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Risk assessment of lidocaine residues in food products from cattle, swine, sheep and goats: withdrawal periods for meat and milk

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Risk assessment of lidocaine residues in food products from cattle, swine, sheep and goats: withdrawal periods for meat and milk

1 Summary

The Norwegian Food Safety Authority (Mattilsynet) has asked The Norwegian Scientific Committee for Food Safety (VKM) to complete a risk assessment of whether the withdrawal periods of milk and meat after use of lidocaine in cattle, swine, sheep and goat, as recommended by the Norwegian Food Safety Authority, could be shortened. The assessment should consider human risk as well as animal welfare aspects.

Lidocaine, a local-regional anaesthetic agent, is currently recommended to be used for local-regional anaesthesia in food producing animals. In humans, lidocaine is primarily used for local anaesthesia in a variety of indications.

To guarantee a high level of consumer protection, the toxicity of potential drug residues have to be evaluated before the use of a medicinal substance in food producing animals is authorised. The Committee for Veterinary Medicinal Products (CVMP) at the European Agency for the Evaluation of Medicinal Products (EMEA) is the body responsible for the risk assessment of veterinary medicinal products in the European Union (EU). In accordance to the EEA agreement, Norway has implemented the same legislation for residues of veterinary medicinal products as the EU Member States. EMEA completed a risk assessment of lidocaine residues in 1999 and recommended inclusion of lidocaine in Annex II for horses. In absence of adequate metabolism data, inclusion could not be made for other food animal species.

The use of adequate and appropriate anaesthesia when performing surgery on domestic animals is necessary and required by law. If a veterinary drug is recommended for at least one animal species, this drug may be used in other food producing animal species to prevent unacceptable suffering for animals due to lack authorized veterinary medicinal products for the relevant animal species. If no withdrawal periods are set for this drug for the animal species in question, the minimum withdrawal period would be 7 days for milk and 28 days for meat. The withdrawal periods of milk and meat presently recommended by the Norwegian Food Safety Authority following use of lidocaine in other food animals than horses are 7 and 28 days, respectively.

Alternative anaesthetic agents to lidocaine include only procaine and xylazine. Compared to lidocaine procaine has lower potency and slower onset as well as shorter duration and causes more side-effects. Xylazine is a veterinary sedative-analgesic drug, but the analgesic effect is insufficient for any type of surgical procedure in any species of animal. The Norwegian Scientific Committee for Food Safety is therefore of the opinion that there are no relevant alternatives to the use of lidocaine as a local anaesthetic in food producing animals.

It is acknowledged that the lidocaine metabolite, 2,6-xylidine, is a critical metabolite in regard to human health safety as 2,6-xylidine is shown to be a nasal carcinogen in rat and is classified as a potential carcinogen in man. Few data are available regarding the pharmacokinetic and toxicology of lidocaine in food producing animals. In addition, a substantial part of the cited studies are old and thus carried out with non-GLP methods.

As a NOEL and consequently an ADI could not be established for lidocaine, alternative methods for the evaluation of human health safety after ingestion of food containing residues

of the lidocaine metabolite 2,6-xylidine were considered. In a new draft document from the Scientific Committee of the European Food Safety Authority (EFSA) margin of exposure (MOE) is suggested as a new approach for harmonising risk assessment for compounds that have both genotoxic and carcinogenic properties. The EFSA Scientific Committee is of the opinion that a MOE of a magnitude of 25000 or higher, if based on T25, would be of low health risk and might be viewed as low priority for risk management. The Norwegian Scientific Committee for Food Safety is of the opinion that the MOE approach, suggested by EFSA, can be used for the risk characterisation of 2,6-xylidine.

The usage of lidocaine in food producing animals is calculated on the basis of data on numbers of relevant disease cases in food animals in 2004 for which lidocaine could have been used. Such data were collected primarily from the Norwegian animal health recording systems.

As it is the lidocaine metabolite 2,6-xylidine which seems to be the critical substance with regard to human health safety and few data as regards the metabolism of lidocaine in the target animal species is published, a worst case scenario would be that all lidocaine calculated to have been administered in the target animal species in 2004 is metabolised to 2,6-xylidine on a molar basis.

The calculations of average daily intake of 2,6-xylidine residues from food products derived from exposed animals are based on the following:

- All cases (indications) likely to have had lidocaine administered prior to local surgery in 2004 were originally included in the assessment (to enable validation of the data), however,
- All cases for which the carcasses, due to economic reasons (e.g., transport costs), were unlikely to be delivered (e.g., castrated piglets and dehorned calves) for human consumption after euthanization for animal welfare reasons were excluded from the final assessment
- The lidocaine dosages used for the assessment are the assumed maximum dosage for the various indications
- For dairy cattle and dairy goats the total amount of 2,6-xylidine is assumed to be localized in the milk at the time of milking
- It is assumed that the exposed milk was diluted in the total volume of milk produced in Norway in 2004, as the milk from every dairy farm is regularly mixed with milk from many other dairy farms
- For animals for which the carcass could be delivered for human consumption after emergency slaughter the total amount of 2,6-xylidine is assumed to be localized in the edible tissue at the time of slaughtering
- It is assumed that exposed meat was “diluted” in the total amounts of meat of the relevant animal species, produced in Norway during 2004, as it is highly improbable that one person would consume meat only from exposed animals on a daily basis
- The cases for which lidocaine could have been used in food animals are assumed to occur randomly throughout the country as well as throughout the year

The Norwegian Scientific Committee for Food Safety is of the opinion that:

- The use of adequate and appropriate anaesthesia when performing surgery on domestic animals is necessary. There are no relevant alternatives to the use of lidocaine as a local anaesthetic in food producing animals.
- The lidocaine metabolite 2,6-xylidine, which is classified as a potential carcinogen in man, is the critical metabolite with regard to human health safety.
- Few data are available regarding the pharmacokinetics of lidocaine and particularly as regard the formation of 2,6-xylidine in food producing animals. However, lidocaine and the metabolite 2,6-xylidine are assumed to be rapidly excreted.
- Any intake of 2,6-xylidine through consumption of food following use of lidocaine in goat and sheep is highly improbable, while intake of this substance may occur through consumption of cow milk, beef and pork
- It is unlikely that the estimated daily average intake (worst-case scenario) of 2,6-xylidine ('lidocaine') from milk and meat produced in Norway would cause any hazard to human health. In experimental animals only a minor fraction of lidocaine is metabolized to 2,6-xylidine. The MOE approach has been used for the risk characterization of 2,6-xylidine ('lidocaine') and all estimated MOEs are above 25000.
- The amount of 2,6-xylidine in milk from exposed animals, as presented to the consumers, is likely to be insignificant shortly after administration of lidocaine.
- The amount of 2,6-xylidine in meat from an exposed animal is likely to be insignificant 24 hours after administration of lidocaine.

Conclusion: The current withdrawal periods of milk (7 days) and meat (28 days) after use of lidocaine in cattle, goats, swine and sheep, can be shortened.

2 Background

2.1 CLINICAL USE OF LIDOCAINE

2.1.1 VETERINARY MEDICINE

Lidocaine (hydrochloride) is a water-soluble local-regional anaesthetic agent. In Norway, this drug is currently recommended to be used for local-regional anaesthesia in food producing animals. Injectable lidocaine preparations for use in animals in Norway are prescription drugs only and have to be administered by a qualified veterinarian. Lidocaine is used as a sterile aqueous solution in cattle, horses, swine, goats and sheep prior to surgery for low and high epidural anaesthesia (cattle), local anaesthesia (cattle, horses, sheep, goats, swine) and regional anaesthesia (horses, cattle). Generally, lidocaine is administered as a single treatment prior to surgical procedures.

2.1.2 HUMAN MEDICINE

In humans, lidocaine is primarily used for local anaesthesia in a variety of indications and the injected dosage range varies between 10-600 mg per individual. The maximum lidocaine dosage recommended for local anaesthesia in children is 5 mg/kg (Tørisen, 2005). Generally, lidocaine is administered as a single treatment prior to surgical procedures. Lidocaine is also marketed as topical ointment. Furthermore, lidocaine is marketed as non-prescription preparations for rectal administration and the recommended daily dosage of these formulations is in the range of 60 mg–200 mg and is usually administered for many days and sometimes also for weeks. None of the abovementioned lidocaine formulations are contraindicated in pregnancy, in breast-feeding women or in children (Tørisen 2005). Lidocaine is also occasionally used as an anti-arrhythmic drug in humans.

2.2 REGULATION OF RESIDUES OF VETERINARY MEDICINAL PRODUCTS IN FOOD

Residues of a veterinary medicinal product, which remain in foodstuffs obtained from animals to which the veterinary medicinal product in question has been administered, may consist of the parent substance and/or their metabolites.

2.2.1 LEGISLATION

To guarantee a high level of consumer protection, the toxicity of potential drug residues has to be evaluated before the use of a medicinal substance in food-producing animals can be authorized. The Committee for Veterinary Medicinal Products (CVMP) at the European Medicines Agency (EMEA) is the body responsible for the risk assessment of veterinary medicinal products in the European Union (EU).

The risk assessment of drug residues in food for human consumption includes three critical evaluations and decisions: 1) determination of an acceptable daily intake (ADI) for consumption of residues for the life span of an individual; 2) maximum residue limits (MRL) (if considered necessary) allowable in all edible foodstuffs derived from treated animals to be consumed by humans such that the ADI is not exceeded and 3) withdrawal times needed after

the drug is administered for residues to fall below the MRLs, so animals may be slaughtered for subsequent processing and consumption and safely consumed.

The ADI is determined as a conservative estimate of the safety ingestion levels by the human population and is based on the lowest "no (adverse) effect level" (NOEL) which is the highest dose that produces no untoward effect in the exposed animals. A human health protective level is calculated by dividing the NOEL by an uncertainty factor that may be either 100 or 1000, depending on the circumstances, to compensate for various uncertainties in risk estimation (e.g., extrapolation of animal model data to humans).

In accordance to the EEA agreement, Norway has implemented the same legislation for residues of veterinary medicinal products as the EU Member States (Council Regulation (EEC) No. 2377/90 with amendments).

MRL is defined as the maximum concentration (expressed in mg/kg or µg/kg on a fresh weight basis) of a residue resulting from the use of a veterinary medicinal product, which may be accepted as legally permitted or recognized as acceptable in a food product.

Annex I-IV in the Regulation (No. 2377/90) refers to lists of substances that have been evaluated:

- Annex I: The list of pharmacologically active substances used in veterinary medicinal products for which maximum residue limits have been established.
- Annex II: The list of pharmacologically active substances used in veterinary medicinal products where evaluation indicates that it is not necessary for the protection of public health to establish a maximum residue limit.

The NOEL-uncertainty factor approach is not applicable to non-threshold effects. In such cases the applicant must propose and justify an alternative approach to the safety evaluation of residues, taking into account the assessment of the benefits and risks of the product as a whole (http://pharmacos.eudra.org/F2/eudralex/vol-8/pdf/Vol8rev0Final_11June2001.pdf, accessed 12 May 2005). In such cases, an alternative approach to safety evaluation is applied on a case-by-case basis, considering all the data available. In special cases, it may be possible to justify the entry of a substance into Annex II of Regulation (EEC) 2377/90, even in the absence of a safety limit, if the quality of the full package of data is sufficient to ensure that there is no risk to human health.

- Annex III: The list of pharmacologically active substances used in veterinary medicinal products for which provisional maximum residue limits have been established.

- Annex IV: The list of prohibited substances.

With effect from 1 January 2000, the administration to food producing animals of veterinary medicinal products containing pharmacologically active substances, which are not placed in Annexes I, II or III, are prohibited.

In Directive 2001/82/EC regarding Community code relating to veterinary medicinal products, it is stated in article 10:

"Where there is no authorized medicinal product for a condition, Member States may exceptionally, in particular in order to avoid causing unacceptable suffering to the animals concerned, permit the

administration by a veterinarian or under his/her direct personal responsibility to an animal or to a small number of animals on a particular holding:

(a) of a veterinary medicinal product authorized …. for use in another animal species, or for another condition in the same species; or…"

This implies that if a veterinary drug is placed in Annex I, II or III for at least one animal species, this drug may be used in other food producing animal species. Minimum withdrawal period would be 7 days for milk and 28 days for meat.

The purpose of article 10 is primarily to prevent unacceptable suffering to animals due to lack of MRL authorized veterinary medicinal products for the relevant animal species.

It is the producer of a pharmaceutical preparation that is responsible for applying for the establishment of MRLs for the actual substance. Some veterinary medicinal preparations, even though they have been used for years, may not have been placed in any of Annexes I-III or only for one or a limited number of animal species. The reason for this would be that the holder of the preparation has not applied for an MRL establishment, or that the documentation for the actual substance is insufficient for the recommendation for such a placement. This may be the case for old substances where the patent period has expired or for preparations with low turnover (low profit). Lidocaine would fall into this category.

2.2.2 MRL-EVALUATION COMPLETED BY EMEA

EMEA completed a risk assessment of lidocaine residues and the summary report was published in 1999 (http://www.emea.eu.int/pdfs/vet/mrls/058499en.pdf, accessed 9 March 2005). This report contains the following conclusions and recommendations:

"Having considered that:

- lidocaine is used in a small number of individual animals only, for infrequent and non-regular treatments
- the animals are unlikely to be sent for slaughter during or immediately after treatment,
- lidocaine is rapidly metabolized and extensively excreted in horses,
- in absence of adequate metabolism data on animal species other than horses, no recommendation could be made for other target species

the Committee for Veterinary Medicinal Products (CVMP), European Agency for the Evaluation of Medicinal Products (EMEA) concludes that there is no need to establish a MRL for lidocaine and recommends its inclusion in Annex II of council Regulation (EEC) No. 2377/90 for use in horses. "

In the summary report it was concluded that the data provided by the applicant were insufficient to derive a NOEL and consequently, ADI and MRL values could not be determined.

The risk assessments completed by EMEA are usually based on data provided by the pharmaceutical industry, in the present case by the international animal health industry (FEDESA). The lidocaine evaluation did not include all the relevant published data, e.g., on metabolism and excretion of lidocaine and its metabolites. Furthermore, EMEA's risk assessment did not include a quantitative exposure characterization.

2.2.3 CURRENT WITHDRAWAL TIMES

For the lidocaine preparation approved for local-regional anaesthesia in horses in Norway, the Norwegian Medicine Agency recommends elimination of the injection site, liver and kidney if the horse is slaughtered within 24 hours after administration of the drug. This recommendation applies for corresponding preparations produced by authorized Norwegian pharmacies. The withdrawal periods of milk and meat presently recommended by the Norwegian Food Safety Authority following use of lidocaine in other food animals than horses are 7 and 28 days, respectively. This is in accordance with the EU-directive 2001/82/EF.

2.3 ALTERNATIVE ANAESTHETIC AGENTS

Only anaesthetic agents included in Annex I, II or III might be alternatives to lidocaine; presently this includes procaine and xylazine.

2.3.1 PROCAINE

Procaine (p-aminobenzoyl-diethylaminoethanol) is a water-soluble local anaesthetic, which was previously used in veterinary medicine. Procaine is an aminoester, whereas lidocaine is an aminoamid. Aminoesters (e.g., procaine, tetracaine) are hydrolyzed rapidly in plasma by pseudocholinesterases. Aminoamids (e.g., lidocaine) are metabolized in the liver. Procaine is included in Annex II of council Regulation (EEC) No. 2377/90 for all food producing animals (http://www.emea.eu.int/pdfs/vet/mrls/021797en.pdf, accessed 7 March 2005).

Compared to lidocaine this substance has lower potency and slower onset as well as shorter duration and causes more side effects. Furthermore, the tissue penetration of this drug is poor. Procaine has a short duration of action because of rapid hydrolysis by pseudocholinesterases (Thurmon et al 1996). The duration of action may be increased 45-90 minutes if adrenaline is added (http://www.emea.eu.int/htms/vet/mrls/m-rmrl.htm, accessed 5 April 2005). Contraindications for the use of procaine are intravenous, intra-articular and epidural anaesthesia (Bishop 2001).

In the body, procaine is hydroxylated to the metabolite para-aminobenzoic acid (PABA), which inhibits the action of sulphonamides. Concurrent sulphonamide treatment is listed as a contraindication to the use of procaine (Bishop 2001). The PABA metabolite is the likely cause of allergic side effects observed in humans.

2.3.2 XYLAZINE

Xylazine is a veterinary sedative-analgesic drug included in Annex II of council Regulation (EEC) No.2377/90 for cattle and horses (http://www.emea.eu.int/pdfs/vet/mrls/083602en.pdf accessed 12 May 2005). The approved withdrawal periods for milk and meat after use of xylazine are 0 days and 1 day, respectively. Xylazine can be administered systemically, and high doses will cause profound sedation and analgesia. However, the analgesic effect is insufficient for any type of surgical procedure in any species of animal (Thurmon et al 1996).

3 Terms of reference

The Norwegian Food Safety Authority (Mattilsynet) has asked The Norwegian Scientific Committee for Food Safety (VKM) to complete a risk assessment on whether the withdrawal periods of milk and meat after use of lidocaine in cattle, swine, sheep and goats, as recommended by the Norwegian Food Safety Authority, could be shortened. The assessment should consider human risk as well as animal welfare aspects.

4 Animal welfare aspects

In Norway, the Animal Welfare Act (§ 7) requires that a veterinarian completes the surgery and decides the need for total or partial anaesthesia if the medical treatment or surgery will cause the animal pain and suffering. The animal welfare aspects of the present assessment are described on the assumption that every part of the legislation is obeyed, and that no animal suffers unnecessarily.

4.1 PAIN IN ANIMALS

Higher vertebrates have a highly developed nerve system and a well-developed brain, and are assumed to be conscious of pain. Afferent nerve fibres enter the spinal cord through the dorsal root, where further processing of the signals takes place. Sensory information relevant to pain sensation is transmitted through specific pathways to distinct areas of the brain such as the thalamic region and reticular system. From here onward the information is relayed to the sensory cortex of the brain where the conscious experience takes place (Hellebrekers 2000). If an animal is unconscious it cannot feel pain, although lower levels of the nervous system will still detect noxious stimuli.

4.2 ANAESTHESIA

The term anaesthesia is used to describe the loss of sensation to the entire or any part of the body. Analgesia refers to freedom from or absence of pain (Thurmon et al 1996). In humans, as well as in animals, a balanced total anaesthesia should result in unconsciousness, analgesia, and muscle relaxation.

Since pain perception is well developed in mammals, e.g., cattle, swine, sheep and goats, anaesthesia is mandatory when performing surgery.

Local or regional anaesthesia is a preferred anaesthetic method in food-producing animals. Many surgical procedures are performed safely and humanely using a combination of physical restraint, mild sedation and local or regional anaesthesia. The techniques should provide loss of pain to a limited body area with minimal effects on other organ systems. The standing position is optimal for several surgical procedures in ruminants as it reduces problems associated with accumulation of gas in the rumen, salivation, recumbence related regurgitation, and nerve or muscle damage (Thurmon et al 1996).

Local anaesthetics, such as lidocaine, block the impulse transmission in the nerve cells by blocking of the sodium (Na^+) channels, thereby preventing the action potentials from being formed.

It is concluded that the use of adequate and appropriate anaesthesia when performing surgery on domestic animals is necessary.

4.3 CONCLUSION

The use of adequate and appropriate anaesthesia when performing surgery on domestic animals is necessary and required by law.

There are no relevant alternatives to lidocaine as a local anaesthetic in food producing animals.

5 Assessment – human health safety

5.1 HAZARD IDENTIFICATION

Lidocaine [2-(diethylamino)-N-(2,6-dimethylphenyl) acetamide] hydrochloride is a water-soluble local-regional anaesthetic agent.

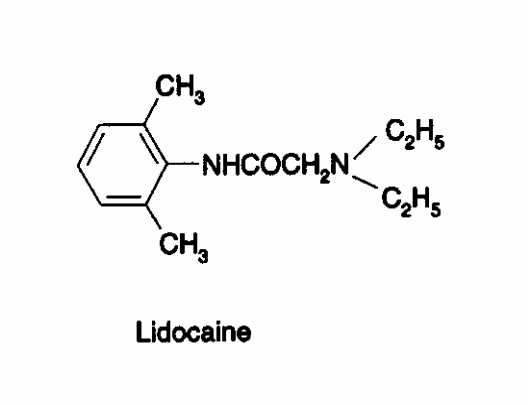

Figure 1. Molecular structure of lidocaine

As drug residues in foods of animal origin are generally considered to have the potential to cause human health hazards, this also applies to residues of lidocaine and its metabolites.

It is acknowledged that the lidocaine metabolite, 2,6-xylidine, is the critical metabolite with regard to human health safety, as this substance has been shown to be a nasal carcinogen in rats (NTP 1990) and is classified as a potential carcinogen in man (IARC 1993).

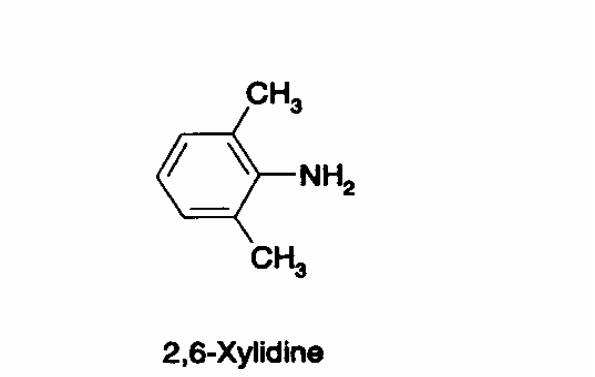

Figure 2. Molecular structure of 2,6-xylidine (2,6-dimethylaniline)

2,6-xylidine is a chemical intermediate used in the production of various dyes. It is also a component of tobacco smoke, a degradation product of aniline-based pesticides and a metabolite of certain drugs, particularly the xylide group of the local anaesthetics (including lidocaine) as well as a metabolite in horses, cattle and rats of the α_2-agonist xylazine (Putter & Sagner 1973, Yasuhara 2000, Spydridaki 2004), a commonly used veterinary drug.

5.2 HAZARD CHARACTERIZATION

The pharmacokinetic data given in the present evaluation is a synopsis of EMEAs summary report on lidocaine (EMEA 1999). This summary is based on the Expert report by the international pharmaceutical industry (FEDESA) as forwarded in the application for inclusion of lidocaine on Annex II of council Regulation (EEC) No. 2377/90 (Lourge 1995). Furthermore, additional data from studies performed in various animal species has been reviewed and included in the present hazard characterization.

It should be emphasized that few data are available regarding the pharmacokinetic, and more especially, the metabolic features of lidocaine in food producing animals. In addition, a substantial part of the cited studies are old and thus carried out with non-GLP methods.

With regard to toxicology, VKM has reviewed the Expert report from FEDESA (Lourge 1995) and the summary report on lidocaine published by EMEA (EMEA 1999) and summarized those parts of these reports relevant in the context of residual levels of lidocaine and its metabolites in food of animal origin. Furthermore, additional data on general toxicity of 2,6-xylidine is included.

5.2.1 PHARMACOKINETIC DATA

The pharmacokinetics of lidocaine are best described by an open two-compartment kinetic model. The central compartment includes circulating blood and highly perfused tissues (liver, heart, kidney, lung, and brain), and the peripheral compartment includes poorly perfused tissues (muscle, skin, body fat) (Benowitz 1974, Greenblatt et al 1976).

5.2.1.1 Absorption

Lidocaine is rapidly absorbed from different injection sites. However, the oral bioavailability of lidocaine in humans is low (around 30 %) because of an extensive first-pass metabolism (Karlaganis & Bircher 1987, de Boer et al 1979, Perucca & Richens 1979). In rats and dogs, the oral bioavailability of lidocaine is reported to be 16 % and 31 % respectively (de Leede et al 1983, Ritschel et al 1987)

Published data on the oral bioavailability of 2,6-xylidine could not be located. However, in an unpublished study where Sprague Dawley rats were administered a single oral dose of 63 mg/kg bw (body weight) radioactively labelled 2,6-xylidine, it was found that the parent substance and/or metabolites were well absorbed (Ethyl Corporation 1982).

5.2.1.2 Distribution

The distribution half-lives of lidocaine in man, rats, dogs, horses, sheep and pigs are very short (Finholt et al 1986, Rowland et al 1971, Thomson et al 1987, Nakamoto et al 1997, Wilson et al 2004, Mets et al 1993, Bloedow et al 1980, Engelking et al 1987). The

distribution phase represents a rapid equilibrium of lidocaine between plasma and the highly perfused tissues in the central compartment.

Lidocaine has been found to be widely distributed in the animal species studied. The apparent volume of distribution (the fluid volume in which the drug appears to be dissolved) is high for all species investigated (Table 1). The apparent volume of distribution is calculated as the ratio of amount of drug in body/drug concentration in plasma. A small volume of distribution indicates that a drug is distributed mainly in the plasma (i.e., high binding to plasma proteins). A large volume of distribution indicates a wider distribution or strong binding in some extra-vascular tissue(s).

5.2.1.3 Metabolism/excretion

The elimination of lidocaine is rapid in the animal species studied, i.e., plasma clearance (the volume of plasma cleared of drug pr. time unit) is high and the elimination half-lives in the various animals are short (Table 1).

Elimination of lidocaine seems to be more rapid in sheep than in humans. Studies in cattle were not located, but according to Baggott (2001), the general trend is that drug half-lives are shorter in cattle and horses (herbivorous species) than in dogs and cats (carnivorous species), while the half-lives in general are considerably longer in humans than in domestic animals.

Lidocaine is eliminated primarily by hepatic metabolism (cytochrome P450 system) in various species (Stenson et al 1971, Tucker et al 1977, Lelorier et al 1977, Mather et al 1986, Mets et al 1993).

The metabolic pathways are complex and there seem to be quantitative differences in metabolism in various species (Keenaghan & Boyes 1972).

Lidocaine and its metabolites are excreted primarily through the kidneys in the different species studied (man, dogs, rats, guinea pigs and horses) (Keenaghan & Boyes 1972, Short et al 1988).

Table 1. Pharmacokinetic parameters of lidocaine in man and in various animal species. Information about dosage, way of administration and number of subjects in the different studies are given in the footnotes (i.v.= intravenous; i.m.=intramuscular ; i.p.=intraperitoneal; p.o.= per oral)

Pharmacokinetic parameter	**Man (adults)**	**Man (children)**	**Rats**	**Dogs**	**Horses**	**Sheep**	**Pigs**
$T_{1/2}$ elimination	43[1]	58[7]	45[10]	53* [16]	48.4[21]	41.5[23]	67.2[31]
(min)	134[2]	155[8]	90–126[12]	60* [17]	39.6[22]	54.4[24]	82.8[32]
	120[3]	189.6[9]	57[13]	70.2[18]		17.8[25]	42[33]
	58.3[4]		60[14]	11.18* [19]		38[26]	52–326[34]
	180[5]		27[15]	11.6[20]		31.9[27]	
	88[6]					31[28]	
						51[29]	
Plasma clearance	9.8[1]	11.1[7]	95[10]	40[16]	52[22]	38[23]	24.2[31]
(ml/kg/min)	9.83[2]	15.4[8]	47.9[11]	41.3[17]		38[24]	17.3[32]
	22.5[3]	10.2[9]				32.5[25]	18.1[33]
	24.2[4]					44.1[26]	4.01[34]
	12.2[5]					99.6[27]	
	6.9[6]					41[28]	
						53[29]	
						68.1[30]	
Volume of distribution	0.71[1]	1.1[7]	9.8 – 16.7[12]	1.44**[16]	2.86[22]	1.1[23]	2.2[31]
(l/kg)	1.47[2]	3.05[8]	1.0[13]	1.82**[17]		2.2[24]	2.0[32]
	3.9[3]	2.75[9]		0.66**[19]		0.6[25]	0.74[34]
	2.18[4]			0.88[20]		1.88[26]	
	3.1[5]					3.24[27]	
	0.78[6]					2.0[30]	

* Calculated from the elimination rate constants given in the manuscript; ** Volume of the central compartment

1. 1 mg/kg i.v. N = 8 (Finholt et al 1986)
2. 1 mg/kg i.v. N = 10 (Orlando et al 2003)
3. Approx. 1 mg/kg i.v. N = 7 (Ochs et al 1983)
4. 1 mg/kg i.v. N = 17 (Goldberg et al 1982)
5. 5.8 mg/kg perineal, pregnant women giving birth. N = 23 (Cavalli et al 2004)
6. 1.5 mg/kg i.v., critically ill patients. N = 24 (Berkenstadt et al 1999)
7. 1 mg/kg i.v. N = 10 (Finholt et al 1986)
8. 5 mg/kg i.v. N = 11 (Ecoffy et al 1984)
9. Newborn (Mihaly et al 1978)
10. 10 mg/kg i.v. N = 8. (Nakamoto et al 1997)
11. 5 mg/kg i.v. N = 18 (Gawronska-Szklarz et al 2003)
12. 50 mg/kg i.m. N = 70 (Bruguerolle et al 1983)
13. 2.5 – 10 mg/kg i.v. N = 20 (Supradist et al 1984)
14. 50 – 90 mg/kg p.o. N = 24 (Supradist et al 1984)
15. 31 mg/kg I.v. N = 6 (de Leede et al 1983)
16. 6 mg/kg i.v. N = 9 (Wilcke et al 1983)
17. 6 mg/kg i.m. N = 8 (Wilcke et al 1983)
18. 8.8 mg/kg i.p. + 2 mg/kg in the wound. N = 6 (Wilson et al 2004)
19. 31 mg/kg i.v. infusion (1 h). N = 6 (Boyes et al 1970)
20. 4 mg/kg i.v. N = 8. Puppies 6 months old (Hastings et al 1986)
21. 0.6 mg/kg infiltrated. N = 4 (Kristinsson et al 1996)
22. 0.424 mg/kg i.v. N = 3 (Engelking et al 1987)
23. 1 mg/kg i.v. N = 3 (Bloedow et al 1980)
24. 1 mg/kg i.v. N = 14, pregnant sheep (Bloedow et al 1980)
25. 0.5 mg/kg i.v. N = 5 (Tufenkji et al 1987)
26. 4-5 mg/kg i.v. N = 6 (Santos et al 1988)
27. 4-5 mg/kg i.v. N = 10, pregnant sheep (Santos et al 1988)
28. 5 mg/kg i.v. N =7 (Morishima et al 1979)
29. 10 mg/kg i.v. N = 7, newborn lambs (Morishima et al 1979)
30. 12 mg/kg i.v. infusion N = 5, lambs (Bokesch et al 1987)
31. 4.8 mg/kg i.v. N = 5 (Mets et al 1993)
32. 5 mg/kg, epidural. N = 9. Not corrected for systemic availability (Lacoste et al 1996)
33. 2 mg/kg i.v. N = 8. During cardiopulmonary resuscitation (Hörnchen et al 1990)
34. 2 mg/kg i.v. N = 11. Newborn piglets (Satas et al 1997)

Man

In man, the main metabolism of lidocaine is through N-dealkylation to monoethylglycinexylidide (MEGX) and glycinexylidide (GX), mainly mediated by CYP3A4. These metabolites are hydrolyzed to 2,6-xylidine, which is converted to 4 hydroxy-2,6-xylidine (mediated by CYP2A6), the major urinary metabolite in man (Keenaghan & Boyes 1972, Parker et al 1996, Abdel-Rehim et al 2000). In a risk evaluation of 2,6-xylidine completed by ASTRA (unpublished data) and reported by Lourge (1995), it was determined that anaesthetic (injection) use of lidocaine (dosages not given) resulted in the production of 0.1-2.5 mg/kg bw of 2,6-xylidine. After repeated dosing the concentration could be 2-3 times higher. After topical administration, the concentration of 2,6-xylidine would be less than 1 mg/kg bw. If lidocaine is used as an anti-arrhythmic agent, up to 6-9 mg/kg bw of 2,6-xylidine may be produced.

Keenaghan & Boyes (1972) have quantified the urinary metabolites in man in 24 h urine after oral administration of radioactively labelled lidocaine (Table 2). After oral administration of 3 mg/kg bw to two healthy volunteers, the main urinary metabolite (24 hour urine) was 4-hydroxy-2,6-xylidine, while MEGX, GX, 2,6-xylidine, 3-hydroxylidocaine and 3-hydroxy-MEGX were minor metabolites. Unchanged lidocaine accounts for less than 3 % of the dose recovered in urine. The hydroxylated metabolites were excreted almost exclusively as acid-hydrolyzable conjugates. Of the administered dose, 83.8 % was recovered in urine after 24 hours.

Table 2. Interspecies variation in urinary excretion (24 hours) of lidocaine and its metabolites. The figures are given as percentage of the administered dose following oral administration of lidocaine (Keenaghan & Boyes 1972)

	Lidocaine	**Monoethyl-glycine-xylidine**	**Glycine-xylidine**	**2,6-xylidine**	**4-hydroxy-2,6-xylidine**	**3-hydroxy-lidocaine**	**3-hydroxy-monoethyglycine xylidine**
Rat*	0.2	0.7	2.1	1.5	12.4	31.2	36.9
Guinea pig*	0.5	14.9	3.3	16.2	16.4	0.5	2.0
Dog**	2.0	2.3	12.6	1.6	35.2	6.7	3.1
Man***	2.8	3.7	2.3	1.0	72.6	1.1	0.3

* 20 mg/kg bw peroral, N = 6; **10 mg/kg bw. peroral, N = 3; ***150 mg or approximately 3 mg/kg bw peroral, N = 2

2,6-xylidine has been shown to be excreted in human milk after administration of lidocaine to breast-feeding women during dental procedures (Puente & Jacoby 2001, Zeisler et al 1986).

Rats

In rats, the main metabolic pathway of lidocaine seems to differ from that which is observed in man. Coutts et al (1987) showed that 3-hydroxy-MEGX was the only main metabolite after intraperitoneal administration of lidocaine (40 mg/kg bw) to male Sprague-Dawley rats, while MEGX, GX, 2,6-xylidine, 4-hydroxy-2,6-xylidine and 3-hydroxy-2,6-xylidine were found as minor metabolites. Keenaghan & Boyes (1972) observed a different pattern of metabolites in the urine of female Sprague Dawley rats after oral administration of lidocaine (20 mg/kg). They found that about 85 % of the administered dose was excreted in urine within 24 hours

and that 3-hydroxy-lidocaine and 3-hydroxy-MEGX were the major metabolites. 4-hydroxy-2,6-xylidine, MEGX and GX were found to be minor metabolites. The discrepancies between these two studies may be explained by the use of different genders and ages of rats, different doses and administration routes, or different techniques for identification of metabolites (Alexson et al 2002).

Studies in Sprague Dawley rats after oral administration of radioactive labelled 2,6-xylidine (63 mg/kg bw) showed that the major part of the radiolabel was eliminated through the urine, while a minor part was eliminated through faeces and expired air. Only small amounts of the radiolabel were recovered in tissues 24 hours after the dose was administered. Accumulation was shown to occur when an oral dose of 63 mg/kg bw was administered daily in 10 days; the greatest accumulation occurred in red blood cells and liver. High concentrations were also found in the kidneys, whole blood and in nasal tissues (Ethyl Corporation 1982)

In a study where rats were administered 2,6-xylidine at a dose of 262.5 mg/kg bw orally in corn oil gavages daily for ten days, analysis of collected urine at 24 hours and on day 10 after administration, showed that 2,6-xylidine was excreted in urine either as the parent compound or as 4-hydroxy-2,6-xylidine (Short et al 1989).

Dogs

In dogs, the main metabolite after oral administration of lidocaine (10 mg/kg bw) was shown by Keenaghan & Boyes to be, as in man, 4-hydroxy-2,6-xylidine. GX was also an important metabolite, whereas 3-hydroxylidocaine, 3-hydroxy-MEGX, MEGX and 2,6-xylidine were excreted in the urine in small amounts. Altogether 63.5 % of the administered dose was recovered in the urine within 24 hours after administration (Keenaghan & Boyes 1972). Ngo et al (1997) showed that MEGX and GX were the principal metabolites in plasma after intravenous infusion of lidocaine to dogs.

Short et al (1989) administered 2,6-xylidine orally to dogs in doses of 25 mg/kg bw daily for ten days. It was shown that the main urinary metabolite of 2,6-xylidine in dogs was 4-hydroxy-2,6-xylidine.

Horses

In horses, following subcutaneous administration of radioactively labelled lidocaine (200 mg per animal), the percentages excreted in the urine were 0.2 % unaltered and 0.4 % conjugated lidocaine, 1.5 % unaltered and 2.4 % conjugated MEGX, 0.8 % unaltered and 0 % conjugated GX, 0 % unaltered and 10.1 % conjugated 3–hydroxylidocaine, 0 % unaltered and 3.8 % conjugated 3-hydroxy-MEGX, 2.5 % unaltered and 0 % conjugated 2,6-xylidine. After 58 hours, 77 % of the administered radioactivity had been excreted in the urine (EMEA 1999, Short et al 1988). The major urinary metabolite of lidocaine in horses has also been shown by others to be a hydroxy-lidocaine glucuronide (Harkins et al 1998, Dirikolu et al 2000).

Pigs

In pigs, Mets et al (1993) have identified MEGX, 3-hydroxy-MEGX, GX, 3-hydroxylidocaine, 2,6-xylidine and 4-hyroxy-2,6-xylidine in the hepatic venous effluent after intravenous infusion of lidocaine.

No studies that quantify the amount of 2,6-xylidine formed after therapeutic use of lidocaine in pigs could be located.

Cattle

Studies identifying and quantifying the metabolites of lidocaine in ruminants could not be located.

In a study by Puente & Josephy (2001), seven Holstein cows were injected with lidocaine before surgery in dosages of 2.9-3.9 mg/kg. Milk samples were obtained prior to surgery and at a single time point 2.5-6 h after lidocaine injection. The metabolite 2,6-xylidine was detected in milk at levels ranging from 14.5 µg/kg - 66 µg/kg.

Summary

Lidocaine seems to be rapidly absorbed from the major administration routes. Oral bioavailability is low because of extensive first-pass hepatic metabolism. The parent substance is rapidly eliminated via hepatic oxidative pathways. Lidocaine and its metabolites are rapidly excreted in the animal species studied, mainly via the renal route. The amounts of 2,6-xylidine excreted in urine after administration of lidocaine are low (except in guinea pigs). 2,6-xylidine has been shown to be excreted in bovine milk.

5.2.2 TOXICOLOGY

The toxicological data presented below is a summary of the most relevant issues of the Expert report (safety file) by the international pharmaceutical industry (FEDESA) as forwarded in the application for inclusion of lidocaine on Annex II of council Regulation (EEC) No. 2377/90 (Lourge 1995).

Furthermore, data on general toxicity of 2,6-xylidine are included and are mainly based on toxicology and carcinogenesis studies of 2,6-xylidine in rats completed as part of the U.S. National Toxicology Program (NTP 1990).

5.2.2.1 Single dose toxicity (acute toxicity)

Various LD_{50} values (mg/kg bw) of lidocaine in laboratory animals are shown in Table 3.

Table 3. Various LD_{50} (mg/kg bw) values of lidocaine in laboratory animals (Lourge 1995)

	Mice	**Rats**	**Rabbits**	**Guinea pigs**
Oral	220 – 292	-	-	-
Intravenous	15 – 28	21	25.6	24.5
Intramuscular	260	-	-	-
Subcutaneous	163 – 450	570	-	-
Intraperitoneal	63 – 132	122	-	-

LD_{50} values of 2,6-xylidine (NTP 1990) in female Charles River rats and F 344/N rats were 1.27 g/kg bw and 1.16 g/kg bw, respectively. The corresponding figure for male Charles River rats was 1.31 g/kg bw. An LD_{50} value could not be calculated for male F 344/N rats because survival in all dose groups was either 0% or 100%, but LD_{50} was probably between 0.62-1.25 g/kg bw. Previous studies have shown LD_{50} values in rats between 0.84 and 2.06 g/kg bw (Short et al 1983, Lindstrom et al 1963).

In the NTP study (1990), rats were given 2,6-xylidine orally in corn oil by gavages in single doses from 0.31 to 5 g/kg bw. Reduced activity was observed in all the rats during the study period of 14 days. Dyspnea and shallow breathing occurred in all rats administered 1.25 g/kg bw or more. The groups administered 0.62 g/kg bw or more had reddened renal medullae and the groups administered 1.25 g/kg bw or more had reddened gastric mucosa and thick oily yellow fluid in the stomach and intestines (NTP 1990).

5.2.2.2 Repeated dose toxicity

Lidocaine

No data on repeated dose toxicity in laboratory animals were located.

Lidocaine has been widely used in human and veterinary medicine for several decades. Its main use is as a local-regional anaesthetic and lidocaine is therefore usually administrated as a single dose.

2,6-xylidine

Aromatic amines and their derivatives, including 2,6-xylidine, are shown to produce methaemoglobinaemia in several species. Cats are more susceptible than humans while dogs are less susceptible (McLean et al 1969).

As part of the NTP study (1990), rats were administered 2,6-xylidine orally in doses between 0 and 1.25 g/kg bw 5 days a week for 2 weeks. Compound-related deaths occurred in groups receiving doses of 0.62 g/kg bw or more. All animals administered 1.25 g/kg bw died before the termination of the study. Depression of the mean body weight gain relative to controls was observed. General leukocytosis and an increase in the number of nucleated red blood cells were also observed (NTP 1990).

No noteworthy clinical signs were observed in rats receiving 2,6-xylidine orally in doses between 0 and 0.31 g/kg bw 5 days a week for 13 weeks. At the highest dose (0.31 g/kg bw), increases in mean liver weights and decrease in mean body weights were observed. Histological examination revealed minimal to moderate inflammatory changes in the nasal mucosa, but this was also observed in the control rats (NTP 1990).

A study where Charles River CD rats were fed diets containing 0, 300, 1000 or 3000 ppm (0, 15, 50 or 150 mg/kg bw) of 2,6-xylidine daily over the course of two years (NTP 1990), showed that this substance is carcinogenic in rats (for details see 5.2.2.6). High dose rats had a marked reduction in mean body weight gain relative to controls and there was reduced survival in high- and mid dose males. There was no significant difference in survival in the different groups of female rats. The increased mortality in the high dose male rats did not appear to have been caused primarily by nasal cavity tumours, since a comparable increase in nasal cavity neoplasms in the female rats was not associated with increased mortality. Acute

inflammation (rhinitis), epithelial hyperplasia, and squamous metaplasia occurred at increased incidences in the high dose rats. Inflammation of the epithelium lining the nasal cavity occurred both in the control and the dosed rats (NTP 1990).

Repeated administration of 2,6-xylidine at 100 mg/kg bw orally was found to induce gastric ulcers in dogs (Magnusson et al 1971).

2,6-xylidine produced a marked fatty degeneration in the livers of dogs receiving oral doses ranging from 2 – 50 mg/kg bw daily for two weeks (Magnusson et al 1971).

5.2.2.3 Tolerance in the target species (animals)

There are no published experimental data regarding lidocaine tolerance in the target species. Lidocaine has been used in veterinary medicine for several decades without any significant intolerance problems.

5.2.2.4 Reproductive toxicity (including developmental toxicity)

Studies in laboratory animals (non GLP studies) show no particular reproductive or teratogenic effects after administration of lidocaine (Lourge 1995).

Behavioural effects have been shown in the offspring of female rats administered lidocaine during the gestation period (Lourge 1995).

5.2.2.5 Mutagenicity

Lidocaine

The Ames test (*Salmonella* strains TA100 and TA98) with or without metabolic activation did not reveal any mutagenic potential of lidocaine. Neither the Ames test (*Salmonella* strain TA1538 with 1, 10, 100 and 500 µg/plate) with or without metabolic activation (S9 fraction) with several metabolites of lidocaine, including 2,6-xylidine, revealed any mutagenic activity (Lourge 1995).

2,6-xylidine

Mutagenic tests were carried out with the metabolite 2,6-xylidine: Ames test, forward mutation in the mouse lymphoma TK locus assay, chromosoma aberration and sister chromatid exchange in Chinese Hamster ovary cells, unscheduled DNA synthesis in rat hepatocytes in the *in vitro/in vivo* UDS assay, covalent binding to DNA in rat liver and ethmoid turbinates *in vivo*, micronuclei in mouse polychromated erythrocytes and the preferential killing of DNA repair deficient *E. coli* bacteria *in vivo*, using a host-mediated assay in the mouse. These tests indicated that 2,6-xylidine is a weak mutagenic agent *in vitro* and has weak genotoxic characteristics *in vivo* (Lourge 1995).

5.2.2.6 Carcinogenicity

Lidocaine

Data on potential carcinogenic effects of lidocaine could not be located.

2,6-xylidine

A study in which Charles River CD rats during a two years period were fed diets containing 0, 300, 1000 or 3000 ppm (0, 15, 50 or 150 mg/kg bw) of 2,6-xylidine daily, showed that this substance is carcinogenic in rats (NTP 1990). A significant increase in adenomas and carcinomas of the nasal cavities in rats fed 3000 ppm 2,6-xylidine in the diet (150 mg/kg bw) daily for 102 weeks was observed (Table 4). It should be noticed that in this study it was shown that some of the 2,6-xylidine was evaporating from the feed and that the rats were likely to have inhaled this substance throughout the study period. Subcutaneous fibromas/fibrosarcomas and hepatic neoplastic nodules were observed in the NTP study; however, these findings were not significant (Table 5). The incidence of these tumours appeared to be dose dependent.

Table 4. Incidences of nasal cavity tumours in rats fed 2,6-xylidine daily for 102 weeks. Significant results are in bold (NTP 1990)

	Controls	**15 mg/kg bw**	**50 mg/kg bw**	**150 mg/kg bw**
Papillary adenoma ♂	0/56	0/56	2/56	**10/56 (18 %) (p ≤ 0,001)**
Adenoma ♀	0/56	0/56	1/56	6/56 (11 %)
Carcinoma ♂	0/56	0/56	0/56	**26/56 (46 %) (p < 0,001)**
Carcinoma ♀	0/56	0/56	1/56	**24/56 (43 %) (p < 0,001)**
Carcinoma or adenocarcinoma ♂	0/56	0/56	0/56	**28/56 (50 %) (p < 0,001)**
Carcinoma or adenoma ♀	0/56	0/56	2/56	**29/56 (52 %) (p < 0,001)**
Adenoma, adenocarcinoma or carcinoma ♂	0/56	0/56	2/56	**33/56 (59 %) (p < 0,001)**

Table 5. Incidences of subcutaneous tissue tumours and liver tumours in rats fed 2,6-xylidine daily for 102 weeks (NTP 1990)

	Control	**15 mg/kg bw**	**50 mg/kg bw**	**150 mg/kg bw**
Subcutaneous tissue tumours				
Fibroma ♂	0/56	1/56	2/56	4/56 (7 %)
Fibroma ♀	0/56	2/56	1/56	4/56 (7 %)
Fibrosarcoma ♀	1/56	0/56	1/56	3/56 (5 %)
Fibroma or fibrosarcoma ♂	0/56	2/56	2/56	5/56 (9 %)
Fibroma or fibrosarcoma ♀	1/56	2/56	2/56	6/56 (11 %)
Liver tumours				
Neoplastic nodule ♀	0/56	1/56	2/56	4/55 (7 %)
Neoplastic nodule or hepatocellular carcinoma ♀	1/56	1/56	3/56	5/55 (9 %)

5.2.2.7 Establishment of T25 for tumours in experimental animals

As a NOEL could not be established for lidocaine, alternative methods for the evaluation of human health safety after ingestion of food containing residues of the lidocaine metabolite 2,6-xylidine were considered. In a new draft document from the Scientific Committee of the European Food Safety Authority (EFSA) (EFSA 2005) margin of exposure (MOE) is suggested as a new approach for harmonising risk assessment for compounds that have both genotoxic and carcinogenic properties.

MOE is the ratio between a defined point on the dose-response curve (point of comparison) for the adverse effect of a compound in the animal bioassay and the estimated daily human intake of the compound. T25, a tumour dose descriptor, could be used as such a point of comparison. The EFSA Scientific Committee is of the opinion that a MOE of a magnitude of 25000 or higher, if based on T25, would be of low health risk and might be viewed as low priority for risk management.

The Norwegian Scientific Committee for Food Safety is of the opinion that this approach could be used for the risk characterization of 2,6-xylidine.

Historical, quantitative assessments of risks from exposure to genotoxic and carcinogenic substances have a basic assumption that such substances do not show a dose threshold for their effects. This means that any exposure dose has a certain level of risk and that the level of risk is dose-related.

T25 may be used as a basis for quantitative hazard characterization using a linear extrapolation. This method has already been used a number of times in connection with risk assessments of chemicals and cosmetic ingredients. Sanner and co-workers described this method in 2001. This method defines the tumour dose indicator T25, the dose at which the tumour incidence increases by 25 % under standard conditions (Dybing et al 1997), as a starting point for linear extrapolation to zero.

Table 6 shows calculated T25 (mg/kg body weight)[1] for different tumours detected after daily oral exposure of 150 mg of 2,6-xylidine per kilo body weight for 102 weeks (only significant results included).

Table 6. T25 (mg/kg body weight) for different nasal cavity tumours in rats fed 150 mg 2,6-xylidine/kg bw daily for 102 weeks

	Controls	**150 mg/kg bw**	**T25 mg/kg bw**
Papillary adenoma ♂	0/56	10/56 (18 %) ($p \leq 0{,}001$)	**208.3**
Adenoma ♀	0/56	6/56 (11 %)	
Carcinoma ♂	0/56	26/56 (46 %) ($p < 0{,}001$)	**81.5**
Carcinoma ♀	0/56	24/56 (43 %) ($p < 0{,}001$)	**87.2**
Carcinoma or adenocarcinoma ♂	0/56	28/56 (50 %) ($p < 0{,}001$)	**75.0**
Carcinoma or adenoma ♀	0/56	29/56 (52 %) ($p < 0{,}001$)	**72.1**
Adenoma, adenocarcinoma or carcinoma ♂	0/56	33/56 (59 %) ($p < 0{,}001$)	**63.5**

[1]The T25 is defined as the chronic dose rate which will give 25% of the animals tumours at a specific tissue site, after correction for spontaneous incidence, within the standard life-time of that species

T25 = Dose rate in the experimental animal * 25/tumour frequency (%) observed

The lowest T25 dose is calculated to be 63.5 mg/kg body weight. It is likely that the animals in the NTP study also inhaled 2,6-xylidine, due to evaporation of 2,6-xylidine from the feed. Concentration of 2,6-xylidine in the nasal epithelium could therefore have been much higher than the systemic administration. It is not possible to calculate this additional exposure and the T25 dose must be considered as conservative.

5.3 EXPOSURE CHARACTERIZATION

The exposure characterization is completed essentially as a worst-case scenario and especially the assessment on usage of lidocaine is more thoroughly described and discussed in Appendix I.

5.3.1 DEMOGRAPHIC DATA; PRODUCTION DATA

Numbers of food animals to which lidocaine may have been administered in Norway in 2004 are shown in Table 7.

Table 7. Numbers of food animals to which lidocaine may have been administered in Norway in 2004. Data are obtained from Statistics Norway[1,2]

	Horse*	Dairy cattle	Other cattle	Dairy goats	Sheep > 1 year	Slaughter swine**
Numbers	28 400	271 100	666 300	44 700	945 500	1 316 500

[1] http://www.ssb.no/emner/10/04/10/jordbruksareal/tab-2005-02-16-03.html, accessed 10 March 2005;

[2] http://www.ssb.no/emner/10/04/10/jordhus/tab-2004-05-14-03.html, accessed 10 March 2005;

*Includes only registered horses (assumed to be twice as many); **Annual numbers slaughtered

The production of cow and goat milk in 2003, and of meat from various food animal species, in Norway in 2004 is shown in Table 8.

Table 8. Production of cow and goat milk[1] (in million litres) in 2003 and of meat[2] (in metric tonnes) from various food animal species in Norway in 2004

	Cow milk	Goat milk	Horse meat	Cattle meat	Goat meat	Sheep/lamb meat	Pig meat	Poultry[3] meat
Litres x 1 mill./tonnes	1 526	21	532	86 074	222	25 524	112 943	54 219

[1] Bjørlo, B., Statistics Norway, personal communication, 14 March 2005; [2] Norwegian Agricultural Authority 2005; [3] Lidocaine not used in poultry

5.3.2 FOOD CONSUMPTION DATA - HUMANS

The European Agency for the Evaluation of Medicinal Products (EMEA), Committee for Veterinary Medicinal Products (CVMP) assumes that every day an average individual consumes 500 g meat products (300 g of muscle, 100 g liver, 50 g kidney, 50 g fat) and 1.5 litres of milk.

National data on food consumption among adults were obtained from the national dietary survey NORKOST 1997 (Johansson & Solvoll 1999) and among children from the national dietary survey UNGKOST 2000 (Øverby & Andersen 2002). In NORKOST 1997, a sample of 2 672 persons between the ages of 16 to 79 years participated (average body weight=73 kg). The method used in NORKOST was a quantitative food frequency questionnaire, which was distributed and collected at four separate periods throughout a year. The survey tried to capture information about the usual diet among the participants during the previous year. UNGKOST 2000 was carried out in Norway in the period of 2000-2001. The sample consisted of children aged 4 years (n=391), 9 years (n=810) and 13 years (n=1 005). The methodology used was a pre-coded 4-day record using photographs of foods items and data refer to food as consumed with weight of food.

Table 9. Daily consumption of meat, milk and milk products and cheese among different consumers groups in Norway. Data for mean and high consumption (95-percentile)

Consumers	**Meat g/day**		**Milk/Milk products g/day**		**Cheese g/day**		**Men/ Boys Weight**	**Women/ Girls Weight**
	Mean	*95-perc*	*Mean*	*95-perc*	*Mean*	*95-perc*	*Kg*	*Kg*
18-79 years[1]	106	206	463	1092	33	84	81	66
13 years[2]	111	269	391	901	30	76	49	49
9 years[2]	97	212	440	824	25	63	32	32
4 years[2]	65	142	393	690	19	45	18	18

[1]The national dietary survey NORKOST 1997; [2]The national dietary survey UNGKOST 2000

One of the weaknesses of the survey NORKOST 1997 is that the questionnaires, on which the data are based, do not differentiate between the consumption of different types of meat, e.g, beef, pork, and mutton.

Food consumption has also been calculated through the Household Budget Surveys completed by Statistics Norway during 2001-2003. The average daily consumption of meat and meat products is estimated to be 115 g. Daily intake of milk products (e.g., milk, yoghurt, ice cream) is approximately 280 g, while for cheese this figure is estimated to be 37 g (Trygg K, University of Oslo, personal communication, 6 April 2005). One of the weaknesses of these surveys is that they do not include food consumed outside the household, e.g., foods eaten at restaurants. Further, data from the Household Budget Surveys give only information about the average consumption in the population and, thus, it is not possible to estimate intake among high consumers. In the present exposure characterization, data obtained through NORKOST 1997 and UNGKOST 2000 are used (Table 9).

5.3.3 ASSESSMENT OF LIDOCAINE RESIDUES IN MILK AND MEAT

The estimation of usage of lidocaine in the various food producing animals, as well as the assessment of potential residues, is comprehensively described in Appendix I.

The use of lidocaine in food producing animals is calculated from data on numbers of relevant disease cases in food animals in 2004 for which lidocaine could have been administered. These data were collected primarily from the Norwegian animal health recording systems.

As it is the lidocaine metabolite, 2,6-xylidine, which seems to be the critical substance with regard to human health safety and few data on the metabolism of lidocaine in the target animal species are published, a worst-case scenario would be that all lidocaine administered to the target animal species in 2004 is metabolized to 2,6-xylidine on a molar basis. The preparations approved in Norway contain lidocaine hydrochloride monohydras and 1 g of this substance would result in 0.42 g of 2,6-xylidine.

The calculations of average daily intake of 2,6-xylidine residues from food products derived from exposed animals are based on the following:

- All cases (indications) likely to have had lidocaine administered prior to local surgery in 2004 were originally included in the assessment (to enable validation of the data), however,
- All cases for which the carcasses, due to economic reasons (e.g., transport costs), were unlikely to be delivered (e.g., castrated piglets and dehorned calves) for human consumption after euthanization for animal welfare reasons were excluded from the final assessment
- The lidocaine dosages used for the assessment are the assumed maximum dosage for the various indications
- For dairy cattle and dairy goats the total amount of 2,6-xylidine is assumed to be localized in the milk at the time of milking
- It is assumed that the exposed milk was diluted in the total volume of milk produced in Norway in 2004, as the milk from every dairy farm is regularly mixed with milk from many other dairy farms
- For animals for which the carcass could be delivered for human consumption after emergency slaughter the total amount of 2,6-xylidine is assumed to be localized in the edible tissue at the time of slaughtering
- It is assumed that exposed meat was “diluted” in the total amounts of meat of the relevant animal species, produced in Norway during 2004, as it is highly improbable that one person would consume meat only from exposed animals on a daily basis
- The cases for which lidocaine could have been used in food animals are assumed to occur randomly throughout the country as well as throughout the year

5.3.3.1 Assessment: Milk

Cow milk

The maximum average amount of 2,6-xylidine in cow milk is estimated to be approximately 3 µg/kg (worst-case scenario). Assuming that the daily intake of milk is 1.5 litres (EMEA standard), the maximum daily intake of 2,6-xylidine from cow milk would be 4.5 µg. This figure is used for the calculation of worst-case MOE value for cow milk. With a daily intake of 1.09 l milk (high consumption - Norway) or 0.46 l milk (mean consumption - Norway) this figure would be 3.3 µg and 1.4 µg**,** respectively.

A major use of lidocaine in dairy cows in 2004 could have been for the indication dystocia. As delivery of milk for human consumption within the first 5 days following calf delivery is prohibited, a 5 day withdrawal time for milk is in place automatically. The lidocaine used in cattle would be assumed to be completely excreted from the treated animal within this period; thus the average amounts of 2,6-xylidine in diluted cow milk would be approximately 1.3 µg/kg. Assuming a daily intake of 1.5 l (EMEA standard)**,** 1.09 l (high consumption Norway) and 0.46 l (mean consumption Norway) of milk, the daily intake of 2,6-xylidine from cow milk would be 2 µg, 1.4 µg and 0.6 µg, respectively.

Goat milk

The maximum average amount of 2,6-xylidine in goat milk produced in Norway in 2004 is estimated to 0.2 µg/kg (worst-case scenario).

In Norway, goat milk is used almost exclusively for the production of a cheese product (goat cheese), basically made from goat milk whey to which goat milk and cream is added. A similar and more popular cheese is made from cow milk whey, milk and cream in addition to a smaller amount of goat milk. The daily intake of these two cheeses in Norway is estimated to be approximately 6 g (Trygg K, University of Oslo, personal communication, 6 April 2005). The daily intake of lidocaine residues from goat milk is thus regarded as insignificant.

5.3.3.2 Assessment: Meat

Beef

The maximum single lidocaine dosage that is assumed to be administrated to cattle prior to surgery is 2000 mg. The estimate of maximum single exposure of 2,6-xylidine through meat from treated cattle is calculated for a 200 kg calf, as this is assumed to be the lowest live weight for cattle which have been administered lidocaine and for which the carcass would be delivered for human consumption after emergency slaughter (economic reasons, e.g., transport costs). The amount of 2,6-xylidine in edible tissue would then be approximately 4.2 mg/kg. Assuming an intake of edible tissue of 500 g (EMEA standard), one individual could be exposed to 2.1 mg of 2,6-xylidine in a meal from a treated animal. With a daily intake of 0.206 kg meat (high consumption - Norway) or 0.106 kg meat (mean consumption - Norway), this figure would be 0.9 mg and 0.4 mg, respectively.

It is, however, highly improbable that any person in Norway would eat meat only from cattle treated with lidocaine on a regular basis. An alternative approach for estimating the daily intake of 2,6-xylidine in beef would be to calculate the distribution of 2,6-xylidine residues in all beef intended for human consumption. Such a theoretical assumption could be adequate for a risk characterization of repeated human exposure of 2,6-xylidine from cattle meat.

The average amount of 2,6-xylidine in edible tissue from "diluted" beef is estimated to be approximately 60 µg/kg (worst-case scenario). This figure is used for the calculation of a worst-case MOE value for meat. Assuming EMEA's standard of daily intake of meat products, daily intake of this metabolite would be 30 µg. With a daily intake of 0.206 kg meat (high consumption - Norway) or 0.106 kg meat (mean consumption - Norway) this figure would be 12.4 µg and 6.4 µg, respectively.

A major proportion of the lidocaine that could have been administered to cattle in 2004, would have been to dairy cows. Assuming that this amount is completely excreted in milk as

2,6-xylidine, the amounts of 2,6-xylidine in "diluted" meat in 2004 would have been approximately 7.1 µg/kg and the daily intake 3.6 µg assuming EMEA standard meat intake. With a daily intake of 0.206 kg meat (high consumption - Norway) or 0.106 kg meat (mean consumption - Norway), the daily intake of 2,6-xylidine would be 1.5 µg and 0.7 µg, respectively.

Based on the assumption that all the 2,6-xylidine is localized in the edible tissue of the treated cattle (no excretion in milk) at the time of slaughter, the calculated proportion of beef produced in Norway in 2004 that could contain 2,6-xylidine was at maximum 5 %. Provided the total amounts of lidocaine used in dairy cows are excreted in milk (no residues in edible tissue), the maximum proportion of beef that could contain 2,6-xylidine would have been 0.3 %.

Pork

The major indication for use of lidocaine in swine production is castration of male pigs, usually completed within 2 weeks after birth. If these piglets are euthanized for animal welfare reasons within 4 weeks after castration (current withdrawal time for lidocaine is 28 days), it is unlikely that they would be delivered for human consumption for economic reasons (e.g., transport costs).

The only indication of significance in swine, for which residues of lidocaine would be of any concern with regard to human health safety, is surgical removal of a damaged tail, following tail biting. In Norway, routine tail docking of pigs to prevent tail biting is banned for animal welfare reasons. Some cases of tail biting may consequently occur. Provided that 40 mg lidocaine (gives approximately 16.8 mg 2,6-xylidine) is used before surgical removing of a damaged pigs tail close to slaughter (100 kg live weight) and the total dose is localized and evenly distributed in the animal as 2,6-xylidine at the time of slaughter, the average amount in edible tissue would be approximately 168 µg/kg. Assuming an intake of edible tissue of 500 g (EMEA standard), one person could be exposed to 84 µg of 2,6-xylidine through meat from a treated animal. With a daily intake of 0.206 kg meat (high consumption - Norway) or 0.106 kg meat (mean consumption - Norway) this figure would be 35 µg and 18 µg, respectively.

It is, however, highly improbable that any person in Norway would eat meat from pigs that have been slaughtered soon after the damaged tail has been removed by surgery on a regular basis. An alternative way to estimate daily intake of 2,6-xylidine in pork would be to look at the distribution of lidocaine in all pork produced in Norway. Such a theoretical assumption could be adequate for a risk characterization of regular human exposure of 2,6-xylidine from pork.

The average amount of 2,6-xylidine in edible tissue of "diluted" pork is calculated to be approximately 5.8 µg/kg. The daily intake of 2,6-xylidine from "diluted" pork would be 2.9 µg, assuming EMEA standard meat intake (500 g). With a daily intake of 0.206 kg meat (high consumption Norway) or 0.106 kg meat (mean consumption Norway) this figure would be 1.2 µg and 0.6 µg, respectively.

As the damaged tail is usually infected with bacteria, pigs that have surgical treatment of their damaged tails are regularly treated with benzylpenicillinprocaine i.m. The recommended withdrawal time for meat following i.m. injection of benzylpenicillinprocaine is 14 days. This

withdrawal time will thus automatically apply to the lidocaine. As both lidocaine and its metabolites are assumed to be rapidly excreted after injection, it is unlikely that there will be any residues of 2,6 xylidine in pork at the slaughter time.

Of the Norwegian pork produced in 2004 a maximum of 2.4 % could contain 2,6-xylidine.

Mutton/Lamb

It would be expected that the annual numbers of cases for which lidocaine is used in sheep is quite low. Of these only a few are likely to be euthanized for animal welfare reasons, but due to economic reasons (e.g., transport costs) delivery of the carcasses for human consumption is unlikely.

Lambs, which are slaughtered at 7-8 months of age, will only very rarely suffer from diseases where surgery, and the use of lidocaine, is indicated. Furthermore, economic factors as well as the Norwegian production system, with grazing in remote areas, make the use of lidocaine unlikely.

It is concluded that use of lidocaine in sheep is unlikely to contribute to residues of 2,6-xylidine in mutton/lamb.

Goat meat

The major indication for lidocaine use in goats is for dehorning which is usually performed within 2 weeks after birth. Goats intended for meat production are slaughtered at 6 weeks of age, at the earliest, or later.

It would be expected that the annual numbers of other cases where lidocaine is used in dairy goats are quite low. Of these, only a few are likely to have been euthanized for animal welfare reasons, but due to economic reasons (e.g., transport costs) delivery of the carcasses for human consumption is unlikely.

It is concluded that use of lidocaine in goats is unlikely to contribute to residues of 2,6-xylidine in goat meat.

5.3.3.3 Various animals

Assuming that the exposed beef (assuming no exposure in milk) and pork were “diluted” in the complete biomass produced from the major food animal species in Norway in 2004, the amount of 2,6-xylidine in “diluted” meat would be approximately 21 µg/kg (Appendix I). The daily intake of 2,6-xylidine from “diluted” would be 10.5 µg assuming EMEA standard meat intake. With a daily intake of 0.206 kg meat (high consumption - Norway) or 0.106 kg meat (mean consumption - Norway), this figure would be 4.3 µg and 2.2 µg, respectively.

Assuming that the amount of lidocaine used in dairy cattle was totally excreted as 2,6-xylidine in milk, the average amount in “diluted” meat would be 4.5 µg/kg (Appendix I); the daily intake of 2,6-xylidine from “diluted” meat would be 2.2 µg assuming EMEA standard meat intake. With a daily intake of 0.206 kg meat (high consumption - Norway) or 0.106 kg meat (mean consumption - Norway), this figure would be 0.9 µg and 0.5 µg, respectively.

5.3.4 VALIDATION OF THE EXPOSURE ESTIMATES

By calculating the approximate quantities of lidocaine that could have been used in animals, that could then have been slaughtered for emergency reasons, and for which the carcass could have been delivered for human consumption, results in a huge overestimate of potential exposure (Appendix I). This is also the case for the estimates with regard to dairy cows.

5.4 RISK CHARACTERIZATION

The metabolism and excretion of lidocaine in humans and laboratory animals are fairly well described. 2,6-xylidine has been shown to be a metabolite of lidocaine in all species studied (including cattle, swine, and also horses). This substance has been shown to be carcinogenic in rats. However, detailed data on the metabolism of lidocaine, particular the metabolism of lidocaine to 2,6-xylidine in cattle, pigs, sheep and goats, are lacking. Therefore, the present risk assessment of lidocaine residues in food products from various food producing animals in Norway is completed as a worst-case scenario, assuming that the complete lidocaine dosages administered are metabolized to 2,6-xylidine on a molar basis.

It is concluded that while any intake of 2,6-xylidine through consumption of food following use of lidocaine in goat and sheep is highly improbable, intake of this substance may occur through consumption of cow milk, beef and pork following use of lidocaine in cattle and swine.

5.4.1 INTAKE OF A SINGLE DOSE OF 2,6- XYLIDINE IN MEAT FROM AN EXPOSED ANIMAL

The worst-case scenario is that an individual could be exposed to 2.1 mg (30 µg/kg bw for a person weighing 70 kg) of 2,6-xylidine ('lidocaine') from meat from an animal (cattle) administered lidocaine for local anaesthesia, assuming EMEA standard food intake (500 g meat products). This estimate is based on the assumption that the complete dosage of lidocaine is metabolized to 2,6-xylidine on a molar basis, and that this amount is localized in edible tissue when the animal is slaughtered.

However, lidocaine is rapidly absorbed from the various injection sites. Lidocaine has been shown to be rapidly eliminated in the various target animals and 2,6 xylidine is rapidly excreted in the urine in the animal species studied. The Norwegian Scientific Committee for Food Safety is of the opinion that if the animal is slaughtered 24 hours after lidocaine treatment the concentration of 2,6-xylidine in meat derived from that animal would be very unlikely to be of concern to the safety of human health.

As milk from exposed dairy cows is regularly diluted with milk from various farms at the dairies before it reaches the consumer, it is not relevant to calculate exposure through milk from a single treated cow.

5.4.2 CALCULATION OF MARGIN OF EXPOSURE (MOE)

The maximum daily average intake of 2,6-xylidine from milk and/or meat per person, as derived through the various methods/calculations, is summarized in Table 10.

With regard to cow milk, the worst-case scenario would be the daily intake of 4.5 µg of 2,6-xylidine per individual, assuming EMEA standard of milk intake.

If it is assumed that the daily intake of meat comprises solely of beef and/or pork (i.e. not poultry, lamb, mutton etc), then assuming the EMEA standard for meat consumption (500 g/day) the worst-case scenario would be a daily average intake of 30 µg of 2,6-xylidine per individual through beef, assuming no excretion in milk (Table 10).

The lowest T25 dose for the metabolite 2,6-xylidine is calculated to be 63.5 mg/kg (63500 µg/kg) body weight (Table 6).

Table 10. Estimated daily average intake of 2,6-xylidine per individual (adults), as derived through various assessment methods, calculated from EMEA standards of daily intake of milk and edible tissue from meat and from Norwegian estimates of daily intake of milk and the various meat products (Johansen & Solvoll 1999; Øverby & Andersen 2002)

Exposed food product	**EMEA standard of food intake**	**Norwegian estimates of food intake – 95% percentile**	**Norwegian estimates of food intake – mean value**
Milk			
Cow milk[1]	**4.5 µg**	3.3 µg	1.4 µg
Cow milk[1] – use in dystocia excluded (as delivery of milk prohibited for 5 days after calf delivery)	***2 µg***	1.4 µg	0.6 µg
Meat			
Intake of beef only[2] – assuming no excretion in milk	**30 µg**	12.4 µg	6.4 µg
Intake of beef only[2] – use in dairy cow excluded (assuming complete excretion in milk)	***3.6 µg***	1.5 µg	0.8 µg
Intake of pork only[3]	2.9 µg	1.2 µg	0.6 µg
Intake of pork and/or beef (assuming no excretion in milk) "diluted" in total amounts of various meat[4]	10.5 µg	4.3 µg	2.2 µg
Intake of pork and/or beef (assuming complete excretion in milk) "diluted" in total amounts of various meat[4]	2.2 µg	0.9 µg	0.5 µg

[1]Diluted in total amounts of cow milk produced in Norway; [2]Diluted in total amounts of beef produced in Norway; [3]Diluted in total amounts of pork produced in Norway; [4]Cattle, swine, sheep, goat, horse and poultry meat produced in Norway

Calculation of MOE - milk

2,6-xylidine excreted in milk is assumed to be diluted at the dairies with milk from many farms. MOE (worst-case scenario) of daily intake of 2,6-xylidine from milk would be:

4.5 µg/70kg = 0.064 µg/kg body weight

MOE: 63 500µg/kg body weight /0.064 µg/kg body weight = 992 000

As delivery of dairy milk for human consumption is prohibited earlier than 5 days after calf delivery (use in dystocia), and lidocaine and its metabolites seem to be rapidly excreted, the most likely scenario is a daily intake of 2 µg 2,6-xylidine from milk:

2 µg/70kg =0.029 µg/kg body weight

MOE: 63 500µg/kg body weight/0.029 µg/kg body weight = 2 190 000

Calculation of MOE – meat

The worst-case scenario of daily intake of 2,6-xylidine from meat, assuming no excretion in milk would be:

30 µg/70kg = 0.43 µg/kg body weight

MOE: 63 500µg/kg body weight/0.43 µg/kg body weight = 148 000

Calculation of MOE – meat and milk

2,6-xylidine is shown to be excreted in cow milk. However, as lidocaine and its metabolites seem to be rapidly excreted from the body, the amounts of 2,6-xylidine in cow milk 5 days (withdrawal period after calf delivery) after administration of lidocaine is insignificant.. Therefore, a more "realistic" worst-case scenario, but still considered as a huge overestimation, of 2,6-xylidine intake from beef and cow milk, and assuming EMEAs standards of daily food intake, would be 3.6 µg and 2 µg respectively (Table 10).

Estimated daily intake of 2,6-xylidine from meat and milk would be:

(3.6 µg+2 µg)/70kg=0.08 µg/kg body weight

MOE: 63 500µg/kg body weight /0.08 µg/kg body weight = 794 000

5.4.3 DISCUSSION

Lidocaine is a local-regional anaesthetic agent. In Norway, this drug is currently the drug of choice for local-regional anaesthesia in food producing animals. Generally, lidocaine is administered as a single treatment prior to surgical procedures.

Alternative anaesthetic agents to lidocaine include only procaine and xylazine. Compared to lidocaine, procaine has lower potency and slower onset, as well as shorter duration and causes more side effects. Furthermore, the tissue penetration of this drug is poor. Xylazine is a veterinary sedative-analgesic drug, but the analgesic effect is insufficient for any type of surgical procedure in any species of animal. The Norwegian Scientific Committee for Food Safety is therefore of the opinion that there are no relevant alternatives to the use of lidocaine as a local anaesthetic in food producing animals.

It is acknowledged that the lidocaine metabolite, 2,6-xylidine, is the critical metabolite with regard to human health safety, as it has been shown to be a nasal carcinogen in rats and is classified as a potential carcinogen in man. The acute toxicity of 2,6-xylidine is very low. 2,6-

xylidine is shown to be a metabolite of lidocaine in all species studied, including man, cattle, swine and horses.

In humans, lidocaine is primarily used for local anaesthesia in a variety of indications. Lidocaine is also marketed as non-prescription preparations for rectal administration. Although 2,6-xylidine has been shown to be a metabolite of lidocaine in man, none of the abovementioned lidocaine formulations are contraindicated in pregnant women, in breast-feeding women or in children.

It should be emphasized that few data are available regarding the pharmacokinetics and toxicology of lidocaine in food producing animals. In addition, a substantial number of the cited studies are old, and thus carried out with non-GLP methods. Based on the sparse data available, The Norwegian Scientific Committee for Food Safety is of the opinion that lidocaine would be excreted rapidly from a treated animal, and that only a minor proportion of lidocaine would be metabolized to 2,6-xylidine.

As a NOEL could not be established for lidocaine, alternative methods for the evaluation of human health safety after ingestion of food containing residues of the lidocaine metabolite 2,6-xylidine were considered. In a new draft document from EFSA's Scientific Committee margin of exposure (MOE) is suggested as a new approach for harmonising risk assessment for compounds that have both genotoxic and carcinogenic properties. The EFSA Scientific Committee is of the opinion that a MOE of a magnitude of 25000 or higher, if based on T25, would be of low health risk and might be viewed as low priority for risk management. The Norwegian Scientific Committee for Food Safety is of the opinion that the MOE approach, suggested by EFSA, can be used for the risk characterization of 2,6-xylidine.

All calculated MOE values of 2,6-xylidine ('lidocaine') with different scenarios of daily intake of milk and meat are higher than 25000. MOE of 2,6-xylidine is even likely to be significantly higher than the examples given above. Firstly, the daily intake of meat and milk in Norway, even among high consumers, is lower than the EMEA standard (Table 9). Secondly, in the exposure characterization, the number of cases that could have been administered lidocaine prior to local surgery in 2004 is a significant overestimate. This has been demonstrated through validation of the estimated usage data. Furthermore, for animals where the carcass or milk could be delivered for human consumption, it is assumed that the total dose administered of lidocaine is metabolized to 2,6-xylidine and is localized in the edible tissue or in the milk. Lidocaine has been shown to be metabolized to a variety of metabolites, only a minor proportion of which is for 2,6-xylidine. The lowest T25 dose for the metabolite 2,6-xylidine is 63.5 mg/kg body weight. It is likely that the animals have also inhaled 2,6-xylidine, due to evaporation of 2,6-xylidine from the feed. Concentration of 2,6-xylidine in the nasal epithelium could therefore have been much higher than obtained through the systemic administration and the T25 dose must be considered as conservative.

At present, no appropriate methods exist to assess the risk to human health after a single dose of a genotoxic carcinogenic substance. The worst-case scenario is that a person could be exposed to 2.1 mg of 2,6-xylidine from meat from an animal administered lidocaine for local anaesthesia. This estimate is based on the assumption that the complete dosage of lidocaine is metabolized to 2,6-xylidine (which, in view of the pharmacokinetic properties of lidocaine, is improbable). The Norwegian Scientific Committee of Food Safety is of the opinion that the levels 2,6-xylidine in meat derived from food producing animals slaughtered later than 24

hours after lidocaine treatment is not of any concern as regard human health safety. This concurs with the approved withdrawal time of xylazine (24 hours), which also has 2,6-xylidine as a metabolite (horses, cattle). Xylazine is included in Annex II for horses and cattle.

As milk from an exposed dairy cow is regularly diluted with milk from various producers before it reaches the consumer, the Norwegian Scientific Committee for Food Safety is of the opinion that it is not relevant to calculate exposure through milk from a single cow.

6 Conclusions

The Norwegian Scientific Committee for Food Safety is of the opinion that:

- The use of adequate and appropriate anaesthesia when performing surgery on domestic animals is necessary. There are no relevant alternatives to the use of lidocaine as a local anaesthetic in food producing animals.
- The lidocaine metabolite 2,6-xylidine, which is classified as a potential carcinogen in man, is the critical metabolite with regard to human health safety.
- Few data are available regarding the pharmacokinetics of lidocaine and particularly as regard the formation of 2,6-xylidine in food producing animals. However, lidocaine and the metabolite 2,6-xylidine are assumed to be rapidly excreted.
- Any intake of 2,6-xylidine through consumption of food following use of lidocaine in goats and sheep is highly improbable, while intake of this substance may occur through consumption of cow milk, beef and pork
- It is unlikely that the estimated daily average intake (worst-case scenario) of 2,6-xylidine ('lidocaine') from milk and meat produced in Norway would cause any hazard to human health. In experimental animals only a minor fraction of lidocaine is metabolized to 2,6-xylidine. The MOE approach has been used for the risk characterization of 2,6-xylidine ('lidocaine') and all estimated MOEs are above 25000.
- The amount of 2,6-xylidine in milk from exposed animals, as presented to the consumers, is likely to be insignificant shortly after administration of lidocaine.
- The amount of 2,6-xylidine in meat from an exposed animal is likely to be insignificant 24 hours after administration of lidocaine.

Conclusion: The current withdrawal periods for milk (7 days) and meat (28 days) after use of lidocaine cattle, goat, swine and sheep, can be shortened.

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