Appendix I

Risk assessment of lidocaine residues in food products from cattle, swine, sheep and goats: exposure characterization

Content

Exposure characterization

1 Introduction

The exposure characterization is completed essentially as a worst-case scenario. 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 animals have been published, a worst-case scenario would be that all lidocaine administered is metabolized to 2,6-xylidine on a molar basis. The preparations approved in Norway contain lidocaine hydrochloride monohydras, and thus 1 g of this substance would, as a worst-case, be metabolised to 0.42 g of 2,6-xylidine.

2 Demographic data. Production data

Numbers of food animals to which lidocaine may have been administered in Norway in 2004 are shown in Table 1.

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

	Horses*	**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 2.

Table 2. 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

3 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.

The 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 (Overby & 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 the 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=1005). The methodology used was a pre-coded 4-day record using photographs of foods items and data refers to food as consumed with weight of food.

Table 3. Daily consumption of meat, milk and milk products and cheese among different consumer 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, of which beef, pork and mutton meat comprises 12 g, 16 g and 6 g, respectively. 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 eaten outside the home, 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 risk characterization, data obtained through NORKOST 1997 and UNGKOST 2000 are used (Table 3).

4 Assessment of lidocaine residues in milk and meat

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 from the Norwegian animal health recording systems and other

relevant information obtained from the various Norwegian animal health services. 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.

4.1 ASSESSMENT: MILK

4.1.1 COW MILK

The Norwegian Cattle Health Recording System (NCHRS) for dairy cows, established in 1975, is a basic part of the Norwegian Cattle Health Services and includes 95% of Norwegian dairy cattle. The numbers of cases/individuals for which lidocaine is used are not recorded in NCHRS. However, based on numbers of reported treatments in 2004 (NCHRS), it can be judged that lidocaine could have been used in a maximum of approximately 14 000 treatments of single dairy cattle (Table 4) that year (Østerås 2005). The data in NCHRS are validated on a regular basis and the proportion of diseases reported, as well as the quality of the data, has been found to be high (Østerås O, NCHS, personal communication, 5 April 2005)

The lidocaine dosage for local anaesthesia in cattle varies between 100 mg - 2000 mg per animal, depending on the indication for surgery/anaesthesia (Thurmon et al 1996).

It is estimated that the maximum total amounts of lidocaine administered to dairy cows in Norway in 2004 could have been 10 820 g (Table 4), which corresponds to 4544 g of 2,6-xylidine. It is assumed that the complete dosage of lidocaine administered to dairy cattle is rapidly excreted into the milk as 2,6-xylidine and that the dilution effect caused by mixing of milk from several cows and farms is random (1 526 millions of litres produced in Norway in 2003). Based on these assumptions, the maximum average amount of 2,6-xylidine in cow milk is estimated to 3 µg/kg. 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 for cow milk. With a daily intake of 1.09 l milk (high consumption in adults in Norway – 95% percentile) and 0.46 l milk (mean consumption in adults in Norway) this figure would be 3.3 µg and 1.4 µg**,** respectively.

Table 4. No. of recordings of treatments of various diseases or disease categories in single dairy cows (all records) in 2004 (Østerås 2005), the assumed maximum dosage that could have been used (Thurmon et al 1996) for the various diagnoses/diseases, and the calculated amounts used

Diagnosis; disease (Assumed maximum dosage used)	**No. of dairy cows**	**Amounts lidocaine (g)**
Colic/gastrointestinal dislocation/abomasal dislocation/(2000 mg)	638	1 276
Bloat/(200 mg)	94	18.8
Dehorning due to injury/(400 mg)	42	16.8
Dehorning/(200 mg)	85	17
Hoof diseases/(800 mg)	1 855	1 484
Wounds; injuries (except teat injuries)/(2000 mg)	473	946
Extirpation of supernumerary teats/(100 mg)	11	1.1
Teat injuries/(100 mg)	6 868	686.8
Uterine prolapse/(200 mg)	421	84.2
Dystocia[1]/(2000 mg)	3 104	6 208
Vaginal prolapse/(200 mg)	403	80.6
Castration/(200 mg)	1	0.2
Total no. of cases/amounts lidocaine used (g)	**13 995**	**10 819.5**

[1]Includes Caesarean section

Approximately 6 208 g of the lidocaine that could have been used in dairy cattle in 2004 would have been for the indication dystocia. As delivery of milk for human consumption is prohibited within the first 5 days after calf delivery, a withdrawal time of milk of 5 days is in place automatically. If the lidocaine used is completely excreted within this period, 4 612 g (10 820 g – 6 208 g) of lidocaine, i.e., 1 937 g 2,6-xylidine, would contribute to residues in cow milk. The average amounts of 2,6-xylidine in cow milk would then be 1.3 µg/kg. Assuming a daily intake of 1.5 l, 1.09 l and 0.46 l of milk, respectively, the daily intake of 2,6-xylidine in milk would be 2 µg, 1.4 µg and 0.6 µg.

4.1.2 GOAT MILK

The Norwegian Goat Health Recording System (NGHRS), established in 1996, is a basic part of the Norwegian Goat Health Services (NGHS) and includes 71% (n=402) of the Norwegian dairy goat farms (N=564) (http://www.ssb.no/emner/10/04/10/jordhus/tab-2004-05-14-01.html; accessed 15 March 2005). In 2004, disease data were reported to NGHRS from 221 Norwegian goat farms (39% of the farms), of which 33 were cases for which lidocaine might have been used (Lunder 2005). Assuming that these farms/farmers are representative of the Norwegian dairy goat farms/farmers, the total number of dairy goats that could have had lidocaine administered in 2004 can be estimated to be 85 (Table 5). However, it is likely that only a minor proportion of these animals were exposed to surgery/lidocaine, e.g., only a minor proportion of the teat injuries would be treated through surgery (Lunder T, NGHS, personal communication, 15 March 2005).

The lidocaine dosage for local anaesthesia in dairy goat varies between 100 mg - 200 mg per individual, depending on the indication for surgery/anaesthesia (Thurmon et al 1996).

Table 5. Estimated maximum number of cases for the various diagnoses and diseases in dairy goats in 2004 for which lidocaine could have been used (Lunder 2005), the assumed maximum dosage that could have been used (Thurmon et al 1996) for the various diagnoses/diseases, and the calculated amounts used

Diagnosis; disease(Assumed maximum dosage used)	**Teat injuries (100 mg)**	**Uterine prolapse (100 mg)**	**Dehorning (200 mg)**	**Total**
Estimated no. of cases	59	21	5	**85**
Estimated amounts used (g)	5.9	2.1	1	**9**

The maximum total amounts of lidocaine administered to dairy goats in Norway in 2004 could have been 9 g (Table 5), which corresponds to 3.8 g of 2,6-xylidine. Assuming that the complete dosage of lidocaine administered to dairy goats is excreted in the milk as 2,6-xylidine, and that the mixing (dilution effect) of milk from several goat farms at the dairies is random, the average amounts of 2,6-xylidine in goat milk produced in Norway in 2004 is calculated to 0.2 be g/kg.

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 cows milk whey, milk and cream. 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). As the sales of cheese with goat milk in Norway is only 14 % of the total sales of that product group (Klafstad 2005), the daily intake of lidocaine residues from goat milk is insignificant.

4.2 ASSESSMENT: MEAT

4.2.1 BEEF

Dehorning and most castrations of calves are usually completed within 4 weeks after birth. If these calves are euthanized for animal welfare reasons within 4 weeks after treatment, they are unlikely to be delivered for human consumption due to economic reasons (e.g., transport costs). The amounts of lidocaine used for dehorning and castration of calves should therefore not be included as sources of lidocaine residues in cattle meat.

The maximum single lidocaine dosage assumed to be administered to cattle prior to surgery is 2000 mg (Thurmon et al 1996) and the dosage per kg animal would be highest in calves. As carcasses from young calves are unlikely to be delivered for human consumption after an animal is euthanized for animal welfare reasons, the maximum single exposure estimates of 2,6-xylidine from treated cattle is calculated for a calf of 200 kg. Assuming that the maximum dosage of lidocaine (2000 mg, i.e., 840 mg 2,6-xylidine) is used in a calf of 200 kg and the total dose is contained and evenly distributed throughout the animal as 2,6-xylidine at slaughter, the average amount in edible tissue would 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 an exposed animal. With a daily intake of 0.206 kg meat (high consumption in adults in Norway – 95% percentile) and 0.106 kg meat (mean consumption in adults in 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 that have been slaughtered just after treatment with lidocaine on a regular basis. An alternative approach to estimate daily intake of 2,6-xylidine in beef would be to consider the distribution of 2,6-xylidine residues in all cattle meat intended for human consumption. Such a theoretical assumption would be a more adequate method for the risk characterization of human exposure of lidocaine residues through cattle meat.
The maximum amount of lidocaine likely to result in 2,6-xylidine in edible beef in Norway in 2004 is estimated to be 12 279 g (378.4 g +1 081.3 g + 10 819.5 g, see Table 6), i.e., 5 157.2 g of 2,6-xylidine. A worst-case scenario is that all the cattle are slaughtered for emergency reasons and that the complete dosage of lidocaine administered to each animal remains evenly distributed as 2,6-xylidine in the edible tissues at the time of slaughter (no excretion in the milk). Meat containing 2,6-xylidine is assumed to be “diluted” with unexposed meat, as it is highly improbable that a person will consume meat only from exposed animals throughout a year. Provided that the exposed meat is evenly distributed at the market, both geographically and throughout the year, the daily average amount of the 2,6-xylidine in edible tissue from “diluted” beef (annual amount produced in 2004 was 86 074 tonnes slaughter weight, see Table 2) is estimated to approximately 60 µg/kg. Assuming EMEA’s standard of daily intake of meat products, daily intake of this metabolite would be 30 µg per individual. This figure is used for the calculation of worst-case MOE value for beef. With a daily intake of 0.206 kg meat (high consumption in Norway – 95% percentile) and 0.106 kg meat (mean consumption in Norway) this figure would be 12.4 µg and 6.4 µg, respectively.

Table 6. No. of recordings (all records) of treatments of various diseases or disease categories in bulls/bullocks, heifers/female calves and dairy cows during 2004 for which emergency slaughter or euthanasia could have occurred (Østerås 2004). The assumed maximum dosage that could have been used (in parentheses) in each indication, the calculated amounts used per category cattle and diagnosis/disease and the calculated amounts (in metric tonnes) of emergency slaughter that could have been delivered for human consumption. Assumed used in bulls (B) (600 kg); heifers (H) (400 kg); dairy cows (600 kg)

Diagnosis; disease/ (Assumed maximum dosage used)	**No. males (bulls and male calves)**	**Total amounts used (g)**	**Weight treated (in tonnes)**	**No. heifers; female calves**	**Total amounts used (g)**	**Weight treated (in tonnes)**	**No. dairy cows**	**Total amounts used (g)**	**Weight treated (in tonnes)**
Colic/gastrointestinal dislocation/abomasal dislocation/(2000 mg)	43 (B)	86	25.8	53(H)	106	21.2	638	1 276	382.8
Bloat/ (200 mg)	14 (B)	2.8	8.4	28 (H)	5.6	11.2	94	18.8	56.4
Dehorning due to injury/(400 mg)	47 (B)	18.8	28.2	45 (H)	18	18	42	16.8	25.2
Hoof diseases/(800 mg)	86 (B)	68.8	51.6	275 (H)	220	110	1 855	1 484	1 113
Wounds; injuries (except teat injuries)/(2000 mg)	101 (B)	202	60.6	254 (H)	508	101.6	473	946	283.8
Extirpation of supernumerary teats/(100 mg)	-			52 (H)	5.2	20.8	11	1.1	6.6
Teat injuries/(100 mg)	-			41(H)	4.1	16.4	6 868	686.8	4 120.8
Uterine prolapse/(200 mg)	-			2 (H)	0.4	0.8	421	84.2	252.6
Dystocia/(2000 mg)	-			105 (H)	210	42	3 104	6 208	1 862.4
Vaginal prolapse/(200 mg)	-			20 (H)	4	8	403	80.6	241.8
Dehorning/(200 mg)							85	17	51
Castration/(200 mg)							1	0.2	0.6
Subtotal	**291**	**378.4**	**174.6**	**875**	**1 081.3**	**350**	**13 995**	**10 819.5**	**8 397**
	Subtotal: Amounts (g) of lidocaine that at a maximum could have been used in cattle								***12 279.2***
	Maximum amounts of live weight (tonnes) that could have been treated								***8 921.6***
Dehorning[2] (200 mg) calves	140 000	28 000		130 000[3]	26 000				
Castration/(200 mg) calves	345	69		4	0.8				
Subtotal		**28 069**			**26 000.8**				
	Total: Amounts (g) lidocaine that at a maximum could have been used in cattle								***62 991.4***

[1]Includes Caesarean section; [2]Number of cases/animals of dehorning is underreported as dehorning is not considered a disease; therefore the number of cases is defined as numbers of calves born in 2004 minus 10% (that are assumed to die before dehorning) (Østreås 2004); [3] Calves only

The average age of the dairy cattle slaughtered in Norway in 2003 was 47.8 months (Roaldkvam 2004). The likelihood of cattle being slaughtered for emergency reasons is assumed to be only slightly elevated for animals exposed to lidocaine, as compared to unexposed animals. Hence, a significant proportion of the dairy cows treated with lidocaine in 2004 were not slaughtered that year. As a major part of lidocaine use in cattle is considered to have been in dairy cattle (88 %), the amounts of lidocaine likely to have caused residues in beef during 2004, due to emergency slaughter, would be significantly below 12 279 g.

Of the 12 279 g of lidocaine that could have been administered to cattle in 2004, 10 820 g were estimated to have been used in dairy cattle. Provided that this amount is completely excreted in milk, only 1 459.7 g (= 613 g of 2,6-xylidine) could have contributed to residues in beef. The amounts of 2,6-xylidine in "diluted" meat in 2004 (86 074 tonnes, see Table 2) would then have been approximately 7.1 µg/kg. With a daily intake of 500 g meat (EMEA standard), 0.206 kg meat (high consumption in Norway – 95% percentile) and 0.106 kg meat (mean consumption in Norway), the daily intake of 2,6-xylidine per individual would be 3.6 µg, 1.5 µg and 0.8 µg, respectively.

The average slaughter weight of cattle is approximately 50 % of the live weight. Of the 8 922 metric tonnes (males: 175 tonnes; heifers/female calves: 350 tonnes; dairy cattle: 8 397 tonnes, see Table 6) of biomass of cattle that, at a maximum, could have been exposed to lidocaine (assuming no excretion in milk) in 2004, approximately 4 500 tonnes would be edible tissue. As the amount of meat that originates from cattle produced in Norway was 86 074 tonnes in 2004 (Table 2), the calculated proportion of Norwegian beef that could contain 2,6-xylidine in 2004 is 5 %. Assuming that the lidocaine used in dairy cattle was not distributed in the edible tissue at all (i.e., the total amount was excreted in milk), the biomass of cattle that could have been exposed to lidocaine was 525 tonnes (175 tonnes + 350 tonnes). As this corresponds to approximately260 tonnes slaughter weight (i.e. 50% of the 525 tonnes biomass), the proportion of beef that, at a maximum, could contain 2,6-xylidine would have been 0.3% (annual amount produced in 2004 was 86 074 tonnes, see Table 2).

4.2.2 PORK

The Norwegian Pig Health Recording System (NPHRS) was established in 2000 by the Norwegian Pig Health Service (NPHS). However, numbers of cases likely to have been treated with lidocaine are not recorded in NPHRS. Knowledge about occurrence of such diseases/indications in the various age groups of swine was therefore obtained from NPHS. The veterinarians employed at NPHS have extensive and continuous contact with swine veterinarians as well as the pig farmers throughout Norway and are therefore assumed to be a reliable source regarding use of lidocaine in the various indications in swine. Such data were therefore obtained from NPHS.

The major indication for use of lidocaine in swine production is castration of male pigs, usually completed within 2 weeks after birth (Baustad B, NPHS, personal communication, 7 March 2005). In Norway, all male pigs are castrated, and it is mandatory to use local anaesthesia prior to castrating. Lidocaine is the drug currently recommended for this indication. In 2004, approximately 700 000 male piglets were castrated in Norway and the dosage used is assumed to be 40 mg. Thus approximately 28 kg lidocaine was used for castration of male piglets in 2004. If these piglets are euthanized for animal welfare reasons

within 4 weeks after castration (current withdrawal time is 28 days), it is unlikely that they would be delivered for human consumption for economic reasons (e.g., transport cost).

The only indication of significance in swine for which residues of lidocaine would be of any concern with regard to safety of human health is surgical removal of the 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 the maximum recommended dosage of 40 mg lidocaine (corresponds to 16.8 mg of 2,6-xylidine) is used before surgical removal of a damaged tail close to slaughter (100 kg), and that the total dose is contained and evenly distributed in the animal as 2,6-xylidine at the time of slaughter, the average amount in edible tissue would be 0.168 mg/kg. Assuming an intake of meat products of 500 g (EMEA standard) one person could be exposed to 84 µg of 2,6-xylidine in a meal from a treated animal. With a daily intake of 0.206 kg meat (high consumption in adults in Norway – 95% percentile) and 0.106 kg meat (mean consumption in adults in Norway) this figure would be 35 µg and 18 µg, respectively.

It is, however, highly improbable that any person in Norway would eat meat only from swine that have been slaughtered soon after treatment with lidocaine on a regular basis. An alternative approach to estimate daily intake of 2,6-xylidine residues would be to consider the distribution of 2,6-xylidine residues in all pork intended for human consumption. Such a theoretical assumption would be more adequate for a risk characterization of human exposure of 2,6-xylidine from pork.

Data recorded at slaughter houses in Norway in 2004, indicate evidence of tail biting in approximately 3 % of the slaughtered pigs annually. In 2004, 1.3 million pigs were slaughtered in Norway and therefore 39 000 pigs could, theoretically, have been exposed to surgical removal of the damaged tail. As the assumed maximum dosage is 40 mg (Thurmon et al 1996), approximately 1 560 g lidocaine (corresponds to 655.2 g of 2,6-xylidine) could have been used prior to surgery following tail biting. The average amount (worst-case) of 2,6-xylidine from “diluted” pork (annual amounts produced in 2004 were 112 943 tonnes slaughter weight; Table 2) is calculated to be 5.8 µg/kg. The daily intake of 2,6-xylidine from “diluted” pork would be 2.9 µg assuming EMEA standard meat intake. With a daily intake of 0.206 kg meat (high consumption in adults in Norway – 95% percentile) and 0.106 kg meat (mean consumption in adults in Norway) this figure would be 1.2 µg and 0.6 µg, respectively.

The proportion of the 39 000 pigs likely to have been exposed to lidocaine injection and surgical treatment of the damaged tail is considered to be very low (Baustad B, NPHS, personal communication, 30 March 2005).

As the damaged tail is usually infected with bacteria, pigs that are exposed to surgical treatment of the damaged tail are regularly treated with benzylpenicillinprocaine i.m. (Baustad, B., NPHS, personal communication, 30 March 2005). The recommended withdrawal time for meat following i.m. injection of benzylpenicillinprocaine is 14 days. This withdrawal time will thus automatically be applied for lidocaine. As both lidocaine and its metabolites seem to be rapidly excreted after injection, it is unlikely that there will be any residues of 2,6 xylidine in meat from treated animals.

The average slaughter weight of pigs is approximately 70% of the live weight. Edible tissue of pigs estimated to have been subjected to surgical treatment of the damaged tail in 2004 and subjected to emergency slaughter within 28 days after treatment could, at maximum, have

been 2 730 tonnes (39 000 x 100 kg x 70%). Therefore the maximum calculated proportion of Norwegian pork containing 2,6-xylidine in 2004 could have been 2.4%.

4.2.3 MUTTON/LAMB

In Norway, it has been possible to report disease data to the Norwegian Sheep Recording System (NSRS) since the late 1990s. Presently, 25 % of Norwegian sheep farms are registered at NSRS, but only 10% report occurrence of diseases to this database. In 2004, 1 500 disease cases for which lidocaine could have been used were reported for sheep aged 1 year or older (Vatn 2005). Assuming these farms/farmers are representative for all Norwegian sheep farms/farmers, the maximum annual number of cases/individuals where lidocaine could have been used in sheep in 2004 could have been 15 000. However, based on knowledge from the field, it is likely that the actual annual number of cases where lidocaine was used was quite low (Vatn 2005). Of these, only a few are likely to have been euthanized for animal welfare reasons. Due to economic reasons (e.g., transport cost) it is unlikely that such carcasses would be delivered for human consumption.

Lambs, which are slaughtered at 7-8 months of age, 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 give rise to residues of 2,6-xylidine in meat.

4.2.4 GOATS' MEAT

The major indication for lidocaine use in goats is dehorning, which is usually performed within 2 weeks after birth (Lunder T, NGHS, personal communication, 14 March 2005). Goats intended for meat production are slaughtered at the age of 6 weeks (at earliest) or later.

Other indications for the use of lidocaine in dairy goats are Caesarean section and teat surgery following injuries (Table 5). Based on knowledge from the field, the number of such cases/individuals is likely to be very low and of these only a few are slaughtered for emergency reasons (Lunder 2005), but due to economic reasons (e.g., transport costs) it is unlikely that such carcasses would be delivered for human consumption.

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

4.2.5 VARIOUS ANIMALS

The estimated maximum total amount of lidocaine that could have been administered to cattle (12 279.2) and swine (1 560 g) and thus give rise to residues of 2,6-xylidine, is 13 839.2 g. This corresponds to 5 812.5 g of 2,6-xylidine. Assuming that this amount was "diluted" in the total amount of meat produced from the major animal species in Norway in 2004 (279 514 tonnes), the average amount of 2,6-xylidine in "diluted" meat would have been approximately 21 µg/kg. Daily intake of 2,6-xylidine from "diluted" meat would then be 10.5 µg, assuming EMEA standard meat intake. With a daily intake of 0.206 kg meat (high consumption in adults in Norway – 95% percentile) or 0.106 kg meat (mean consumption in adults in Norway), this figure would be 4.3 µg and 2.2 µg, respectively.

Provided that all the lidocaine used in dairy cattle was excreted as 2,6-xylidine in milk, the amounts that could give rise to residues in cattle (378.4 g + 1 081.3 g) and swine (1 560 g) meat would be 3 019.7 g, i.e., 1 268.3 g of 2,6-xylidine. Assuming that this amount was "diluted" in the total amount of meat produced from the major animal species in Norway in 2004 (279 514 tonnes), the average amount in "diluted" meat would be 4.5 µg/kg. Thus, the daily intake of 2,6-xylidine from "diluted" cattle and swine meat would be 2.2 µg, assuming EMEA standard meat intake. With a daily intake of 0.206 kg meat (high consumption in adults in Norway – 95% percentile) or 0.106 kg meat (mean consumption in adults in Norway), this figure would be 0.9 µg and 0.5 µg, respectively.

4.3 VALIDATION OF THE EXPOSURE ESTIMATES

In Norway, lidocaine preparations for use in animals must be dispensed through pharmacies, that in turn have to obtain all drugs from authorized wholesalers. The wholesalers are mandated to report drugs sales data to the pharmacies to the Norwegian Institute of Public Health (NIPH). Sales data in 2004, given as number of packages, for injectable veterinary lidocaine preparations, both approved preparations and preparations prepared by authorized Norwegian pharmacies, were collected from NIPH (Litleskare 2005). Annual sales of the lidocaine preparations from wholesalers to pharmacies are considered to be a good estimate of the sales of these drugs from pharmacies to veterinarians, assuming that the amounts stocked in pharmacies are maintained at the same level each year.

The calculated amounts of lidocaine sold for use in animals in Norway in 2004 are estimated to 76.5 kg active substance. The estimated usage is summarized in Table 7.

Table 7. Estimated amounts of lidocaine used in 2004 in various food animal species and diseases/indications

Diseases/indications	**True usage**	**Could have been used**
Dehorning of calves[1]	54 kg	
Castration of calves[1]	0.07 kg	
Castration of piglets[1]	28 kg	
Cattle – various diseases		12.28 kg
Dairy goat		0.09 kg
Subtotal	82.07 kg	12.29 kg
Total		**94.36 kg**

[1]If the animal is euthanized for animal welfare reasons, the carcass will not be delivered for human consumption for economic reasons (e.g., transport cost)

As the use of lidocaine is mandated for dehorning and castration, the estimated amount (82.1 kg) for these indications is thought to be a reliable estimate and is therefore indicated as "True usage" in Table 7. However, the "True usage" estimate is based on the recommended maximum dosage being administered in each case and lower dosages might sometimes have been used for these indications. This may explain why "True usage" is higher than the sold amounts. It is concluded that the estimated usage of 12.3 kg lidocaine for animals that could possibly have been slaughtered for emergency reasons ("Could have been used") and for

which the carcass could have been delivered for human consumption, is a huge overestimate. This conclusion is strengthened by the fact that lidocaine use in horses and sheep and companion animals was not included in the estimate of 93.36 kg (data to complete such an assessment were not available).

4.4 SUMMARY: ESTIMATED INTAKE OF RESIDUES

It is concluded that while it is unlikely that there will be any intake of 2,6-xylidine through food following use of lidocaine in goats and sheep, intake of this substance may occur through cow milk, beef and pork. Daily intake of 2,6-xylidine per individual (adults), estimated by application of various methods, is summarized in Table 8.

Table 8. 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 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 not permitted 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, goats, horses and poultry meat produced in Norway

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