The NRA Review of

SULPHONAMIDES

Final Report

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FOREWORD

The National Registration Authority for Agricultural and Veterinary Chemicals (NRA) is an independent statutory authority with responsibility for the regulation of agricultural and veterinary chemicals. One of the NRA's regulatory responsibilities is to conduct reviews of registered agricultural and veterinary chemicals to ensure that they continue to do the job that they are supposed to do and that they do not pose unacceptable risks to people, the environment or trade.

The Special Review Program examines urgent or specific concerns about a currently registered agricultural or veterinary chemical which may require a rapid resolution. It addresses one or more specific aspects of a given chemical, and can be triggered, for example, by the findings of new research, the availability of new scientific data or concerns raised about the use or safety of a chemical.

In undertaking reviews, the NRA works in close co-operation with advisory agencies including the Department of Health and Aged Care (Chemicals and Non-Prescription Medicines Branch), Environment Australia (Risk Assessment and Policy Section), National Occupational Health and Safety Commission (Agricultural and Veterinary Chemicals Section) and State Departments of Agriculture.

The NRA has a policy of encouraging openness and transparency in its activities and community involvement in decision-making. When the NRA decides that a review is to be conducted, it consults parties affected by the review (such as applicants, commodity groups, State regulatory agencies) and gives them an opportunity to respond to concerns raised and participate in the review. All participants are notified of the Board's decision and outcomes of special reviews are published in the NRA's Agricultural and Veterinary Chemicals Gazette.

The review report provides an overview of the review that has been conducted by the NRA and advisory agencies. The review findings are based on information collected from a variety of sources, including data packages and information submitted by registrants, information submitted by members of the public, and government organisations and literature searches.

The NRA also makes these reports available to the public and regulatory agencies of other countries that are part of the OECD *ad hoc* exchange program and as part of bilateral exchange agreements with other countries. Under the OECD *ad hoc* exchange program, it is proposed that countries receiving these reports will not utilise them for registration purposes unless they are also provided with the raw data from the relevant applicant.

The information and technical data required by the NRA to review the safety of both new and existing chemical products must be derived according to accepted scientific principles, as must the methods of assessment undertaken. Details of required data are outlined in various NRA publications.

The NRA welcomes comment on this review and the review program. They can be addressed to Manager, Chemical Review, National Registration Authority for Agricultural and Veterinary Chemical, PO Box E240, Kingston, ACT 2604, Australia.

EXECUTIVE SUMMARY

Sulphonamides are one of the oldest groups of antimicrobial compounds. They have been in clinical use for over 50 years and were first registered in Australia in the 1940s.

Conditions for the continued use of sulphonamide products in livestock production have been reviewed in a number of countries. Deficiencies in toxicology and residue data, as well as concerns over the development of human resistance, have resulted in sulphonamide residues being a particularly sensitive issue in international trade. In addition to the development of microbial resistance, concern has also focused on the possible carcinogenicity of some sulphonamides in laboratory animals. These two key issues (toxicology and residues) have stimulated and directed most of the regulatory activities on sulphonamides and has been the driving force in establishing the need for this NRA review.

Objectives

The objective of this review was to determine whether Maximum Residue Limits (MRLs) could be established for sulphonamides where current ones did not exist and where they were established whether the use patterns were supported by appropriate residue data (trade aspects of the use of these compounds was not taken into consideration).

The Therapeutic Goods Administration (TGA's) Chemicals and Non-Prescription Medicines Branch (and its predecessors), and the NRA Residue Evaluation Section, evaluated the available toxicology and residue data on the sulphonamides in terms of their suitability for use on food producing animals only.

The registered products subject to the recommendations made in this review, are listed in Appendix A, grouped according to active constituent. Appendixes B to G contain summaries of the data submitted for the review.

Recommendations

The toxicology evaluation resulted in only 5 sulphonamides being recommended for use in food producing species. Initially only 3 were approved for continued use (sulphadimidine, sulphadiazine, sulphatroxazole), with 2 more being added to this list later (sulphadoxine, sulphaquinoxaline).

The residue evaluations carried out on the sulphonamides has resulted in the following recommendations, which are product specific:

Either:

- no changes to the current product use patterns;or
- minor amendments, such as a modification to Withholding Periods; or
- withdrawal of certain use patterns due to lack of appropriate data.

MAIN REPORT

1. Introduction

Sulphonamides are registered in Australia as antibacterials and are used widely in food producing animals because of their relatively low cost and ease of administration. Their use in veterinary medicine is widespread, particularly as mass medicants for the control of diseases in food producing species. They are marketed in Australia either alone, or formulated in combination with other sulphonamides and/or antibiotics. They are presented as feed additives, or oral, topical, intrauterine pessaries and injectable preparations. Sulphonamides have a broad spectrum of bacteriostatic activity, affecting gram positive, gram negative and many protozoan organisms. Sulphonamides are commonly used for the treatment of infections of the central nervous system, respiratory tract, gastrointestinal tract and the urinary tract.

2. Previous Regulatory Action

Several unsuccessful attempts have been made in the past years in Australia and elsewhere, including Codex Alimentarius, to establish MRLs for certain sulphonamides.

2.1 United States

Sulphonamide residues have been an issue in the USA for at least 25 years. During the last 20 years, sulphonamides have produced more residue violations than any other drug, with the highest incidence occurring in pork, followed by veal and poultry.

The US Food and Drug Administration (FDA) began investigating sulphonamides in the early 1970s, when registrants were asked for data to enable the FDA to better evaluate the toxicity of these compounds. Their potential thyrotoxicity was of particular concern. In 1990 the FDA initiated withdrawal procedures against sulphadimidine (the most widely used sulphonamide). It had been shown to cause tumours in laboratory animals.

2.2 Joint FAO/WHO Expert Committee on Food Additives (JECFA)

At the 42nd meeting of the JECFA (February 1994), studies investigating the mechanism of action of sulphadimidine on the thyroid gland and additional information regarding genotoxicity, embryotoxicity and teratogenicity were reviewed.

Although it was recognised that primates (including humans) are less susceptible than rats and pigs to the anti-thyroid effect of sulphonamides, the Committee noted the possibility that in the case of sensitisation to sulphonamides, hypersensitivity reactions might occur as a result of the ingestion of sulphonamide residues in food of animal origin. The Committee recognised that this information would be extremely

difficult if not impossible to obtain. In line with a previous evaluation (34th Meeting, 1989), the Committee recommended that MRLs should be set as low as practicable in accordance with good practice in the use of veterinary drugs. The values recommended for cattle, sheep, pigs and poultry were 0.1 mg/kg as sulphadimidine in muscle, liver, kidney and fat. The recommended MRL for sulphadimidine in milk was 0.025 mg/L.

The residue data available for eggs indicated that use of sulphadimidine in egg production would result in very high concentrations of sulphadimidine in eggs. For this reason the Committee considered that sulphadimidine should not be used in laying hens and did not recommend an MRL for eggs.

2.3 Australia

The Pesticides and Agricultural Chemicals Standing Committee (PACSC) of the National Health and Medical Research Council (NHMRC) had been concerned about the effect of sulphonamides on the thyroid gland since the mid 1980s. Like the US, sulphonamide residues in meat have been a significant concern to Australia.

The existence of frequent MRL violations in Australian and export markets led to the recommendation by the NHMRC that all sulphonamides used in food producing animals be assigned MRLs. As a result, in 1989 sulphonamide registrants were asked by the NHMRC to provide all relevant toxicological, residue and metabolism data to support either the establishment, or continuation, of existing Acceptable Daily Intakes (ADIs) and MRLs for their products.

2.3.1 National Antibacterial Residue Minimisation (NARM) Program

The National Antibacterial Residue Minimisation (NARM) program is a joint Industry/State/Commonwealth initiative aimed at increasing awareness amongst producers, processors and other industry groups on the risk to trade associated with the detection of antibacterial residues above the maximum residue limit (MRL). This increased awareness is designed to assist the beef and veal industries to minimise antibacterial residue contamination levels of dairy cows, feedlot cattle, bulls and bobby calves.

The presence of antibacterial residues in meat products has the potential to restrict the market access of Australia's produce. For instance, in early 1987, the United States advised that it would deny market access of meat products from countries where violative levels of sulphonamides were detected. However the United States also stated that this ban would not be applied if satisfactory antibacterial detection and traceback programs were in place in the country of origin.

The aim of the NARM program is to maximise the detection of antibacterial residues in calves, cull dairy cows, bulls and feedlot cattle slaughtered at domestic and export abattoirs. It enables 'high risk' groups of animals such as cull and feedlot cattle and

bobby calves that are commonly treated with antibacterial agents to be tested inexpensively
and at times of the year when antibacterial use is greatest due to disease prevalence or periods of stress.

Results 1997/1998

Location/year	Number tested	Number positive	Detections
Qld1997 - Calves	2974	58 (2%) (urine - MIT)	Of the positives, 57% were above the MRL, of those 47% were sulphonamides (detected in kidney)
Qld1998 - All groups	2730	61 (2.2%) (kidney screen)	Of the positives, 8.1% were sulphonamides and were greater than the MRL (kidney) - Sulphadiazine and sulphadimidine
Victoria 1997 - Bobby calves	260,000	639 (0.2%) (urine – MIT)	Secondary screening on 164 of the positive urine samples was taken – 38% detected sulphonamides Confirmatory testing of muscle/kidney samples from 146 'positive' calves was done – 46 (31.5%) were greater than the MRL, of these 92% were sulphonamides
- Cull cows	3900	16 (0.4%) (urine - MIT)	Secondary screening of MIT positive urine samples identified 13% containing sulphonamides (Sulphadiazine and sulphadimidine)
Victoria 1998 - Bobby calves	116,000	348 (0.3%) (urine – MIT)	52% of positive detections were sulphonamides. Confirmatory testing on kidney samples showed that 88% of positive detections were greater than the MRL A trace back indicated that 79% of sulphonamide detections were from calf scour treatments
- Cull cows	250	29 (11.6%) (tissue screen)	14% of positive detections were sulphonamides. Confirmatory testing on kidney samples showed that 21% of positive detections were above the MRL
NSW 1997 Export calves	18,142	90 (0.5%) (urine – MIT)	21 (23%) of the positive detections were sulphonamides. Confirmatory testing on urine and kidney samples showed that 19 (95%) of positive detections were above the MRL
Export adults	1293	54 (4.2%) (urine – MIT)	Following confirmatory testing, none of the positive detections (urine-MIT) were due to sulphonamides)
Domestic calves	466	5 (1%) (urine – MIT)	None of the positive samples were above the MRL. It was not determined which antibiotic the detections were attributed to.

Results 1997/1998 (cont'd)

NSW 1998**			
Export calves	>15,540	32 (≤0.2%) (urine – MIT)	17 (53%) of positive detections were sulphonamides (sulphadimidine11; sulphadiazine 5 and sulphamerazine 1). Confirmatory testing on urine and kidney samples showed that 10 (59%) of positive detections were above the MRL
Export adults	467	5 (1%) (urine – MIT)	None of the positive detections were due to sulphonamides.
Domestic calves	654	5 (0.8%) (urine – MIT)	2 (40%) of positive detections were sulphonamides. Confirmatory testing on kidney samples showed that only 1 of the positive detections were above the MRL (sulphadiazine)

** when sulphonamide residues were detected there was frequently a range of sulphonamides. Only the one with the highest concentration was reported.

The main reason for the residue violations in calves was attributed to failure to adhere to the withholding periods.

3. EARLY TOXICOLOGICAL AND RESIDUE EVALUATION - AUSTRALIA

3.1 Background

In October 1990, the NHMRC called for information on the use of sulphonamides in food producing animals in order to conduct a review. This review was to focus on the toxicological, residue and metabolism aspects of all registered sulphonamides.

In response, the Sulphonamide Task Force was convened with the purpose of ascertaining what data were available to either support or to recommend changes to the existing sulphonamide MRLs and to set MRLs for those compounds that did not have them. The Task Force was composed of representatives from the Australian Veterinary Association (AVA), Agricultural and Veterinary Chemicals Association (AVCA now AVCARE), and the Veterinary Manufacturers and Distributors Association (VMDA).

In 1991, the Agricultural and Veterinary Chemicals Unit of the then Department of Primary Industries and Energy presented a paper to the Australian Agricultural and Veterinary Chemicals Council (AAVCC) on sulphonamides. At this time only three of the sixteen registered sulphonamides were supported by MRLs. These were sulphadimidine, sulphadiazine and sulphatroxazole. In all cases the MRL was 0.1 ppm in meat and milk. The paper focused mainly on the use of registered sulphonamide products which did not have an established MRL and the potential that these could have to jeopardise Australian trade. The paper noted that the high incidence of residue violations with sulphonamides in meat products resulted from their use as feed additives and the failure in these cases to observe the prescribed Withholding Period. Carry-over of sulphonamide in feed mills into non-medicated feed was also implicated.

The three major issues that were raised in this paper were:

- the continued use of registered sulphonamides for which there are no established MRLs;
- protection of overseas trade in meat products; and
- public health considerations.

Without appropriate data, public health authorities could not assess the likely toxicological and public health effects or set the regulatory MRLs for sulphonamides.

The proposal subsequently put forward by the Task Force to the AAVCC was that MRLs be established by 1994, and any sulphonamide without an MRL after this time be de-registered for use in food producing species.

The AAVCC agreed that clearance and registration would be revoked for those sulphonamide products that did not have an established MRL by 31 December 1993. Industry was encouraged to generate the necessary data for the establishment of MRLs for sulphonamide actives used in Australia.

In response to this request the Sulphonamide Task Force submitted an extensive data package in November 1992. The information presented was confined to sulphadimidine, sulphadiazine and trimethoprim in sheep, cattle, pigs and poultry, and sulphaquinoxaline in poultry.

In October 1994 a notice was placed in the NRA Gazette providing an update on the status of the sulphonamide review. It was announced that sulphadimidine, sulphadiazine, sulphatroxazole, and sulphaquinoxaline were approved for use in food producing animals. The continued registration of sulphaquinoxaline for use in food producing species was to be provisional up to 31 December 1996. Sulphathiazole, sulphanitran, sulphamonomethoxine, sulphafurazole, sulphaguanidine, sulphachloropyridazine, and sulphamethoxydiazine were to be banned in food producing animals due to inadequate toxicological data. Sulphadoxine and sulphamerazine uses in food producing animals at this time were dependent on review of additional data submitted. This review of additional data resulted in sulphadoxine being found acceptable on toxicological grounds for use in food producing species whereas the use of sulphamerazine was restricted to companion animals.

The NRA's decisions relating to the continued use of various sulphonamides announced at this time applied only to their toxicological evaluation. At this time, the residue evaluation of these compounds had not been completed.

Since this time the NRA has continued the residue review of the remaining sulphonamides (sulphadimidine, sulphadiazine, sulphaquinoxaline, sulphadoxine, sulphatroxazole). In June 1998 the NRA contacted registrants by letter to advise them of the preliminary findings from the evaluation of residue data. Many registrants considered that the review had been completed in 1994, or were not aware that a residues review had been conducted.

At a meeting with the VMDA in August 1998, the NRA agreed to evaluate the Sulphonamides Task Force literature survey as well as other available data to determine whether any of the data gaps identified in June 1998 could be filled.

In June 1999, all registrants were given the opportunity to provide additional residue data for the review. Any data submitted at this time was also taken into consideration in the evaluation.

3.2 Initial Review Findings 1993 - NHMRC

The initial review of the group of sulphonamides was completed in July 1993. This focused on the toxicology and residue data that had been submitted by the Sulphonamide Task Force. The findings from this evaluation are noted below.

Toxicology

The sulphonamides in general are thought to have low potential for adverse health effects, supported by their long history of safe therapeutic use in humans. Acute toxic effects have rarely been reported and these compounds are also non-teratogenic in laboratory animals at concentrations similar to therapeutic levels in humans. The Australian Drug Evaluation Committee has listed sulphonamides as a category C risk to humans during pregnancy, indicating the possibility of harmful effects to the foetus without causing malformations. It was therefore recommended that acute, reproduction and developmental studies would not be mandatory to support the existing use of sulphonamides in food producing animals.

The available data suggests that the sulphonamides are non-genotoxic. The target organ and most sensitive parameter for toxicity of sulphonamides in laboratory animals is the thyroid gland, with prolonged administration resulting in follicular cell hyperplasia leading to follicular cell adenomas and carcinomas. Although only sulphadimidine has been tested for toxicity in a lifetime study, it is generally regarded that the mechanism causing the changes to the thyroid is an effect on the synthesis and excretion of competent thyroid hormone. Feedback mechanisms due to decreased thyroid hormone are then instituted which result in the pituitary secreting higher levels of Thyroid Stimulating Hormone (TSH), signalling the thyroid to increase production and secretion of thyroid hormone. A functional hypertrophy therefore ensues which can lead to tumour production. Rodents appear to be very sensitive to this effect but a definite threshold dose exists. It seems likely that the sulphonamides as a class may have the same toxicological mechanism to that described above. If so, a threshold dose is expected to exist in other species including humans, below which no significant health effects should occur.

Based on the evaluation of available information on the toxicology of the sulphonamides, the following No Observable Effect Levels (NOELs) and ADIs are recommended.

(a) sulphadimidine
NOEL: 2 mg/kg/day in a 2 year rat study based on thyroid follicular cell hyperplasia and tumours at higher doses
ADI: 0.02 mg/kg/day using a safety factor of 100

(b) sulphadiazine
NOEL: 37.5 mg/kg/day in a rat reproduction study based on fetotoxicity at higher doses
ADI: 0.02 mg/kg/day using a safety factor of 2000

(c) sulphatroxazole
NOEL: 100 mg/kg/day in a 13 week monkey study based on anaemic effects
ADI: not established as information on metabolism/pharmacokinetics in laboratory animals is unavailable.

Residues

In past reviews, the NHMRC had adopted a policy of requiring that there should be no residues of these chemicals in food, and hence had set MRLs at or about the limit of determination. In this review a policy that the establishment of finite MRLs was not incompatible with sound public health principles was adopted, provided that the toxicology data was of sufficient quality to set a reliable ADI and that estimated dietary exposure did not exceed the ADI.

Applying this principle, and following evaluation of the appropriate data, it was determined that MRLs could be established for the following (all MRLs were 0.1 mg/kg) [trimethoprim has an MRL of 0.05 mg/kg]:

sulphadimidine	* edible offal (mammalian)
	* meat (mammalian)
	* poultry edible offal (except turkey)
	* poultry meat
sulphadiazine	* edible offal (mammalian)
	* meat (mammalian)
	* poultry edible offal
	* poultry meat
trimethoprim	* edible offal (mammalian)
	* meat (mammalian)
	* poultry edible offal
	* poultry meat

Existing label uses for compounds other than those specified above were not supported.

The exclusion of turkeys from the entries for sulphadimidine resulted from the finding that violations of the MRL would be expected to occur in the skin and liver of turkeys at the proposed dosage and Withholding Periods. It was decided that, provided adequate residue data was generated, it was likely that MRLs could be established consistent with the known ADI for this compound. On this basis it was recommended that temporary MRLs of 0.2 mg/kg be set for sulphadimidine in turkey tissue while data was generated. These were to expire in December 1994 however this was subsequently reconsidered in light of additional information presented for evaluation.

The initial toxicology assessment and recommendations concerning the continued use of sulphonamides in food producing animals had been completed. Industry was advised in January 1994 of the outcomes of this evaluation.

This advice contained a list of the sulphonamides approved for use in food producing animals and a timetable for various regulatory actions including:

(i) Cessation of sale January 1994;
(ii) Formal deregistration 1 September 1994
(iii) Required label changes 1 September 1994

(iv) Proscribe use in food producing animals 1 March 1995.

Because of the fact that industry had submitted data well after decisions were made, it was necessary to amend this withdrawal schedule. While undesirable to amend the agreed phase out periods, the NRA considered that the importance of sulphonamides to the veterinary profession required consideration of all data before making finals decisions. As a result, three categories of sulphonamides were developed.

Category 1 – sulphonamides approved for use in food producing animals

Sulphadimidine
Sulphadiazine
Sulphatroxazole
Sulphaquinoxaline (was originally placed into Category III – subsequently provisional approval up to 31 December 1996 was given).

Category II – sulphonamides still under evaluation

Additional data was submitted in support of two sulphonamides (sulphadoxine and sulphamerazine) after the deadline for submission of data. The evaluation was scheduled to be completed in November 1994.

Category III – sulphonamides to be banned in food producing species

Sulphathiazole
Sulphamonomethoxine
Sulphafurazole
Sulphanitran
Sulphaguanidine
Sulphachloropyridazine
Sulphamethoxydiazine

3.3 Subsequent reconsiderations following 1993 review

3.3.1 Sulphaquinoxaline

Concerns were raised by industry regarding the decision to place sulphaquinoxaline on the list of products to be withdrawn (Category III). Following a submission from VMDA and the Advisory Committee on Therapeutics, it was agreed that, based on its history of safe use and importance to the poultry industry, sulphaquinoxaline registration should be maintained while further data was evaluated. It was therefore placed into Category I with an expiry date of 31 December 1996.

Continuation of an MRL was not possible without determination of an ADI for sulphaquinoxaline. A three-year period (ending 31 December 1996) was given for industry to provide the appropriate data. Withdrawal action was recommended should the appropriate data not be submitted by this time. During this interim period, a temporary MRL of T0.1 mg/kg for poultry edible offal and meat was given. An MRL

for sulphaquinoxaline beyond this date could not be justified without acceptable sub-chronic toxicological studies being provided.

In view of the trade and potential public health significance of allowing the continued use of sulphaquinoxaline under the above conditions, the inclusion of sulphaquinoxaline into the National Residue Survey monitoring program was recommended.

In response to the data deficiencies for sulphaquinoxaline, additional data was provided by Merck, Sharp and Dohme (Aust) Pty Ltd, to support retention of sulphaquinoxaline. It should be noted that Merck never had and still do not have any commercial interest in sulphaquinoxaline products.

Outcome: It was concluded that there were no objections on toxicology grounds to the continued use of sulphaquinoxaline in the poultry industry. An MRL of 0.1 mg/kg/day for poultry edible offal and meat was confirmed. An ADI of 0.01 mg/kg/day was established based on a NOEL of 1.0 mg/kg/day in a 90 day dog study and a safety factor of 100.

3.3.2 Sulphatroxazole

Sulphatroxazole was another compound originally listed to have its registration cease due to lack of available data for establishment of an MRL. There had been no pharmacokinetic or metabolism data submitted.

Since the major metabolite of sulphatroxazole in target animals is also produced in humans, it was considered that any adverse effects of this metabolite would have been identified during human therapy. As sulphatroxazole had been administered to humans in high doses with no major side effects, it was concluded that the low level of residues following the veterinary use of sulphatroxazole would be unlikely to result in a significant concern for public health.

Outcome: Therefore amendments to the original recommendation were made and an MRL of 0.1 mg/kg was set for sulphatroxazole for edible offal (mammalian) and meat (mammalian). An ADI of 0.05 mg/kg/day was also established based on a NOEL of 100 mg/kg/day in a 13-week monkey study and a safety factor of 2000.

3.3.3 Sulphamerazine

Metabolism/pharmacokinetic studies, and a subchronic toxicity study for sulphamerazine were required to establish ADIs and MRLs. Until this data was submitted, the use of the compound in food producing animals was not supported.

Sulphamerazine was subsequently withdrawn from the marketplace by the registrant. It therefore was added to the list of sulphonamides that would only be considered for companion animal product registration.

3.3.4 Sulphadoxine

The newly established NRA Residue Evaluation Section evaluated additional data provided for sulphadoxine for the purpose of establishing an MRL. The evaluation of sulphadoxine was limited to data provided for cattle, sheep, and pigs destined for human consumption. Further toxicological data was also provided.

Outcome: The proposed MRLs of *0.1 mg/kg for sulphadoxine for Meat (mammalian), Edible offal (mammalian) and milks with registered withholding periods of 14 days for meat and 3 days for milks of cattle and sheep were accepted. It was therefore possible to also establish a NOEL of 50 mg/kg/day in a subchronic monkey study) and an ADI of 0.05 mg/kg/day using a safety factor of 1000.

4. RESIDUE EVALUATION 1999

In light of the length of time that the review of the sulphonamides had taken, the NRA proceeded to finalise this review by consolidating information from all residue assessments conducted since 1993 relating to the use of sulphadimidine, sulphadiazine, sulphadoxine, sulphaquinoxaline and sulphatroxazole in food producing species.

The Sulphonamide Task Force Submission contained 48 literature-reported residue studies. This data, combined with data submitted in response to a May 1999 request to registrants from the NRA, and data from registration submissions has been considered in the evaluation of these compounds where appropriate.

For many products involved in this review, no residue data had been presented relating specifically to the product. To solve this problem products were grouped according to formulation type and level of active. Any evaluation carried out in the past for one product in these groups has been applied to other products where extrapolations of the data are possible.

When comparisons are made between the literature and label rates, the literature rate is given first. References to “scaling down” with respect to use rates means that the literature rate was greater than the relevant label rate. The evaluators’ interpretation of “scaling down” is that the extrapolation is direct where there is a linear relationship between the dose administered and tissue residue concentrations incurred, or there is an added safety factor where this relationship is non-linear. By contrast, “scaling up” is generally not supported due to the non-linearity that can exist. Only where multiple

data points exist can one have confidence in extrapolating to higher doses i.e. some evidence of linearity is thereby provided.

With respect to WHPs, “scaling down” refers to the literature WHP exceeding the label WHP. Hence from a risk analysis perspective, “scaling up” of a WHP effectively adds a safety margin whereas “scaling down”, e.g. 14 days (literature WHP) to 7 days (label WHP) is not supported.

Individual product evaluations have not been included into this report but have been made available only to the registrant of that product.

Appendix A to E contains a summary of the residue data available for each of the chemicals under review.

5. RESPONSE TO PUBLIC COMMENT PHASE

The draft report was released for public comment in April 2000. Only the summary document was made available for the public to comment on; however registrants received both the summary document and a comprehensive evaluation report for each of their products included in the review.

The NRA targeted a range of groups, including State departments of Agriculture, VMDA, AVCARE, National Residue Survey, cattle industry representatives, Safemeat, AQIS and the Australian Dairy Industry Council in order to obtain the widest range of comments on the draft report. The availability of the draft report was advertised in the NRA Gazette and was made available on the NRA Website and in hard copy on request.

As part of the public comment phase the NRA attended a VMDA meeting in May where a short presentation was given regarding the next stages in the review process and then registrants were able to discuss their concerns with the NRA on an individual basis. This has proven to be a beneficial exercise.

Minimal comments on the recommendations were received from groups other than registrants. The majority of registrants responded to the NRA with their intentions regarding the continued registration of their products/uses and their willingness to generate the necessary data. In addition some registrants submitted data to support uses that were not supported in the draft report. In some cases registrants have chosen not to renew the registration of their product.

As a result of the above the recommendations have changed slightly to those which were in the draft report. These changes have resulted in more uses being supported.

6. RECOMMENDATIONS

Taking into consideration the draft recommendations from this review, comments and data provided in response to the draft release and commitments to generate data to support continued registration, the following recommendations have resulted.

Where commitments to generate data have been given, the NRA will set mutually agreeable timeframes for submission of this data to the NRA.

As in the draft report the individual product evaluation reports have been considered commercial in confidence and are only available to the registrants of the product involved. However some general recommendations can still be made.

6.1 Toxicology

- The following sulphonamides are not supported by appropriate toxicology data and can no longer be used in food producing animals.

Sulphamerazine	Sulphathiazole
Sulphamonomethoxine	Sulphafurazole
Sulphanitran	Sulphaguanidine
Sulphachloropyridazine	Sulphamethoxydiazine

(any other sulphonamides not listed in the approved substances list)

Note: The registration of the above compounds for food producing species was cancelled in September 1994.

- The following sulphonamides have been found satisfactory for use in food producing species from a toxicological perspective.

Sulphadimidine	Sulphadoxine
Sulphadiazine	Sulphatroxazole
Sulphaquinoxaline	

- The following Acceptable Daily Intakes (ADIs) have been established.

Compound	ADI
Sulphadimidine	0.02 mg/kg/day (using a safety factor of 100)
Sulphadiazine	0.02 mg/kg/day (using a safety factor of 2000)
Sulphaquinoxaline	0.01 mg/kg/day (using a safety factor of 100)
Sulphatroxazole	0.05 mg/kg/day (using a safety factor of 2000)
Sulphadoxine	0.05 mg/kg/day (using a safety factor of 1000)

6.2 Residues

The table below notes the MRLs either confirmed or established as a result of this review.

Compound	Food	New MRL mg/kg
SULPHADIMDINE		
Residue definition: sulphadimidine		
MO 0105	Edible offal (mammalian)	0.1
MM 0095	Meat (mammalian)	0.1
PO 0111	Poultry [except turkey], edible offal of	0.1
PM 0110	Poultry meat	0.1
ML 0812	Cattle Milk	0.1
SULPHADIAZINE		
Residue definition: sulphadiazine		
ML 0812	Cattle milk	0.1
MO 0105	Edible offal (mammalian)	0.1
MM 0095	Meat (mammalian)	0.1
PO 0111	Poultry, edible offal of	0.1
PM 0110	Poultry meat	0.1
SULPHADOXINE		
Residue definition: sulphadoxine		
ML 0812	Cattle milk	*0.1
MO 0105	Edible offal (mammalian)	*0.1
MM 0095	Meat (mammalian)	*0.1
SULPHAQUINOXALINE		
Residue definition: Sulphaquinoxaline		
PO 0111	Poultry, edible offal of	0.1
PM 0110	Poultry meat	0.1
SULPHATROXAZOLE		
Residue definition: Sulphatroxazole		
ML 0812	Cattle milk	0.1
MO 0105	Edible offal (mammalian)	0.1
MM 0095	Meat (mammalian)	0.1
TRIMETHOPRIM		
Residue definition: Trimethoprim		
ML 0812	Cattle milk	0.05
MO 0105	Edible offal (mammalian)	0.05
MM 0095	Meat (mammalian)	0.05
PO 0111	Poultry, edible offal of	0.05
PM 0110	Poultry meat	0.05

6.2.1 Sulphadimidine (sulphamethazine)

The current MRLs for sulphadimidine are 0.1 mg/kg for edible offal (mammalian), meat (mammalian), poultry [except turkey] edible offal and poultry meat. All of these MRLs are supported by appropriate residue data. Additional data was presented during this review to allow the establishment of a cattle milk MRL for sulphadimidine of 0.1mg/kg. The MRL Standard will be amended accordingly.

Sulphadimidine is available for use in a variety of formulations and for a range of indications.

- Registration of all injectable formulations intended for use on cattle, sheep or pigs is supported by the presented residue data.
- Registration of water medications is only supported for poultry and for some products registered for calves. The majority of products for use on calves, pigs or sheep are not supported.
- Registration of only 1 oral formulations is supported by the available residue data (calves, pigs, poultry). The remaining products are not supported and are intended for use on lambs, calves, cattle and sheep.
- Registration of products formulated as feed medications are supported by the residue data for pigs and calves only depending on the level of the active constituent in the product.
- Registration of a product intended for application as a combination of oral and injectable dosing for cattle, sheep and pigs is only supported by residue data for application to cattle.

Products

NCRIS NO	PRODUCT NAME	REGISTRANT
35554	SULFA FG PREMIX MEDICAITON FOR PIGS	AGRIBUSINESS PRODUCTS PTY LTD
47418	TRIPRIM ANTIBACTERIAL INJECTION	AUSRICHTER PTY LTD
41560	ASP PLUS CONCENTRATE ANTIBIOTIC FEED SUPPLEMENT	AUSTRALIA LIVE FOODS ASSOCIATED AUSTRALIA PTY LTD
41406	CLIFTONS COCCEE SOLUTION	CLIFTONS C/ VIRBAC (AUSTRALIA) LTD
48250	TRIDINE TRIMETHOPRIM-SULFADIMIDINE BROAD SPECTRUM ANTI-BACTERIAL INFECTION FOR CATTLE, HORSES, SHEEP, PIGS, DOGS AND CATS	DELVET PTY LTD
36797	ELANCO AF 0909 TYLAN 100 PLUS SULFA G TYLOSIN PHOSPHATE AND SULPHADIMIDINE PREMIX	ELANCO ANIMAL HEALTH
49943	SD333 SULPHADIMIDINE SOLUTION	MALINDI PTYL TD TRADING AS CATTLEKARE
41621	DYNAMUTILIN S FEED OREMIX FOR SWINE	NOVARTIS ANIMAL HEALTH
37721	TRIMIDINE POWDER	PARNELL LABORATORIES
38691	LINCOMAX S ANTIBIOTIC PREMIX	PHARMACIA & UPJOHN
40853	CCD SULPHADIMIDINE	RIDLEY AGRIPRODUCTS PTY LTD
46142	CCD SULPHADIMIDINE SODIUM SOLUBLE	RIDLEY AGRIPRODUCTS PTY LTD

38831	AMPHOPRIM S ANTIBACTERIAL INJECTABLE SOLUTION	VIRBAC (AUSTRALIA) PTY LIMITED

6.2.2 Sulphadiazine

The current MRLs for sulphadiazine are 0.1 mg/kg for cattle milk, edible offal (mammalian), meat (mammalian), poultry edible offal and poultry meat. All of these MRLs are supported by appropriate residue data.

As with sulphadimidine, products containing sulphadiazine are available in a number of different formulations and for a range of indications.

- Registration of feed medications is only supported by the residue data for use in cattle and calves.
- Registration of water medications is supported in pigs and poultry (depending on formulation and use pattern) but not for cattle and sheep.
- Registration of intrauterine/pessary applications of sulphadiazine is supported only when combined with a 14 day withholding period for meat and a restriction against the use of these products in lactating animals.
- Registration of injectable formulations of sulphadiazine is supported by residue data for use in cattle, sheep and pigs.
- Registration of oral medications of sulphadiazine is supported by residue data for use in calves, poultry and non-lactating cattle only. Use in pigs may be supported depending on the formulation and directions for use, and use in sheep is not supported.

NCRIS NO	PRODUCT NAME	REGISTRANT
42336	TRIMETASULPHA	AGRICON PRODUCTS PTY LTD
48512	AGROTECH TRIMETHOSOL – WATER MEDICATION ORAL SULFADIAZINE AND TRIMETHOPRIM	AGROTECH AUSTRALIA PTY LTD
41179	GAH FORMULA TRIMETHOSOL DISPERSIBLE POWDER	ALLIED ANIMAL HEALTH
35640	GASTROZINE A TRIMETHOPRIM SULPHONAMIDE MIXTURE WITH ELECTOLYTES FOR ORAL USE	APEX LABORATORIES PTY LTD
35694	TRIMAZINE BOLUS A SULPHONAMIDE TRIMETHOPRIM PREPARATION	APEX LABORATORIES PTY LTD
42452	BIMOTRIM CO TABLET/PESSARY	BIMEDA AUSTRALIA PTY LTD
35921	BISOLVOMYCIN & SULFA BRONCHOSECRETOLYTIC WITH OXYTETRACYCLINE AND SULPHADIAZINE	BOEHRINGER INGELEHIM PTY LTD
36528	AFS TRIMSUL ANTIMICROBIAL SOLUBLE POWDER	CONTROLLED MEDICATIONS PTY LTD
36529	AFS TRIMSUL ANTIMICROBIAL SOLUTION	CONTROLLED MEDICATIONS PTY LTD
37126	KEYMIX SULPHATRIM ORAL SULPHADIAZINE AND TRIMETHOPRIM MEDICATION	INTERNATIONAL ANIMAL HEALTH
37027	NORODINE 24 SOLUTION	NOVARTIS ANIMAL HEALTH AUSTRALASIA PTY LTD
36003	GEATRIM-BOLUS TRIMETHOPRIM 200	PHARMTECH PTY LTD FOR

	SULPHADIAZINE 1000 MG/BOLUS	BOMAC LABORATORIES LIMITED
36118	TRIBRISSEN BOLUS/PESSARY	SCHERING-PLOUGH ANIMAL HEALTH LTD
36120	TRIBRISSEN INJECTION-480	SCHERING-PLOUGH ANIMAL HEALTH LTD
36206	VR TRIBACTRAL DUALS ANTI-BACTERIAL PESSARY/BOLUS	SCHERING-PLOUGH ANIMAL HEALTH LTD
36207	VR TRIBACTRAL-80 ANTIBACTERIAL TABLETS	SCHERING-PLOUGH ANIMAL HEALTH LTD
48032	VR TRIBACTRAL ANTIBACTERIAL SUSPENSION FOR INJECTION	SCHERING-PLOUGH ANIMAL HEALTH LTD
36123	TRIBRISSEN WATER MEDICATION	SCHERING-PLOUGH ANIMAL HEALTH LTD
36121	TRIBRISSEN PIGLET SUSPENSION	SCHERING-PLOUGH ANIMAL HEALTH LTD
38612	TRISOPRIM-480 ANTI-BACTERIAL STERILE INJECTION	TROY LABORATORIES PTY LTD

6.2.3 Sulphaquinoxaline

Sulphaquinoxaline is formulated for administration to poultry (chickens and turkeys) either as a feed or water medication. The available residue data supports the current MRLs for sulphaquinoxaline of 0.1 mg/kg for poultry (edible offal) and poultry meat. The current MRL is set as a temporary MRL (denoted T in the MRL Standard) however sufficient data allows amendment of this MRL to 0.1 mg/kg.

The residue data also supports the use of most products as described on the product labels. The application rates of some products are not supported and therefore some label uses will change. Use of these products in birds producing eggs for human consumption is not supported by data.

NCRIS NO	PRODUCT NAME	REGISTRANT
35783	TOLTRO COCCIDIOSTAT FOR POULTRY	AGROTECH AUSTRALIA PTY LTD
40531	CCD SULPHAQUINOXALINE	RIDLEY AGRIPRODUCTS PTY LTD
36432	CCD FORMULA 20 DIAVERIDINE	RIDLEY AGRIPRODUCTS PTY LTD
45118	COXITROL SOLUBLE POWDER	CONTROLLED MEDICATIONS PTY LTD
37185	INCA SULFA-QUIN CONCENTRATE FOR THE PREVENTION AND TREATMENT OF COCCIDIOSIS IN POULTRY	INCA FLIGHT COMPANY TRADING AS RECON CHEMICALS
37123	KEYMIX SOLQUIN KEY 125 FOR THE TREATMENT AND PREVENTION OF CAECAL COCCIDIOSIS IN POULTRY	INTERNATIONAL ANIMAL HEALTH PRODUCTS
40297	POULTRO POULTRY COCCIDIOSTAT FOR WATER & FEED MEDICATION	RHONE-POULENC ANIMAL NUTRITION PTY LTD

6.2.4 Sulphadoxine

The current MRLs for sulphadoxine are *0.1 mg/kg for cattle milk, meat (mammalian) and edible offal (mammalian) and these are supported by the available residue data.

All currently registered products are injectable formulations intended for use on cattle, sheep and pigs for a large number of indications. One product is also registered for use on goats. The available residue data supports the use of all of these products, except for lactating goats. This use will be cancelled. Withholding periods of 14 days for meat and 72 hours for milk following multiple treatments are considered appropriate.

NCRIS NO	PRODUCT NAME	REGISTRANT
47147	BIMOTRIM CO AN AQUEOUS INJECTABLE SOLUTION	BIMEDA AUSTRALIA PTY LTD
36703	TRIDOX BROAD SPECTRUM ANTIBACTERIAL INJECTION FOR TREATMENT OF INFECTIONS	DELVET PTY LTD
36215	VR TRIBACTRAL S ANTIBACTERIAL SOLUTION	SCHERING-PLOUGH ANIMAL HEALTH LTD
36308	TRIVETRIN INJECTION	SCHERING-PLOUGH ANIMAL HEALTH LTD
41376	ILIUM TRISOVET ANTI-BACTERIAL INJECTION	TROY LABORATORIES PTY LTD

6.2.5 Sulphatroxazole

The current MRLs for sulphatroxazole are 0.1 mg/kg for cattle milk, meat (mammalian) and edible offal (mammalian) and these are supported by the available residue data.

Sufficient residue data is available to support the continued use on cattle, sheep and pigs as an injectable formulation in currently registered products for control of bacterial conditions.

NCRIS NO	PRODUCT NAME	REGISTRANT
35931	LEOTROX INJECTABLE SULPHONAMIDE AND TRIMETHOPRIM	BOEHRINGER INGELHEIM

6.2.6 Sulphadimidine/sulphadiazine combination products

There are currently 6 registered products containing a combination of sulphadiazine and sulphadimidine and are intended for oral application to a variety of food producing species (cattle, sheep, goats, piglets, calves, lambs).

The current MRLs for sulphadimidine are 0.1 mg/kg for edible offal (mammalian), meat (mammalian), poultry [except turkey] edible offal and poultry meat. The current MRLs for sulphadiazine are 0.1 mg/kg for cattle milk, edible offal (mammalian), meat (mammalian), poultry edible offal and poultry meat. All of these MRLs are supported by appropriate residue data. In addition data was presented in response to the public

comment phase to allow the establishment of a cattle milk MRL for sulphadimidine of 0.1mg/kg.

Although MRLs could be established for both compounds , insufficient residue data was available to support the use of the combination products in food producing species, as intended. As such uses were to be cancelled or data provided.

A commitment has been given by registrants to generate the necessary residue data in support of the continued availability of these products for certain species (varies between products).

Therefore these products will remain registered until data is provided. This will then be evaluated and will allow the NRA to make a final decision on the continued registration for these combination products.

NCRIS NO	PRODUCT NAME	REGISTRANT
36026	SCOURBAN ORAL ANTIDIARRHOEAL SUSPENSION	PHARMTECH PTY LTD FOR BOMAC LABORATORIES LIMITED
36312	VR NEO-SULCIN ORAL ANTI-DIARRHOEAL SUSPENSION	JUROX PTY LTD
49788	SCOUR −X ORAL ANTI-DIARRHOEAL SUSPENSION	JUROX PTY LTD
36323	VR STREPTOSULCIN FORTE CALF SCOUR BOLUSES	JUROX PTY LTD
36265	VR SULCIN BACTERIAL ENTERITIS TREATMENT	JUROX PTY LTD
46414	VR NEO-SULCIN SCOUR TABLETS	JUROX PTY LTD

APPENDIX A SULPHATROXAZOLE DATA

Bogan, JA (1983, 1985). Scotland.

Edwards, HJ (1982). Trial GB44. UK.

Hamza B (1978-9). RCR B-83'519. Switzerland.

Hamza B (1979). RCR B-83'520 and RCR B-83'522. Switzerland.

Hamza, B (1978). RCR B-83'516, RCR B-83'517 and RCR B-83'518. Switzerland.

Kissmeyer, AM; Edwards, HJ (1988). 18-RN 8821/GB 96. UK and Denmark.

Kissmeyer-Nielsen AM (1988). Trial 18-RN-8815/GB 94. Denmark.

Ludwig, B (1984). Trial DK55 (B.Skov, May 83) B-104'412. Denmark.

Magnussen et al (1983). Trial L31.Denmark.

Nielsen, AM (1986). RN 8613. Denmark.

Nielsen, P; et al (1983). Trial DK 47. Denmark.

Nouws, JFM (1982). Netherlands.

Skov, B (1978). Trial L18, Trial L19. Denmark.

Skov, B (1981). Trial L25B. Denmark.

Vuilleumier F, Skov, B (1978). Trial L2 and L3. Denmark.

APPENDIX B SULPHADOXINE DATA

Davitiyananda, D & Rasmussen, F (1974). Half Lives of Sulphadoxine and trimethoprim after a single intravenous infusion in cows. Acta vet. Scand 15, 356-365.

Nielsen, P; Rasmussen, F (1976). Elimination of trimethoprim, sulphadoxine and their metabolites in goats. Acta Pharmacol. Et Toxicol. 38, 104-112.

Nielsen, P (1973). The metabolism of four sulphonamides in cows. Biochemistry Journal 136, 1039-1045.

Malisch, R (1986). Multi method for the determination of residues of chemotherapeutic agents, antiparasitic drugs and growth promoters in feedstuffs of animal origins. Z.Lebensm. Unters. Forsch 182, 385-399.

Malisxh, R (1987). Determination of residues of pharmacologically active substances by WHPLC by means of UV detection within the detection limit. Archiv. Fur Lebensmittelhygiene 38, 41-47.

Srivastava, SP; Dua, VK and Soxena, RC (1979). Z. Fresenius Anal. Chem, 299 p207.

Thomas, G; Millar, R; Anstis, P (1996). Storage stability of sulphonamide antibiotics spiked into porcine liver tissue. Public interest Project no. 468 (VAM 95-002).

Veterinary Pharmacology and Therapeutics, 7th Edition, p32-33 & p 767.

APPENDIX C SULPHAQUINOXALINE DATA

Epstein RL & Ashworth RB (1989) Tissue sulphonamide concentration and correlation in turkeys. Am J Vet Res, 50, 926-928.

Luders et al. (1974) Blood and tissue levels of sulfadimidine and sulfaquinoxaline in broilers after administration in the drinking water. A contribution to the mass therapy of poultry. Vet. Bulletin Abstract 4056 from Zentralblatt fur Veterinarmedican (1974), 21B:110.

Righter HF, Worthington JM, Zimmerman HE & Mercer D (1970) Tissue-residue depletion of sulphaquinoxaline in poultry. Am. J. Vet. Res. 31, 1051-1054.

Righter HF, Lakata GC & Mercer HD (1973) Tissue residue depletion of sulphaquinoxaline in turkey poults. J. Agr. Food Chem. 21, 412-413.

RESIDUE DATA - SULPHAQUINOXALINE

Study Reference	Formulation	Species	Dose	Duration (days)	Numbers of animals	Days after treatment	Residues (mg/kg)				
Sulphaquinoxaline							Muscle	Liver	Kidney	Fat	Skin
Righter et al., 1970[1]. Experiment 1.	Powder or premix; in feed.	Laying hens (1.5-2.5 y/o) and cockerels (6 m/o)	T ; 0.05% (50 mg sulphaquinoxaline /100 g feed)	12d, fed intermittently on days 1, 2, 6, 7, 11, and 12.	C (n =16, 8m, 8f) T (n = 24, 12m , 12 f)	Control	0.02	0.04	0.04	0.02	0.03
						Powder					
						0	9.0	6.9	11	2.3	9.4
						3	0.17	0.53	2.9	0.29	0.81
						5	0.03	0.09	0.42	0.06	0.20
						7	0.02	0.05	0.34	0.04	0.13
					T (n = 24, 12m, 12f)	40% premix					
						0	8.2	11	14	3.1	9.0
						3	0.28	0.87	2.8	0.37	0.61
						5	0.04	0.13	0.30	0.05	0.24
						7	0.02	0.16	0.22	0.03	0.09
Righter et al., 1970[2]. Experiment 2.	Premix in feed or sodium salt; in water medication	Broilers (5 w/o)	P; 0.025% in the feed or the water.	P = 14d, continuously in feed or water.	C (n=32)	Control	0.02	0.03	0.04	0.03	0.03
					P (n=40)	40% premix					
						0	4.9	6.3	12	2.7	8.4
						3	0.12	0.23	0.56	0.04	0.11
						5	0.04	0.05	0.10	0.01	0.09
						7	0.03	0.02	0.07	0.01	0.12
					P (n=40)	3.4% water					
						0	7.9	5.1	17	5.0	19
						3	0.32	0.56	2.3	0.07	0.94
						5	0.10	0.07	0.33	0.01	0.30
						7	0.06	0.03	0.14	0.01	0.13

Study Reference	Formulation	Species	Dose	Duration (days)	Numbers of animals	Days after treatment	Residues (mg/kg)				
Sulphaquinoxaline							Muscle	Liver	Kidney	Serum	Skin
Righter et al., 1973[3].	Powder; in water	Turkeys (11-12 w/o)			C (n=20)	Control	0.0	0.0	0.1	0.3	0.0
			P; 0.0175% in the water	P = 7d	P (n=20)						
						0	6.0	14	25	42	17
						3	0.2	0.4	1.4	1.0	0.4
						5	0.0	0.2	0.2	0.0	0.2
						7	0.0	0.1	0.1	0.0	0.1
						10	0.0	0.0	0.0	0.0	0.1
			T; 0.1% in the water	T = 3d	T (n=20)						
						0	26	18	43	48	34
						3	0.1	0.2	0.5	0.0	0.4
						5	0.0	0.2	0.2	0.1	0.2
						7	0.0	0.1	0.1	0.2	0.2
						10	0.0	0.1	0.1	0.1	0.2
Epstein and Ashworth, 1989[4].	Premix	Turkeys (f)	100 mg sulfaquinoxaline/kg feed (0.01%)	7d	C (n=1)	Control	0	0		0	
					Trial (n = 9)	30 h	0.65	1.7		5.2	
					3 birds killed/time interval.	48 h	0.49	1.2		3.6	
						56h	0.33	0.84		2.6	

C = Control; P = Prophylactic; and T = Therapeutic.

1. Righter et al., 1970. Experiment 1 – Values reported are the mean residue results from 1 to 6 chickens; results have been corrected for mean control values.
2. Righter et al., 1970. Experiment 2 - Values reported are the mean residue results from 1 to 6 chickens; results have been corrected for mean control values.
3. Righter et al., 1973. Tissue results are for composites of two birds. Values reported have been corrected for mean control values.
4. Epstein and Ashworth, 1989. Maximum residue level reported. Analysis was by thin layer chromatography.

APPENDIX D SULPHADIMDINE (SULPHAMETHAZINE) DATA

Bevill RF, Sharma RM, Meachum SH, Wozniak SC, Bourne DWA & Dittert LW (1977b) Disposition of sulphonamides in food-producing animals: concentrations of sulfamethazine and its metabolites in plasma, urine and tissues of lambs following intravenous administration. Am J Vet Res 38, 973-977.

Heath GE, Kline DA, Barnes CJ & Showalter DH (1975) Elimination of sulfamethazine from edible tissues, blood, urine and faeces of turkey poults. Am J Vet Res 36, 913-917.

McEvoy, J.D.G., Mayne, C.S., Higgins, H.C. and Kennedy, D.G. (1999) Transfer of sulphamethazine from contaminated dairy feed to cows' milk. Veterinary Record 144, 471-474.

Messersmith RE, Sass B, Berger G & Gale GO (1967) Safety and tissue residue evaluations in swine fed rations containing chlortetracycline, sulfamethazine, and penicillin. J Am Med Assoc 151, 719-724.

Miller CR, Theodorides VJ & Bernardo P (1972) Sustained sulfamethazine therapy in cattle. Vet Med SAC, 513-516.

Mutha SC, Brown TL, Chamberlain B & Lee CE (1977) Sulfamethazine residue in calf tissue. J Agric Food Chem 25, 556-558.

Nouws JFM, Vree TB, Baakman M, Driessens F, Vellenga L & Mevius DJ (1986) Pharmacokinetics, renal clearance, tissue distribution and residue aspects of sulphadimidine and its N^4-acetyl metabolite in pigs. Vet Quart 8, 123-135.

Righter HF, Worthington JM, Zimmerman HE & Mercer HD (1971) Tissue residue depletion of sulphamethazine in calves and chickens. Am J Vet Res 32, 1003-1006.

Samuelson G, Whipple DM, Showalter DH, Jacobson WC & Heath GE (1979) Elimination of sulfamethazine residues from swine. J Am Vet Med Assoc 175, 449-452.

Saschenbrecker PW & Fish NA (1980) Sulfamethazine residues in uncooked edible tissues of pork following recommended oral administration and withdrawal. Can J Comp Med 44, 338-345.

Whipple DM, Samuelson G, Heath GE & Showalter DH (1980) Tissue residue depletion and recycling of sulfamethazine in swine. J Am Vet Med Assoc 15, 1348-1352.

Yndestad M & Underdal B (1977) Residues of sulfadimidine/sulfanilamide and sulfamethoxypryridazine in sheep tissue. Acta Vet. Scand. 18, 15-22.

Youssef SAH, El-Gendi AYI, El-Sayad MGA, Atef M & Salam SAA (1981) Some pharmacokinetic and biochemical aspects of sulphadiazine and sulphadimidine in ewes. J Vet. Parmacol. Therap. 4, 173-182.

RESIDUE DATA

Study Reference	Formulation	Species	Dose	Duration	Number of animals	Residues (mg/kg)					
Sulphadimidine							Muscle	Liver	Kidney	Fat	Serum
Righter et al., 1971	Oral 25% solution (diluted in water prior to admin) oral	Cattle	154 mg/kg on day 1 followed by 77 mg/kg daily for next 3d	4 days	n=2 n=2 on d0, 4 n=3 on d6, 8, 11	Control Treated: 0 4 6 8 11	0.09 30.4 0.04 0.01 0.01 0	0.11 54.9 0.05 0 0.03 0	0.11 43.2 0.12 0.16 0.02 0	0.10 18.6 0.05 0.07 0.01 0	3.4 107.1 4.1 0 0 0
							Muscle	Liver	Kidney	Fat	Skin
Mutha et al., 1977	Slow release bolus	Cattle	102 mg/kg	N/A	n=2 Each group n=4	Control Treated: 2 5 10 16 21	0.008 73 2.9 0.113 0.012 0.019	0.013 112 7.4 0.504 0.018 0.017	0.023 130 6.4 0.29 0.021 0.019	0003 17 0.74 0.036 0.01 0.005	
Miller et al., 1972	Sustained release	Cattle	220 mg/kg	N/A	Each group n=3	Treated: 2 6 10 11	 17.3 < 0.02 < 0.04 < 0.04	 20.5 0.62 < 0.04 < 0.04	 15.7 0.52 < 0.04 < 0.04	 6.3 0.1 < 0.04 < 0.04	
Messersmith et al., 1967	Feed premix	Pigs	100 g/ton (98.4 g/tonne)	14 weeks	Each group n=3	Treated: 7	 < 0.1	 < 0.1	 < 0.1	 < 0.1	

Study Reference	Formulation	Species	Dose	Duration	Number of animals	Residues (mg/kg)					
Sulphadimidine							Muscle	Liver	Kidney	Fat	Serum
Samuelson et al., 1979	Feed premix	Weanling pigs	500 g/ton	30 days	Each group n=3	Treated: 0 2 4 6 8 10 15	 5.77 0.67 0.09 0.02 0.02 0 0	 18.27 2.81 0.37 0.05 0.1 0.06 0	 16.07 1.86 0.22 0.05 0.12 0.06 0	 4.90 0.43 0.10 0.02 0.01 0 0	
Saschenbrecker and Fish, 1980	Feed premix	Piglets 7 w/o	110 g/tonne	65 days	n=3 (controls) n=5 for d0 n=2 for d7, 14, 21, 28	Controls Treated 0 7 14 21 28	nd 2.0 0.04 < 0.02 nd nd	nd 7.6 0.3 < 0.02 nd nd	nd 6.6 0.10 < 0.02 nd nd		nd 1.14 0.056 < 0.02 nd nd
Whipple et al., 1980	Feed premix	Pigs	98.4 g/tonne	98 days	Each group n=3	0 2 5 7 9 11 15	2.62 0.63 0.10 0.07 0 0 0	6.93 1.67 0.29 0.04 0 0 0	2.82 0.67 0.11 0.10 0 0 0	0.79 0.16 0 0 0 0 0	
Nouws et al., 1986	IM	Pigs 3.5 - 4 months old	20 mg/kg	Single injection	Each group n=4	~ 1d ~ 3d ~ 7d ~ 9d	6.5 0.43 0.14 0.014	2.6 0.28 0.08 0.01	7.5 0.91 0.26 0.026		

Study Reference	Formulation	Species	Dose	Duration	Number of animals	Residues (mg/kg)					
Sulphadimidine							Muscle	Liver	Kidney	Fat	Serum
Bevill et al., 1977b	IV	Lambs 30 - 40 kg	107.25 mg/kg	Single injection	n=1 n=2 for 12, 24, 36,48, 60 and 84h	6h 12h 24h 36h 48h 60h 84h	58.5 23.3 4.2 0.85 0.1 0.06 0.03	68.9 36.8 5.96 1.57 0.21 0.23 0.11	124.2 63.4 18.3 5.2 0.68 0.42 0.14	38.3 15.0 1.7 0.35 0.9 0.03 0.02	
Righter et al., 1971	Water medication	Chickens 4 months old	0.1% SD	6 days	Each group n=1 or 2	Controls Treated: 0 3 5 7 10	0.02 5.7 0.15 0.07 0.04 0.03	0.03 18.7 0.81 0.12 0.11 0.13	0.02 10.7 0.83 0.28 0.16 0.01	0.02 1.64 0.05 0.03 0.04 0.02	0.02 6.6 0.04 0.02 0.01 0.01
	Feed medication	Breeder chick-ens 4 months old	0.4% SD	6 days	Each group n=1 or 2	Controls Treated: 0 3 5 7 10	0.02 74.5 0.77 0.11 0.16 0.04	0.03 78.0 2.6 0.27 1.1 0.47	0.02 103.0 2.8 0.84 1.0 0.19	0.02 8.31 0.3 0.04 0.05 0.03	0.02 57.3 1.0 0.27 0.52 0.1

Study Reference	Formulation	Species	Dose	Duration	Number of animals	Residues (mg/kg)					
Sulphadimidine							Muscle	Liver	Kidney	Fat	Serum
Heath et al., 1975	Water medication	Turkey poults (f)	0.1% SD	6 days	n=5 n=3	Controls 0h Treated: 0h 4h 8h 12h 1d 1.5d 2d 3d 5d 8d 11d 14d	 0 18.5 15.8 4.9 3.5 1.0 0.2 0.1 0 0 0 0 0	 0 24.0 16.5 5.2 3.9 2.1 0.6 0.3 0.3 0.2 0.2 0.4 0.2	 0 33.7 24.7 8.7 8.8 1.9 0.6 0.4 0.1 0 0.1 0.3 0		 0 19.1 23.4 5.7 4.1 1.6 0.6 0.6 0.3 0.3 0.4 0 0.4
Ynstead & Underdal (1977) (5)	IV	Sheep	150 mg/kg (sulphadimidine) 100 mg/kg (sulphanilamide orally) Sulphadimidine once Sulphadimidine orally for 3 days	N=7 N=7		Treated D2 D3 D4 D5 D6 D7 d8	Muscle 16900 1200 261 175 109 75 50		Kidney 19866 3800 850 650 507 300 119	Liver 16500 1900 600 400 265 180 79	

APPENDDIX E SULPHADIAZINE DATA

Dagorn M, Moulin G, Laurentie M & Delmas JM (1991) Plasma and lung pharmacokinetics of trimethoprim and sulphadiazine combinations administered to broilers. Acta Vet Scand Suppl 87, 273-275. Reference as supplied in the report by Dr Pass.

Goren E, de Jong WA & Doornenbal P (1984) Some pharmacokinetic aspects of four sulphonamides and trimethoprim, and their therapeutic efficacy in experimental *Escherichia coli* infection in poultry. The Veterinary Quarterly, 6, 134-140.

Guard CL, Schwark WS, Friedman DS, Blackshear P & Haluska M (1986) Age-related alterations in trimethoprim sulfadiazine disposition following oral or parenteral administration in calves. Can J Vet Res 50, 342-346.

Loscher W, Fassbender CP, Weissing M & Kietzmann M (1990) Drug plasma levels following administration of trimethoprim and sulphonamide combinations to broilers. J. Vet. Pharmacol. Therap. 13, 309-319.

Nouws JFM, Mevius D, Vree TB & Degen M (1989) Pharmacokinetics and renal clearance of sulphadimidine, sulphamerazine and sulphadiazine and the N_4-acetyl and hydroxy metabolites in pigs. Vet. Quart. 11, 78-86.

Nouws, JFM; Vree, TB; Breukink, HJ; Baakman, M; Driessens, F; and Smulders, A (1985). Dose dependent disposition of sulphadimidine and of its N4-acetyl and hydroxy metabolites in plasma and milk of dairy cows. Veterinary Quarterly 7, 177-186.

Shoaf SE, Schwark WS & Guard CL (1989) Pharmacokinetics of sulfadiazine/trimethoprim in neonatal male calves: effect of age and penetration into cerebrospinal fluid. Am J Vet Res, 50, 396-403.

Shoaf SE, Schwark WS, Guard, CL & Schwartsman, RV (1986). Pharmacokinetics of trimethoprim /sulfadiazine in neonatal calves: influence of synovitis. J. Vet Pharmacol. Therap. 9, 446-454.

Soli NE, Framstad T, Skjerve E, Sohlberg S & Odegaard SA (1990) A comparison of some of the pharmacokinetic parameters of three commercial sulphadiazine/trimethoprim combined preparations given orally to pigs. Veterinary Research Communications, 14, 403-410.

Woolley Jr. JL & Sigel CW (1982a) Development of pharmacokinetic models for sulfonamides in food animals: metabolic depletion profile of sulfadiazine in the calf. Am J Vet Res, 43, 768-774.

Woolley Jr., JL & Sigel CW (1982b) The role of dietary nitrate and nitrite in the reductive deamination of sulfadiazine by the rat, guinea pig, and neonatal calf. Life Sciences, 30, 2229-2234.

Woolley, Jr., JL Sigel, CW &Wels, CM (1980) II Novel deaminated sulfadiazine metabolites in neonatal calf tissues, plasma, and urine following oral treatment with ^{14}C-sulphadiazine. Life Sciences, 27, 1819-1826.

Yndestad M & Underdal B (1977) Residues of sulfadimidine/sulfanilamide and sulfamethoxypryridazine in sheep tissue. Acta Vet. Scand. 18, 15-22.

Youssef SAH, El-Gendi AYI, El-Sayad MGA, Atef M & Salam SAA (1981) Some pharmacokinetic and biochemical aspects of sulphadiazine and sulphadimidine in ewes. J Vet. Parmacol. Therap. 4, 173-182.

RESIDUE DATA - SULPHADIAZINE

Study Reference	Formulation	Species	Dose mg/kg bw/day	Duration	Numbers of animals	Days after treatment	Residues (mg/kg)
Dagorn et al. 1991.	IV	Broilers	10	Single injection	80	0-24h	No tissue residue data reported
	Water medication	Broilers	20	4d	120	0-120h	No tissue residue data reported
Goren et al. 1984	250 mg/L water medication	Broilers 3 weeks old	28-44	4d	30-33/group 4 Groups	7	No tissue residue data reported
Loscher et al. 1990	IV	(f) 17-22 days old	100	Single injection	14	0-24h	No tissue residue data reported
	oral	Broilers (f) 17-22 days old	100	Single dose	78	0.25-48 hours	No tissue residue data reported
	Water medication	Broilers (f) 17-22 days old	100	5d	132	3-99h	No tissue residue data reported
Guard et al. 1986	Oral	Calves (m) from 1 days old	12.5	Given at 1d at 7d at 42d	6(2)	0-2d	No tissue residue data reported
	Injection - sc	Calves (m) 7 days old	12.5	Given at 1d at 7d at 42d			No tissue residue data reported
Shoaf et al. 1989	IV injection 24% sterile solution	Calves (m)	25	Single injections at 1d 7d 42d	6(3)	0-1d	No tissue residue data reported
Soli et al. 1990	Oral 12 or 24% powder	Pigs (m, .f)	25	1 dose only	n = 12 (3 m 3f) cross over n=3 (m) 2 studies	0-1d 5d 7d 10d	No tissue residue data reported (1)
Nouws et al. 1989	IV injection	Pigs (m)	40	1 injection only	12	30h	No tissue residue data reported

Woolley et al. 1980	Oral bolus (1g c14 sulphadiazine)	Calves (m) 40 kg bwt 1-2 weeks old	25	5d	n = 2		Muscle	Liver	Kidney	Plasma	
						14d Calf 1	0.05 (65-67)	0.26 (30)	0.16 (47)	0.11 (80)	
						Calf 2	0.04 (62-65	0.37 (21)	0.19 (36)	0.10 (82)	
							Data are ppm total radioactivity (% extractable radio-activity)				
Woolley & Sigel 1982 a (4)	Oral bolus (1g sulphadiazine)						Muscle		Kidney	Liver	Plasma
							Psoas	Thigh			
Experiment 1		Calves 39-46 kg 9 days old	~23	5d	n = 9 (n=3/treatment group)	1d	1.6 2.1 2.7	1.2 1.6 2.2	3.2 5.6 7.4	0.61 1.4 1.6	4.3 7.4 12
						3d	0.09 0.15 0.25	0.07 0.19 0.37	0.30 0.39 0.99	0.03 0.10 0.29	0.21 0.44 1.2
						7d	<0.01 0.02 0.14	<0.01 0.03 0.08	0.03 0.06 0.13	<0.01 0.01 0.07	<0.01 0.06 0.17
Experiment II	Bolus 1g c14 sulphadiazine	Calves (m) 40-51 kgs 14 days old	~21	5d	N=4 (n =2 / group)	7d	0.10 0.39	0.10 0.46	0.38	0.70 1.5	0.30 1.3
						14d	0.04 0.05	0.04 0.05	0.16 0.19	0.26 0.37	0.11 0.10
							Data are ppm of total radioactivity. Concentrations of sulphadiazine in all tissues <0.1 mg/kg.				
Woolley & Sigel 1982b	Oral bolus (1g sulphadiazine)	Calves 38-52 kg bw <14 days old	~19-26	5d	n = 8 (n=2/group (5))		Only plasma results reported. No tissue residue data reported				

Ynstead & Underdal (1977) (5)	IV	Sheep	150 mg/kg (sulphadimidine) 100 mg/kg (sulphanilamide orally) Sulphadimidine once Sulphadimidine orally for 3 days	N=7 N=7	Treated D2 D3 D4 D5 D6 D7 d8	 16900 1200 261 175 109 75 50	 16500 1900 600 400 265 180 79	 19866 3800 850 650 507 300 119		

DAT = Days after treatment unless otherwise specified.
d/o = days old; w/o = weeks old; m = male; f = female.
(1) No unacceptable or antibacterial residues of sulphadiazine or trimethoprim were found in the kidneys of pigs slaughtered at 5, 7, or 10 days after administration.
(2) Six animals/group for the PO and SC administrations. The same calves were used for the PO and SC studies.
(3) Each animal treated at 1, 7 and 42 days. Two additional male calves treated at day 7
(4) TLC analyses
(5) Groups were fed different milk replacement formulations with one group given 137 mg/L sodium nitrate in the drinking water and another group 150 mg/L sodium nitrite in the drinking water