinetic studies in the target species pig as well as in other species were available.

Gaseous isoflurane is readily absorbed by inhalation in pigs but only a fraction of the inhaled isoflurane is retained in the body. The percentage absorption of inhaled isoflurane in piglets is not known. No information regarding other exposure routes was available for pigs.

After inhalation, isoflurane is systemically available and distributed rapidly in the body to different tissues via blood perfusion. The blood/gas partition coefficient for pigs is approximately 1.0. Mean tissue/blood partitioning coefficients for pig tissues were in the range of 1.6 to 2.4 with the exception of fat tissue for which a mean tissue/blood partitioning coefficient of 57 was determined. The high affinity for fat might lead to deposition of isoflurane in adipose tissue.

Limited data regarding metabolism in the target species indicates minor hepatic isoflurane metabolism (approximately 0.2%). Isoflurane treatment can lead to increased plasma levels of inorganic fluoride in pigs. Trifluoroacetic acid is another metabolite known to result from biotransformation of isoflurane in other species and may also occur in the target species. Hepatic metabolism of isoflurane is likely due to microsomal cytochrome P450.

Pharmacokinetic elimination characteristics of isoflurane following exposure in pigs of 20 kg bw receiving 0.4% isoflurane for 30 minutes was described as a five-compartment elimination model (on the basis of exhalation data). Elimination via the lungs occurred rapidly with 95.8% and 97.6% of initially retained isoflurane in the alveoli eliminated within 30 minutes and 60 minutes after end of

treatment, respectively. Elimination half-life times ($t_{1/2}$) derived from the five-compartment elimination model were in the range of 0.219 minutes up to 950 minutes for the 1st and 5th compartment, to which the lungs and fat tissues were assigned, respectively. Therefore, although initial elimination of isoflurane is rapid, elimination of residual isoflurane in the body is likely to be limited by deposited isoflurane in fat tissue.

2.2.2. Residue depletion studies

No residue depletion studies were available.

An estimate of possible isoflurane residues in treated piglets was derived by worst-case estimates using available pharmacokinetic parameters. Results of this calculation were used to conclude on possible consumer exposure (see section 3.3, below).

Selection of marker residue and the ratio of marker to total residues

A “No MRL required” classification is intended and therefore identification of a marker residue or the ratio of marker to total residues is not necessary.

2.2.3. Monitoring or exposure data

No monitoring or exposure data other than that described elsewhere in this report were available.

2.2.4. Analytical method for monitoring of residues

A “No MRL required” status has been proposed and, in line with this, no analytical method for monitoring of residues is presented.

2.2.5. Findings of EU or international scientific bodies

No relevant evaluations by EU or international scientific bodies were identified.

3. Risk management considerations

3.1. Potential effects on the microorganisms used for industrial food processing

As the substance is not expected to possess antimicrobial activity no effects on microorganisms used for industrial food processing are expected.

3.2. Other relevant risk management considerations for the establishment of maximum residue limits

The intended use of isoflurane in porcine species is for anaesthesia of piglets for early castration. This would result in a potentially wide use in a major species while the treated animals are unlikely to be sent to slaughter immediately after treatment.

Isoflurane is a highly volatile compound likely to evaporate from food derived from treated animals during storage and processing like cooking.

Up to now, there are no inhalation anaesthetics authorised for the use in piglets. No other relevant factors were identified for consideration of the risk management recommendations.

3.3. Elaboration of MRLs

Potential consumer exposure to residues of isoflurane in edible tissues of treated piglets was estimated based on the highest intended dose and an elimination model utilizing pharmacokinetic parameters derived in pigs (as referred to in section 2.2.1). Seven day old piglets (2.5 kg bodyweight) were assumed to be exposed by inhalation for 5 minutes with 5.0% (corresponding to about 384 mg/l) isoflurane in inhaled air. Considering a respiration rate of 20 breaths per minute, a tidal volume of 10 ml/kg bw per breath, and an inhalation bioavailability of 20%, the absorbed amount of isoflurane was estimated to be 192 mg (corresponding to 76.8 mg/kg bw). Based on pharmacokinetic modelling it was assumed that 95% of absorbed isoflurane was exhaled within the initial 30 minute period after end of treatment followed by elimination according to a log-linear function with the longest (worst-case) half-life of 950 minutes. Hence, the residual amount of isoflurane was calculated to be 5.80 mg and 3.43 mg per piglet at withdrawal times of 12 hours and 24 hours, respectively (corresponding to 2.32 mg/kg bw and 1.37 mg/kg bw, respectively). The theoretically possible residue intake by consumers (60 kg bw) was calculated assuming either (i) even distribution of isoflurane within the whole piglet and a daily consumption of 500 g meat, or (ii) deposition of residual isoflurane in adipose tissue (considering the body fat content to be approximate 5%) and a daily consumption of 50 g fat. For exposure scenario (i), the calculated potential intake was 1.16 mg/person (0.019 mg/kg bw) and 0.69 mg/person (0.012 mg/kg bw) at the 12 hour and 24 hour time point, respectively. In exposure scenario (ii), the calculated intake amounts were 2.32 mg/person (0.039 mg/kg bw) and 1.37 mg/person (0.023 mg/kg bw) at the 12 hour and 24 hour time point, respectively. All scenarios showed results below the overall ADI of 0.048 mg/kg bw with an intake of approximately 80% of the ADI for the most conservative calculation.

In addition, an exposure estimate for residues of the metabolites, inorganic fluoride and trifluoroacetic acid, in tissues was made assuming 0.2% of absorbed isoflurane in piglets is metabolised. For both metabolites estimated theoretical exposure from consumption of food derived from treated piglets is below 2% of the respective health based reference values reported in section 2.1.8.

Based on the above calculations exposure to residues of isoflurane from treated piglets slaughtered within the first day post treatment is not considered to represent a risk for the consumer. This is a worst case exposure scenario as, in reality, piglets are unlikely to be slaughtered so soon after treatment. Furthermore, isoflurane is a highly volatile compound and so is likely to evaporate during storage and processing, which may further reduce the residues in animal derived food.

In light of the above, a "No MRL required" classification is considered appropriate in piglets. However, as the exposure calculations relate specifically to inhalation treatment of piglets, a restriction on the route of administration and the age of the animals is recommended in order to ensure that consumer exposure remains within the bounds of the above calculations. In addition, in relation to use in *Equidae*, the restriction 'for anaesthetic use only' is not considered necessary from a consumer safety perspective. It is considered that a restriction on the route of administration would be more appropriate and would result in harmonised wording for horses and piglets. This suggested change to the entry for *Equidae* does not represent a change in the scientific evaluation of isoflurane for use in *Equidae*.

3.4. Considerations on possible extrapolation of MRLs

In line with Article 5 of Regulation (EC) No. 470/2009 the CVMP considered the possibility of extrapolating the maximum residue limits recommended for porcine species to other food producing species and commodities, taking into account the provisions laid down in Regulation (EU) 2017/880.

However, as the recommendation for a “No MRL required” status for this application is based on species-specific pharmacokinetic data and consumer exposure scenarios related to conditions used in anaesthesia of piglets for purpose of early castration, an extrapolation to other age groups and species cannot reliably be assessed.

3.5. Conclusions and recommendation for the establishment of maximum residue limits

Having considered that:

- isoflurane is intended for the use as inhalation anaesthetic during early castration in piglets at a limited dose and for a limited duration of treatment,
- a pharmacological ADI of 0.048 mg/kg bw (i.e. 2.88 mg/person) was established as the overall ADI for isoflurane,
- inhaled isoflurane is only partly absorbed and most of the isoflurane dose is rapidly eliminated via exhalation, mostly in unchanged form,
- no residue depletion study for isoflurane is available but an estimate of possible consumer exposure based on model calculations showed that residues in excess of ADI are unlikely to occur, even if animals are slaughtered on the day of treatment,
- isoflurane is a highly volatile compound likely to evaporate during storage and processing, which may further reduce the residues in animal derived food,

The Committee concludes that the establishment of maximum residue limits for the use of isoflurane in porcine species for purpose of early castration is not necessary for the protection of human health, and therefore recommends the extension of maximum residue limits for isoflurane from *Equidae* to porcine species and the amendment of the entry in table 1 of the Annex to Regulation (EC) No 37/2010 in line with the following table:

Pharmaco-logically active substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions	Therapeutic classification
Isoflurane	NOT APPLICABLE	<i>Equidae</i>	No MRL required	NOT APPLICABLE	For use by inhalation	General anaesthetics
		Porcine	No MRL required	NOT APPLICABLE	For use by inhalation in piglets up to 7 days of age.	

Based on a worst case consumer exposure calculation exposure to isoflurane residues will remain below 80% of the ADI even if piglets are slaughtered on the day of treatment.

4. Background information on the procedure

Submission of the dossier

19 April 2017

Steps taken for assessment of the substance

Application validated:	10 May 2017
Clock started:	11 May 2017
List of questions adopted:	7 September 2017
Consolidated response to list of questions submitted:	13 December 2017
Clock restarted:	18 December 2017
CVMP opinion adopted:	15 March 2018