



Australian Government
**Australian Pesticides and
Veterinary Medicines Authority**



Trade Advice Notice

on lignocaine and bupivacaine in the product
Tri-Solfen Wound Anaesthetic & Antiseptic Solution for use on sheep

APVMA product number 88635

September 2023

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This publication is available from the [APVMA website](#).

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Preface

The Australian Pesticides and Veterinary Medicines Authority (APVMA) is an independent statutory authority with responsibility for assessing and approving agricultural and veterinary chemical products prior to their sale and use in Australia.

The APVMA has a policy of encouraging openness and transparency in its activities and of seeking stakeholder involvement in decision making. Part of that process is the publication of Trade Advice Notices for all proposed extensions of use for existing products where there may be trade implications.

The information and technical data required by the APVMA to assess the safety of new uses of chemical products and the methods of assessment must be undertaken according to accepted scientific principles. Details are outlined in regulatory guidance published on the APVMA website.

About this document

This Trade Advice Notice indicates that the APVMA is considering an application to vary the use of an existing registered veterinary chemical product.

It provides a summary of the APVMA's residues and trade assessment.

Comment is sought from industry groups and stakeholders on the information contained within this document.

Making a submission

The APVMA invites any person to submit a relevant written submission as to whether the application to vary Tri-Solfen Wound Anaesthetic & Antiseptic Solution be granted. Submissions should relate only to matters that the APVMA is required by legislation to take into account in deciding whether to grant the application. These grounds relate to the trade implications of the extended use of the product. Submissions should state the grounds on which they are based. Comments received outside these grounds cannot be considered by the APVMA.

Submissions must be received by the APVMA by close of business on 28 October 2023 and be directed to the contact listed below. All submissions to the APVMA will be acknowledged in writing via email or by post.

Relevant comments will be taken into account by the APVMA in deciding whether to grant the application and in determining appropriate conditions of registration and product labelling.

When making a submission please include:

- contact name
- company or organisation name (if relevant)
- email or postal address (if available)
- the date you made the submission.

Please note: submissions will be published on the APVMA's website, unless you have asked for the submission to remain confidential, or if the APVMA chooses at its discretion not to publish any submissions received (refer to the [public consultation coversheet](#)).

Please lodge your submission using the [public consultation coversheet](#), which provides options for how your submission will be published.

Note that all APVMA documents are subject to the access provisions of the *Freedom of Information Act 1982* and may be required to be released under that Act should a request for access be made.

Unless you request for your submission to remain confidential, the APVMA may release your submission to the applicant for comment.

Written submissions should be addressed to:

Residues and Trade
Risk Assessment Capability
Australian Pesticides and Veterinary Medicines Authority
GPO Box 3262
Sydney NSW 2001

Phone: +61 2 6770 2300

Email: enquiries@apvma.gov.au

Further information

Further information can be obtained via the contact details provided above.

Further information on Trade Advice Notices can be found on the APVMA website apvma.gov.au.

Introduction

The APVMA has before it an application from Dechra Veterinary Products (Australia) Pty. Ltd. to vary the registration of Tri-Solfen Wound Anaesthetic & Antiseptic Solution (P88635) containing lignocaine, bupivacaine, adrenaline and cetrimide on sheep and to amend the current meat withholding period (WHP) on sheep from 90 days to zero days whilst retaining the current export slaughter interval (ESI) of 90 days.

Tri-Solfen Topical Anaesthetic & Antiseptic Solution for Pain Relief in Lambs and Calves (APVMA 60099), which contains the same active constituents as the proposed product, was originally approved in December 2011 for use in sheep for pain relief following mulesing with a 90-day meat WHP and ESI. A public release summary was published for this original use in October 2011¹. Since the original approval, use has been extended to include claims for pain relief in lambs for castration and tail docking as well as for pain relief for calves and piglets. Table 5 entries in the APVMA MRL standard currently cover the approved uses as residues are not expected in tissues of animals slaughtered 90 days after treatment.

While the current proposal is for a reduction of the meat WHP from 90 days to zero days, no amendments to the current treatment² regime or an ESI of 90 days for sheep are proposed. Therefore, the theoretical trade risk associated with sheep meat export remains unchanged to that which currently exists. Nevertheless, the trade risk has been assessed based on the new residues data which was submitted with this application to justify the proposed zero-day meat WHP and the current ESI of 90 days for the product. Additionally, consideration to the appropriate residue definition (marker residue) and establishment of MRLs for edible sheep tissues are required for lignocaine and bupivacaine based on the available scientific information provided. The associated trade and safety related aspects with lignocaine and bupivacaine are discussed here.

Adrenaline and cetrimide are currently approved in veterinary medicine products for use in food-producing species (including sheep) with a nil (zero days) WHP. Adrenaline is a hormone produced naturally by the adrenal glands and when it is administered topically, it is poorly absorbed and rapidly metabolised by the liver with a plasma half-life of 2.5 minutes. Cetrimide is poorly absorbed from the gastrointestinal tract after oral dose and is quickly excreted. The use of cetrimide in food producing species should not result in residues in food of animal origin at concentrations which are toxicologically relevant for the safety of consumers. For these reasons, no changes to the existing Table 5 entries in the APVMA MRL standard, which lists situations where residues do not or should not occur in food, where the residues are identical to or indistinguishable from natural food components or are otherwise are of no toxicological significance, are considered necessary for adrenaline and cetrimide. Further consideration of adrenaline and cetrimide is considered unnecessary from residues and trade perspective and these compounds will not be discussed in detail in this Trade Advice Notice.

¹ Australian Pesticides and Veterinary Medicines Authority (APVMA), 2011. [Bupivacaine in the product Tri-solfen Topical Anaesthetic and Antiseptic Solution for Pain Relief in Lambs](#), APVMA website, accessed September 2023.

² PubCRIS, 2023. [PubCRIS database](#), accessed September 2023.

Trade considerations

Commodities exported

Edible sheep commodities (meat, fat, edible offal) are considered to be major export commodities³.

Destination and value of exports

In 2021–22, sheep meat exports were valued at \$4.5 billion^{4 5}. The significant export markets for sheep commodities include the US, China, Malaysia and Korea.

Proposed Australian use

Tri-Solfen Topical Anaesthetic & Antiseptic Solution For Pain Relief In Lambs Following Mulesing (40.6 g/L lignocaine (as hydrochloride), 4.2 g/L bupivacaine (as hydrochloride), 24.8 mg/L adrenaline (as acid tartrate) and 5.0 g/L cetrimide). Table 1 shows the proposed label instructions for Tri-Solfen Topical Anaesthetic & Antiseptic Solution For Pain Relief In Lambs.

³Australian Pesticides and Veterinary Medicines Authority (APVMA), 2020. [Pesticides: Overseas trade \(Part 5B\) – Major export food commodity groups](#), APVMA website, accessed 5 December 2022.

⁴Australian Trade and Investment Commission (Austrade), 2022. [Australian exporters to benefit from growing global appetite for sheepmeat](#), accessed September 2023.

⁵Department of Agriculture, Fisheries and Forestry (DAFF), February 2023. [Snapshot – Australian sheepmeat exports](#), DAFF website, accessed September 2023.

Table 1: Proposed label instructions for Tri-Solfen Topical Anaesthetic & Antiseptic Solution For Pain Relief In Lambs

Claims:	Tri-Solfen is a local anaesthetic and antiseptic spray to provide pain relief for use on lambs following mulesing, tail docking and castration.
Restrains:	DO NOT USE on ewes where milk may be used or processed for human consumption.
Dosage:	Use of the special Tri-Solfen applicator is recommended Dose – lambs Mulesing <ul style="list-style-type: none"> • Lambs (5 to 10 kg): 6 mL • Lambs (11 to 15 kg): 8 mL • Lambs (16 to 20 kg): 10 mL • Lambs (over 20 kg): 12 mL Tail docking (if not concurrently mulesed) <ul style="list-style-type: none"> • Lambs up to 10 kg: 1.5 mL • Lambs over 10 kg: 2 mL Castration <ul style="list-style-type: none"> • Lambs up to 10 kg: 3 mL (total) • Lambs over 10 kg: 4.5 mL (total)
Withholding periods:	Meat (sheep): Zero (0) days.
Trade advice:	Export slaughter interval (ESI) DO NOT USE less than 90 days before slaughter for export. Before using this product confirm the current ESI from Dechra Veterinary Products Australia Pty Ltd on 1300 015 825 or the APVMA website (www.apvma.gov.au/residues).

Results from residues depletion study presented to the APVMA

To support the first use of veterinary medicines which may result in residues in animal food commodities, the APVMA generally requires the submission of radiolabelled depletion studies in the target species based on APVMA⁶ and VICH guidelines. For lignocaine and bupivacaine however, there is a wealth of existing data which addresses the metabolism and pharmacokinetics in a range of animal species including sheep. The APVMA therefore has accepted an approach in which a non-radiolabelled residue depletion study has been conducted in sheep where samples were analysed for lignocaine and bupivacaine and a range of their metabolites. The metabolites included for analysis were selected based on the existing metabolism and pharmacokinetics studies. The existing metabolism and pharmacokinetics studies together with the results of the residue depletion study has been assessed to inform a decision of an appropriate marker residue for lignocaine and bupivacaine while the results of the residue depletion study have been used for the MRL

⁶ Australian Pesticides and Veterinary Medicines Authority (APVMA), 2014. [Veterinary Data Guidelines – Metabolism and kinetics \(Part 4\)](#), APVMA website, accessed September 2023.

consideration, the consumer safety assessment and the trade risk assessments. The available data relevant to the potential for lignocaine and bupivacaine residues in sheep tissues are summarised below.

Metabolism and pharmacokinetics

Lignocaine

In the available metabolism studies, lignocaine was almost completely metabolised in all species studied (humans, rats, guinea pigs, dogs, horses, pigs, sheep and cattle), with the liver and intestine (after oral administration) as the primary sites of metabolism. Three main types of metabolic reactions have been identified: aromatic hydroxylation, N-dealkylation and amide hydrolysis, followed by conjugation. Lignocaine undergoes N-dealkylation to form monoethylglycinexylidide (MEGX), which is further dealkylated to glycinexylidide or hydrolysed to 2,6-xylidine. Glycinexylidide (GX) is further hydrolysed to form 2,6-xylidine. 2,6-xylidine is of potential toxicological concern and the APVMA's toxicological assessment has recommended that the acceptable daily intake (ADI) of 0.01 mg/kg and the acute reference dose (ARfD) of 0.03 mg/kg for lignocaine will cover both lignocaine and 2,6-xylidine.

Lignocaine is metabolised in a similar manner across species, however, there appears to be quantitative differences in the extent to which each pathway is utilised between species, leading to quantitative rather than qualitative differences between the metabolites detected. In rats, sheep and horses, oxidative metabolism via N-dealkylation and 3-hydroxylation predominate and amide hydrolysis is a relatively minor pathway of metabolism. The major metabolites in these species were 3-OH-lignocaine and/or: 3-OH-MEGX, MEGX or GX. Minor metabolites are XYL, 4-OH-Xyl, 4-OH-lidocaine, 4-OH MEGX, Lignocaine-N-oxide. In guineapigs, rabbits, dogs, cattle, pigs and humans N-dealkylation and amide hydrolysis predominate, and 3- and 4-hydroxylation are minor pathways of metabolism. The major metabolites in these species are thus MEGX and/or; GX, 2,6-Xylidine and 4-OH-Xylidine. Minor metabolites are 3-OH- Lignocaine and -MEGX, and 4-OH -lignocaine and -MEGX, and lignocaine-N-oxide. In a comparative pharmacokinetic study involving cattle and sheep, differences in the prevalence of 2,6-xylidine were observed. In cattle, lignocaine primarily metabolises to 2,6-xylidine whereas it was only a minor metabolite in sheep.

In the residue depletion study conducted in sheep, tissues were analysed for parent lignocaine, 2,6-xylidine, monoethylglycinexylidide (MEGX), glycinexylidide (GX), 3-OH lignocaine and lignocaine N-oxide. Generally, parent lignocaine was the predominant component of the total residue, while 2,6-xylidine, MEGX, GX and 3-OH lignocaine were detected. Detectable residues of lignocaine N-oxide were seldom observed in edible tissues.

Lignocaine was found to be a measurable and major component of the residues at all timepoints in the residue depletion study provided and the decline of lignocaine correlated with the total residues in all edible sheep tissues. For this reason, parent lignocaine is considered to be a suitable marker residue for the proposed use with a zero-day meat WHP in sheep. Based on the results of the residue depletion study conducted in sheep in which lignocaine and 5 of its metabolites were measured, the ratio of marker residue to total residues (MR:TR) for lignocaine in sheep tissues was determined to be 0.33 for fat, 0.06 for liver, 0.18 for kidney and 0.20 for muscle.

Bupivacaine

In the available metabolism studies, bupivacaine was extensively and rapidly metabolised in all species investigated (humans, primates, rabbits, rats and sheep). Metabolism of bupivacaine occurs primarily in the liver, with urinary and biliary excretion of bupivacaine and its metabolites. Metabolites of bupivacaine may include 2,6-pipecolylxylidine (PPX; also called desbutyl bupivacaine), 3'-hydroxy-bupivacaine (3-OH-bupivacaine), 4'-hydroxybupivacaine and 2,6-xylidine.

Like for lignocaine, there appears to be quantitative species differences in the extent to which metabolites of bupivacaine may occur. In a comparative pharmacokinetic study involving cattle and sheep, differences in the prevalence of PPX were observed. In cattle, PPX constituted 98.6% of the bupivacaine metabolites recovered in urine, the remainder being parent compounds. Whereas in sheep, 99.99% of bupivacaine is excreted unchanged in the urine, with only a trace of PPX detected.

In the residue depletion study conducted in sheep, tissues were analysed for parent bupivacaine, 3-OH bupivacaine and N-desbutyl bupivacaine. Generally, parent bupivacaine was the predominant component of the total residue, followed by 3-OH bupivacaine and then N-desbutyl bupivacaine.

Bupivacaine was found to be a measurable and major component of the residues at all timepoints in the residue depletion study provided and the decline of bupivacaine correlated with the total residues in all edible sheep tissues. For this reason, parent bupivacaine is considered to be a suitable marker residue for the proposed use with a zero-day meat WHP in sheep. Based on the results of the residue depletion study conducted in sheep in which bupivacaine and 2 of its metabolites were measured, the ratio of marker residue to total residues for lignocaine in sheep tissues was determined to be 0.84 for fat, 0.37 for liver, 0.19 for kidney and 0.59 for muscle.

Analytical methods

Validated methods for the quantification of parent lignocaine and bupivacaine and their metabolites residues in edible sheep tissues (muscle, fat, liver and kidney), as well as plasma, urine and faeces, using LC-MS/MS methodologies, were considered. The method's limit of quantification (LOQ) for liver, kidney, muscle and fat were 0.2 µg/kg each for lignocaine, bupivacaine and their metabolites with exception of lignocaine N-oxide where the LOQ was 0.47 µg/kg in muscle and 0.33 µg/kg in fat.

Residues depletion studies

A pivotal GLP compliant residue depletion study was conducted to determine residues of lignocaine, bupivacaine and their metabolites in edible tissues of sheep after a topical spray application with Tri-Solfen for treatment associated with mulesing and tail-docking or castration, administered to wound via spray applicator.

Tri-Solfen was topically applied directly to mulesing (M) + tail-docking (D), and castration (C) wounds. The treatment regime involved a maximum label dose of 1.8 m/kg (M+D = 1.2 ml/kg + C = 0.6 ml/kg); and C+D only = 0.9ml/kg. Tri-Solfen contains 40.6 mg lidocaine, and 4.2 mg bupivacaine/ml – thus 1.8 ml/kg Tri-Solfen contains ~73 mg/kg lidocaine and 7.6 mg/kg bupivacaine.

In this study, 42 healthy lambs (Breed: Merino; Sex:40M/2F) that were 3 to 6 months of age and 15 to 26.5 kg in weight) were chosen. Tissue samples (muscle (loin), kidney, liver and peri-renal fat) were collected at the following timepoints 4, 10, 24 hrs and 2, 4-, 7-, 14- and 28-days post treatment. Samples were analysed for lignocaine (and metabolites) and bupivacaine (and metabolites). Residue results are reported for marker residues (lignocaine and bupivacaine).

Statistical analysis at the 95th percentile of the lignocaine and bupivacaine residues was performed using the EMA Withdrawal-Time Calculation Program (WT1.4) to estimate the MRL required for a zero day meat WHP. It is noted that the results from 4 hours post treatment were not included in the MRL estimation as the compounds were considered to be in the absorption phase and it is considered unlikely that animals would be slaughtered for human consumption within 4 hours of treatment.

The current label has the restraint "DO NOT USE on ewes where milk may be used or processed for human consumption". Given no residues data is available for estimation of lignocaine or bupivacaine residues in sheep milk, this restraint is considered appropriate.

Lignocaine

In sheep kidney, mean residues 10 hrs post treatment were 92.93 µg/kg that generally declined with time with residues observations of 12.32 µg/kg, 6.14 µg/kg, 2.13 µg/kg, 2.38 µg/kg, 1.22 µg/kg and 0.67 µg/kg detected at 24 hrs and days 2, 4, 7, 14 and 28 respectively. The highest residue of 236 µg/kg was observed at 10 hrs post treatment. The HRs in each sampling point decreased with time with a high residue of 1.22 µg/kg observed at 28 days post-treatment.

Statistical analysis of lignocaine residue depletion data in kidney tissue using WT1.4 shows for a zero-day WHP, an MRL of 0.2 mg/kg for lignocaine for Sheep, kidney (MO 1288) is considered appropriate for the proposed treatment in sheep in conjunction with a zero-day meat WHP.

In sheep fat (peri-renal), mean residues 10 hrs post treatment were 79.10 µg/kg, that declined to 11.20 µg/kg, 7.45 µg/kg, 5.73 µg/kg, 2.11 µg/kg, 1.59 µg/kg at 24 hrs and days 2, 4, 7 day and 14 day and then increased to 2.64 µg/kg at 28 days after treatment. The highest residue of 211 µg/kg was observed in 10 hrs post-treatment and that decreased to 16.9 µg/kg at 4 days after treatment before declining to <10 µg/kg at 7, 14 and 28 days after treatment.

Statistical analysis of the lignocaine residue depletion data in peri-renal fat tissue using WT1.4 shows for a zero-day WHP, an MRL of 0.2 mg/kg for lignocaine for Sheep, fat (MF 0822) is considered appropriate for the proposed treatment in sheep in conjunction with a zero-day meat WHP.

In sheep liver, mean residues 10 hrs post treatment were 16.53 µg/kg, that declined to 1.15 µg/kg at 24 hrs, then increased to 2.34 µg/kg at 2 days and declining thereafter at all time points (4, 7 and 14 and 28 days) with final observation of 0.11 µg/kg at 28 days post-treatment. The highest residue of 36.4 µg/kg was observed at 10 hrs post treatment, and that decreased with time with residues being detected at <5 µg/kg at all time points with final observation being detected at 0.125 µg/kg at 28 days post-treatment.

Statistical analysis of the lignocaine residue depletion data in liver tissue using WT1.4 shows for a zero-day WHP, an MRL of 0.1 mg/kg for lignocaine for Sheep, liver (MO 0822) is considered appropriate for the proposed treatment in sheep in conjunction with a zero-day meat WHP.

In sheep muscle (loin), mean residues of lignocaine 10 hrs post treatment were 22.69 µg/kg, that declined to 0.67 µg/kg at 4 days with an increase observed at 0.95 µg/kg at 7 days that finally declined to 0.23 µg/kg (>LOQ of 0.2 µg/kg) at 28 days post-treatment.

Statistical analysis of the lignocaine residue depletion data in muscle (loin) tissue using WT1.4 shows for a zero-day WHP, an MRL of 0.15 mg/kg for lignocaine for Sheep, meat (MM 0822) is considered appropriate for the proposed treatment in sheep in conjunction with a zero day meat WHP.

The APVMA's toxicological assessment has recommended an ADI of 0.01 mg/kg bw and an ARfD of 0.03 mg/kg bw for lignocaine. The dietary exposure assessment for lignocaine confirmed that these health-based guidance values should not be exceeded as a result of the proposed use of lignocaine with a zero-day meat WHP. It is noted that for the dietary exposure assessments, a conservative factor of 10× was applied to the MR:TR ratio as no radio-labelled study is available and it is possible that some minor metabolites were not accounted for in the residue depletion study conducted in sheep. This approach was consistent with that used by the European Medicines Agency in their 2021 assessment of lignocaine (bovine)⁷.

Bupivacaine

In sheep kidney, mean residues 10 hrs post treatment were 10.77 µg/kg, that declined thereafter to <5 µg/kg at all time points (24 hrs, 2, 4, 7, 14 days) to 0.08 µg/kg at 28 days post-treatment. The highest residue of 17.9 µg/kg was observed at 10 hrs post treatment, with residues declining to <5 µg/kg at 24 hrs, 2, 4, 7, 14 days post-treatment with final observation detected at 0.11 µg/kg at 28 days post-treatment.

Statistical analysis of the bupivacaine residue depletion data in kidney tissue using WT1.4 shows for a zero-day WHP, an MRL of 0.025 mg/kg for bupivacaine for Sheep, kidney (MO 1288) is considered appropriate for the proposed treatment in sheep in conjunction with a zero day meat WHP.

In sheep liver, mean residues 10 hrs post treatment were 10.31 µg/kg, that declined thereafter to <5 µg/kg at all time points (24 hrs, 2, 4, 7, 14 days) to 0.08 µg/kg at 28 days post-treatment. The highest residue of 15.1 µg/kg was observed at 10 hrs post treatment, with residues declining to <5 µg/kg at 24 hrs, 2, 4, 7, 14 days post-treatment with final observation detected at 0.11 µg/kg at 28 days post-treatment.

Statistical analysis of the bupivacaine residue depletion data in liver tissue using WT1.4 shows for a zero-day WHP, an MRL of 0.025 mg/kg for bupivacaine for Sheep, liver (MO 0822) is considered appropriate for the proposed treatment in sheep in conjunction with a zero day meat WHP.

In sheep fat (peri-renal), mean residues 10 hrs post treatment were 19.38 µg/kg, that declined thereafter to <5 µg/kg at all time points (24 hrs, 2, 4, 7, 14 days) to 0.38 µg/kg at 28 days post-treatment. The highest residue of 36.8 µg/kg was observed at 10 hrs post treatment, with residues declining to <10 µg/kg at 24 hrs, 2, 4, 7, 14 days post-treatment with final observation detected at 1.28 µg/kg at 28 days post-treatment.

⁷ [European Medicines Agency](#), EMA website, accessed September 2023.

Statistical analysis of the bupivacaine residue depletion data in peri-renal fat tissue using WT1.4 shows for a zero-day WHP, an MRL of 0.075 mg/kg for bupivacaine for Sheep, fat (MF 0822) is considered appropriate for the proposed treatment in sheep in conjunction with a zero day meat WHP.

In sheep muscle (loin), the mean residues and the highest residues of 2.81 µg/kg and 4.83 µg/kg respectively were detected at 10 hrs with mean residues at the following time points being <0.5 µg/kg. Based on the available information, an MRL of 0.0005 mg/kg is recommended for bupivacaine for Sheep, meat (MM 0822) for the proposed treatment in sheep in conjunction with a zero day meat WHP.

The APVMA's toxicological assessment has recommended that an ADI of 0.002 mg/kg bw and an ARfD of 0.006 mg/kg bw for bupivacaine. The dietary exposure assessment for bupivacaine confirmed that these health-based guidance values should not be exceeded as a result of the proposed use of bupivacaine with a zero-day meat WHP. It is noted that for the dietary exposure assessments, a conservative factor of 10× was applied to the MR:TR ratio as no radio-labelled study is available and it is possible that some minor metabolites were not accounted for in the residue depletion study conducted in sheep.

Overseas registration and approved label instructions

The applicant has indicated that Tri-Solfen is not currently registered for use on ovine species in any overseas markets.

Codex Alimentarius Commission and overseas MRLs

Lignocaine and bupivacaine have not been considered by Codex or other international regulators for use on sheep and no sheep MRLs have been established by Codex or other international regulators.

Proposed Australian MRLs for lignocaine and bupivacaine

The following amendments to the APVMA MRL standard are proposed, shown in Tables 2, 3 and 4.

Table 2: Proposed amendments to Table 1 of the APVMA MRL standard

Amendments to Table 1			
Compound		Food	MRL (mg/kg)
Add:			
Bupivacaine			
Add:			
MF	0822	Sheep fat	0.07
MO	1289	Sheep, kidney	0.02
MO	1289	Sheep, liver	0.02
MM	0822	Sheep muscle	0.0005
Add:			
Lignocaine			
Add:			
MF	0822	Sheep fat	0.2
MO	1289	Sheep, kidney	0.2
MO	1289	Sheep, liver	0.1
MM	0822	Sheep muscle	0.15

Table 3: Proposed amendments to Table 3 of the APVMA MRL standard

Amendments to Table 3	
Compound	Residue
Add:	
Bupivacaine	Bupivacaine
Lignocaine	Lignocaine

Table 4: Proposed amendments to Table 5 of the APVMA MRL standard

Amendments to Table 5	
Substance	Use
Bupivacaine hydrochloride	
Delete:	
	When used in lambs for pain relief following mulesing, castration or tail docking
Lignocaine hydrochloride	
Delete:	
	When used in lambs for pain relief following mulesing, castration or tail docking

Potential risk to trade

Export of treated produce containing finite (measurable) residues of lignocaine or bupivacaine may pose a risk to Australian trade in situations where (i) no residue tolerance (import tolerance) is established in the importing country or (ii) where residues in Australian produce are likely to exceed a residue tolerance (import tolerance) established in the importing country. An Export Slaughter Interval (ESI) can help manage the potential risk to trade arising from the proposed use.

The currently approved ESI for sheep is 90 days on the Tri-Solfen label. The treatment regime for sheep remains unchanged to that currently approved, thus the risk to trade theoretically remains unchanged. However, noting a new residues depletion study is now available, the appropriateness of the current/proposed ESI of 90 days is discussed below.

The available sheep residue depletion study found that finite residues (i.e. above 0.2 µg/kg) of lignocaine, 2,6-xylidine and bupivacaine were observed at the last sampling time of 28 days. Given residues data beyond 28 days is not available, the half-lives for each compound in each sheep tissue were estimated utilizing the results of the residues depletion study and then the time required for residues to decline to below the LOQ (0.2 µg/kg) were estimated. The LOQ of a validated analytical method is typically considered the lowest endpoint for estimation of an ESI in the absence of overseas MRLs in major export markets as is the case here.

The longest estimated time for the residues to decline to below the LOQ was 52 days, and this was for parent lignocaine residues in sheep fat (peri-renal). While there is some uncertainty with the estimated time for residues to decline to <LOQ, given the Applicant has requested a 90-day ESI and that ESI has been on the Tri-Solfen label since 2011, it is considered appropriate to retain a 90-day ESI. The risk to trade remains unchanged and no greater than arising from the current use. The existing ESI of 90 days is considered acceptable and supported from a trade risk management perspective.

Conclusion

Comments are sought on the potential risk to trade in edible sheep tissues from the proposed use and the ability of the industry to manage any potential risk.