Commonwealth Department of Health and Ageing

TGA THERAPEUTIC GOODS ADMINISTRATION

National Drugs and Poisons Schedule Committee

Record of the Reasons

36th Meeting
15-17 October 2002

The *Record of the Reasons* contains the basis of scheduling decisions and other outcomes arising from the meeting. Please note that the Secretariat is moving towards including the edited minutes as the *Record of the Reasons*. With this document, we have included edited extracts relating to scheduling considerations for OTC medicines, domestic poisons and certain matters related to pesticides. The Secretariat is hopeful of including the edited minutes for all sectors following consultation with the respective industry bodies.

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GLOSSARY

ABBREVIATION	*NAME*
AAN	Australian Approved Name
ACSPA	Australian Chemicals Speciality Products Association
ADEC	Australian Drug Evaluation Committee
ADI	Acceptable Daily Intake
ADRAC	Adverse Drug Reactions Advisory Committee
AGRD	Australian Guidelines for the Registration of Drugs
AHMAC	Australian Health Ministers' Advisory Council
ANZFA	Australia New Zealand Food Authority
APAC	Australian Pharmaceutical Advisory Council
APMA	Australian Pharmaceutical Manufacturers Association
AQIS	Australian Quarantine and Inspection Service
ARfD	Acute Reference Dose
ARTG	Australian Register of Therapeutic Goods
ASCC	Australian Society of Cosmetic Chemists
ASCEPT	Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists
BAN	British Approved Name
CAS	Chemical Abstract Service
CHC	Complementary Healthcare Council of Australia
CMEC	Complementary Medicine Evaluation Committee
CMI	Consumer Medicine Information

CNPMB	Chemicals and Non-Prescription Medicines Branch
COAG	Councils of Australian Governments
CPAS	Chemical Product Assessment Section
CPI	Consumer Product Information
CRC	Child-Resistant Closure
CRIH	Chemical Review and International Harmonization
CTFAA	Cosmetic, Toiletry & Fragrance Association of Australia
DAP	Drafting Advisory Panel
DSEB	Drug Safety and Evaluation Branch
EAGAR	Expert Advisory Group on Antimicrobial Resistance
EC	European Community
ECG	Electrocardiogram
ECRP	Existing Chemicals Review Program
EPA	Environment Protection Authority
ERMA	Environmental Risk Management Authority
FAISD	First Aid Instructions and Safety Directions
FDA	Food and Drug Administration (US)
FOI	Freedom of Information
GHS	Globally Harmonised System for Classification and Labelling of Chemicals.
GIT	Gastro-intestinal tract
GP	General Practitioner
GST	Goods and Services Tax
HCN	Health Communication Network

INN	International Non-proprietary Name
ISO	International Standards Organization
JETACAR	Joint Expert Advisory Committee on Antibiotic Resistance
LC_{50}	The concentration of a substance that produces death in 50% of a population of experimental organisms. Usually expressed as mg per litre (mg/L) as a concentration in air.
LD_{50}	The concentration of a substance that produces death in 50% of a population of experimental organisms. Usually expressed as milligrams per kilogram (mg/kg) of body weight
MCC	Medicines Classification Committee
MEC	Medicines Evaluation Committee
MOH	Ministry of Health (NZ)
NCCTG	National Coordinating Committee of Therapeutic Goods
NDPSC	National Drugs and Poisons Schedule Committee
NHMRC	National Health and Medical Research Council
NICNAS	National Industrial Chemicals Notification & Assessment Scheme
NOEL	No Observable Effect Level
NOHSC	National Occupational Health & Safety Commission
NRA	National Registration Authority for Agricultural and Veterinary Chemicals
NZ	New Zealand
OOS	Out of Session
OTC	Over the Counter
PAR	Prescription Animal Remedy
PBAC	Pharmaceutical Benefits Advisory Committee

PEC	Priority Existing Chemical
PGA	Pharmaceutical Guild of Australia
PHARM	Pharmaceutical Health and Rational Use of Medicines
PI	Product Information
PIC	Poisons Information Centre
PMAA	Proprietary Medicines Association of Australia
PSA	Pharmaceutical Society of Australia
RFI	Restricted Flow Insert
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
SVT	First aid for the solvent prevails
TCM	Traditional Chinese Medicine
TGA	Therapeutic Goods Administration
TGAC	Technical Grade Active Constituent
TGC	Therapeutic Goods Committee
TGO	Therapeutic Goods Order
TOR	Terms of Reference
TSB	Toxic Substances Board
TTHWP	Trans-Tasman Harmonization Working Party
TTMRA	Trans-Tasman Mutual Recognition Agreement
UK	United Kingdom
USA	United States of America
WHO	World Health Organization
WP	Working Party

WS	Warning statement

2. PROPOSED CHANGES/ADDITIONS TO PARTS 1 TO 3 AND PART 5 OF THE STANDARD FOR THE UNIFORM SCHEDULING OF DRUGS AND POISONS.

2.1 SUSDP, PART 1

2.1.1 DEFINITION IN PART 1 OF THE SUSDP FOR "AQUEOUS PREPARATIONS"

This item was deferred to the February 2003 Meeting.

2.2 SUSDP, PART 2

2.2.1 VARIATION OF REQUIREMENT FOR CLAUSE 7(1)(D)

PURPOSE

The Committee considered correspondence from XXXXXXXXXXXXXX concerning a requested exemption from Part 2, Clause 7(1)(d) of the SUSDP for pool chemicals containing blends of XXXXXXXXXXXXXX trichloroisocyanuric acid and XXXXXXXXXXXXXX.

BACKGROUND

The proposed exemption was initially reviewed by the NDPSC at the November 1999 Meeting. At the time of the meeting, the Committee was of the opinion that amending the SUSDP to give the requested exemptions presented practical difficulties and did not reflect the openness normally associated with scheduling decisions. The requested restriction on disclosure of ingredients was not acceptable to the Committee. Furthermore, the request for the formulation to remain confidential appeared inconsistent with requirements for all scheduled poisons and actives to be declared on labels. To allow further consideration, it was considered that the Company should obtain a formal opinion on oxidising potential from the Competent Authorities controlling the Australian Dangerous Goods (ADG) Code. The Company should also provide data or reasoned argument to support each of the changes to warning statements and safety directions that it is seeking.

DISCUSSION

The Committee noted correspondence from XXXXXXXXXXXXXX seeking an exemption for the inclusion of "FIRE AND EXPLOSION HAZARD" in the signal heading and warning statement (WS) 23 "May cause fire or explosion" in the safety directions. No other changes or exemptions were requested.

The Committee noted that XXXXXXXXXXXXXX had amended its labels to declare the inclusion of sodium tetraborate, an active that the company had previously not disclosed.

The Committee noted the inclusion of supporting data in the form of chemical reports that appeared to demonstrate that XXXXXXXXXXXXXX's product did not constitute a fire or explosion hazard. XXXXXXXXXXXXXX stated that they had received a letter from the XXXXXXXXXXXXXX WorkCover Authority agreeing that XXXXXXXXXXXXXX was a non-dangerous good and was exempted from carrying a Class 5.1 Oxidising Agent diamond. The Committee noted that the letter from the XXXXXXXXXXXXXX WorkCover Authority was listed at Attachment 1 of the XXXXXXXXXXXXXX submission, but had not been provided.

The Committee acknowledged that the XXXXXXXXXXXXXX proposal contained merit, but the Committee needed to be provided with a copy of the letter from the XXXXXXXXXXXXXX WorkCover Authority before the proposal could be reviewed further.

A Member proposed that the Secretariat contact the Australian Department of Transport and Regional Services to inquire about receiving an expert opinion on XXXXXXXXXXXXXX's proposal and also inform the Committee if the product would be covered by the ADG code. The expert opinion could then be used to guide the Committee.

OUTCOME

The Committee agreed to defer the matter to the February 2003 meeting to allow XXXXXXXXXXXXXX to provide a copy of the letter from the XXXXXXXXXXXXXX WorkCover Authority. The additional time will also allow an expert opinion to be sought, which then may be used to guide to the Committee.

2.4 SUSDP, PART 5

2.4.1 PESTICIDES LISTED IN APPENDIX J

PURPOSE

The Committee considered a request from the XXXXXXXXXXXXXX seeking support to persuade the XXXXXXXXXXXXXX to review the listing of pesticides in Appendix J of the SUSDP.

BACKGROUND

The Committee had previously considered the issue of Appendix J and Restricted Chemical Product (RCP) controls at the November 2000 Meeting. The XXXXXXXXXXXXXX of the XXXXXXXXXXXXXX, considered the appropriateness of declaring agricultural and veterinary chemicals listed in Appendix J to be RCP's under Division 4 of Part 4 of the *Agricultural and Veterinary Chemical* Code, at its 19th (October 2000) Meeting.

Once a substance is declared a RCP, this enables the XXXXXXXXXXXXXX to exercise selected controls over access and set specific conditions associated with its use. These controls need to be enforced under State/Territory control-of-use legislation.

An alternative way for the same controls to be applied over access and use is through poisons legislation in the individual jurisdictions. This may be either by reference or adoption from the SUSDP, where the NDPSC lists a Schedule 7 poison in Appendix J (1) – "*not to be available except to authorised or licensed persons"*.

DISCUSSION

The Committee noted the correspondence from the XXXXXXXXXXXXX. The XXXXXXXXXXXXX made the following recommendation based on the discussions of the XXXXXXXXXXXXX.

That the NDPSC:

- make a recommendation to the XXXXXXXXXXXXX to review the pesticides listed in Appendix J, and provide any information on prioritisation of the pesticides for review or the controls or competencies considered necessary for their use; and
- not list any further pesticides in Appendix J while these matters are being resolved.

The Committee raised the question concerning the basis of having an entry in Appendix J that was not included in the XXXXXXXXXXXXX's RCP list. It was noted by the Committee that there were different sets of criteria for inclusion in Appendix J and inclusion in the XXXXXXXXXXXXX's RCP list. A Member recommended that Appendix J should be reviewed to investigate if any further chemicals listed in Appendix J should also be included in the XXXXXXXXXXXXX's RCP list.

The Committee noted that the lack of uniformity across jurisdictions necessitated the continued parallel use of Schedule 7/Appendix J and RCP. The XXXXXXXXXXXXX Member advised the Committee that the XXXXXXXXXXXXX Government was unable to enforce RCP's other than through its Poisons Act, which references the SUSDP's Appendix J, hence reinforcing the on-going requirement for Appendix J.

The XXXXXXXXXXXXX Member noted that XXXXXXXXXXXXX is currently looking at reviewing its poisons legislation due to outdated references to the old Appendix M and may be able to include a review of Appendix J as part of this project.

A Member noted that the XXXXXXXXXXXXX had requested the States to put forward a list of priority chemicals for the review process to consider.

OUTCOME

The Committee agreed to consider Appendix J at a later Meeting once the proposed review of Appendix J chemicals was completed by XXXXXXXXXXXXX and made available to the Committee Members.

2.4.2 APPENDIX B

PURPOSE

To finalise the proposal to re-instate Appendix B (Substances Considered Not To Require Control By Scheduling) in the SUSDP.

BACKGROUND

Minor changes were agreed to the Introduction of the draft Appendix B at the June 2002 meeting. The Secretariat was requested to divide the pre-1986 entries into groups according to proposed action for consideration at the October 2002 meeting.

DISCUSSION

The Committee noted the draft Appendix B included all the previously proposed amendments to the introduction, amendments to the code tables and all post-1986 entries proposed up to and including, the June 2002 Meeting of NDPSC. After much discussion, the Committee agreed to publish the final draft Appendix B (Attachment 1) to allow public comment, for finalisation at the Feb 2003 meeting and subsequent inclusion in the Standard thereafter.

The Committee was advised that the pre-1986 substances had been divided into four groups:

- substances recommended to be included in Appendix B, where there is some acute toxicology data which combined with known use(s) would suggest these as suitable for inclusion in Appendix B. Many have registered agvet and/or therapeutic products containing the substance.
- substances recommended not to be included in Appendix B, where there are no registered products containing these substances and no supporting data or reasons for inclusion. Non-inclusion of these substances in Appendix B would have no regulatory impact
- substances recommended for consideration of scheduling, for which the toxicity profile and/or use supports the inclusion of the substance in a Schedule of the SUSDP. Continued inclusion in Appendix B of these substances could not be supported as clear evidence of hazard is available to the Committee. It was proposed that these substances remain unscheduled and the Committee consider the scheduling of each substance in small groups (3-5) at subsequent meetings, to ensure that any consumer products including these substances are appropriately labelled in the long term.
- substances already included in the schedules of the SUSDP, therefore no further action is proposed for these substances.

Members agreed to include in the draft, those pre-1986 substances recommended in the list for inclusion in Appendix B.

The Committee also emphasised that only submissions for scheduling would be reviewed by the Committee and submissions for inclusion in Appendix B would be neither accepted nor reviewed.

OUTCOME

The Committee agreed to publish the draft of Appendix B, including the pre-1986 substances that were recommended for inclusion, for public comment and consideration at the February 2003 meeting. The Committee highlighted that substances omitted from the draft Appendix B, but had previously been listed as substances not recommended for scheduling, were not included for one of the following reasons:

- There were no registered products containing that substance or supporting data; or
- The substance now appeared in the schedules of the SUSDP; or
- The available information supports scheduling the substances and these substances would be included in a work plan to be reviewed at a later stage. However, the status of these substances would remain unchanged at this time, that is unscheduled.

APPENDIX B

SUBSTANCES CONSIDERED NOT TO REQUIRE CONTROL BY SCHEDULING

[This appendix should be read in conjunction with Appendix A]

INTRODUCTION

At various times, the NDPSC has considered substances for which the available information suggests that inclusion in the Poisons Schedules is not necessary or not the most appropriate means of controlling the risk to public health.

Listing in Appendix B indicates that a decision has been taken not to list substances anywhere in the Schedules, either for a specific purpose, or generally. It is an inclusive, but not an exhaustive, list ie. there may be substances not included in the Schedules, and not included in Appendix B, which may be hazardous or non-hazardous, but have not been considered in relation to the need for scheduling.

Substances may be included in Appendix B because they have intrinsically low toxicity, or where other factors suggest that the potential public health risk would be minimal. Factors which are considered when determining an Appendix B entry include:

- The toxicology profile was adequately characterised and not consistent with inclusion in any of the Schedules;
- The use, purpose or product presentation minimised any hazard to the public such as to not require scheduling; or
- The public access was limited such that scheduling was inappropriate or unnecessary.

The list has been developed from current scheduling files and historical records. For transparency, where the reason for entry and/or purpose or use for the substance was apparent in the consideration, this has been included in the columns “Reason for Entry” and “Area of Use”

Inclusion in Appendix B will not prevent reconsideration of the scheduling of a substance where adverse information becomes available about the Appendix B entry for that substance.

The NDPSC considers applications for scheduling. Applications for entry into Appendix B will not be accepted.

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PART 1

REASONS FOR ENTRY

a Low Toxicity.
b Use pattern restricts hazard.
c Presentation/packaging restricts hazard.
d Industrial use only

PART 2

AREAS OF USE

1. Agricultural
   - 1.1 Herbicide
   - 1.2 Insecticide
     - 1.2.1 Insecticide for codling moth
   - 1.3 Fungicide
     - 1.3.1 On seed fungicide
   - 1.4 Bird Repellent
   - 1.5 Fertiliser
   - 1.6 Plant Growth Regulator
   - 1.7 Insect Pheromone
   - 1.8 Mushroom Bactericide
   - 1.9 Acaricide

2. Veterinary
   - 2.1 For animal use
   - 2.2 Treatment of mastitis in cows
   - 2.3 Coccidiostat
   - 2.4 Feed additive
   - 2.5 Antiseptic
   - 2.6 Scabicide
   - 2.7 Anthelmintic
   - 2.8 Vitamin/Mineral

3. Domestic
   - 3.1 Aromatherapy
   - 3.2 Food additive
   - 3.3 Cosmetic
   - 3.4 Human use
   - 3.5 Miticide

4. Industrial
   - 4.1 Water Treatment

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4.2 Biological control agent

5. Environmental

5.1 Mosquito control

6. Human therapeutic use

6.1 Diagnostic agent
6.2 Medical device
6.3 Antiseptic
6.4 Sunscreen
6.5 External Use
6.6 Laxative
6.7 Antiseborrheic
6.8 Cytoprotective
6.9 Vitamin/Mineral
6.10 Eye Drops

7. General

7.1 Any use.
7.2 Excipient
7.3 Synergist
7.4 Flux
7.5 Pesticide
7.6 Insect Repellent
7.7 Solvent
7.8 Disinfectant
7.9 Preservative
7.10 Antioxidant
7.11 Resin Activator/Accelerant
7.12 Sweetener Artificial
7.13 Food additive

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PART 3

SUBSTANCES CONSIDERED NOT TO REQUIRE CONTROL BY SCHEDULING

As at November 2002

SUBSTANCE	DATE OF ENTRY	REASON FOR LISTING	AREA OF USE
AGROBACTERIUM RADIOBACTER	Nov 1989	a	1
ALCOHOL, DEHYDRATED	Aug 2000	b	6
ALUM	May 1997	a	7.1
ALUMINIUM AMMONIUM SULFATE	May 1997	a	7.1
ALUMINIUM POTASSIUM SULFATE	May 1997	a	7.1
ALUMINIUM SILICATE	Nov 1974	a	7.1
ALUMINIUM tris (ETHYLPHOSPHONATE)	Aug 1986	a	1
AMINACRINE	Aug 1999	b	6.3
AMMONIUM PHOSPHATE	Nov 1974	a	7.1
AMMONIUM THIOSULPHATE	Nov 1974	a	7.1
AMPROLIUM	Jun 1969	a	2.3
AMYL ACETATE	Nov 1974	a	7.1
ASPARTIC ACID		a	6
ASULAM	May 1986	a	1
BACILLUS THURINGIENSIS (excluding endotoxin)	May 1992	a	5.1
BACULOVIRUS CYDIA POMONELLA (Codling Moth Granulosis Virus)	Oct 2002	a	1.2.1
BENFLURALIN	-	a	1.1
BENSULFURON-METHYL	Aug 1987	a	1
BENTONITE	Jun 2002	a	7.1
BENZYL BENZOATE	Aug 1989	a	1,3.4
BETAINE HYDROCHLORIDE	Nov 1974	a	7.1
BIFENAZATE	Oct 2002	a	1.9
BISMUTH SUBNITRATE	Nov 1999	b, c	2.1
BIURET	Nov 1974	a	2.4
BOVINE SOMATOTROPHIN	May 1992	a	2
BROMACIL	Aug 1987	a	1
BROMOPROPYLATE	Nov 1994	a	1
BUPIRIMATE	Nov 1990	a	1
BUTAFENACIL	May 2000	a	1
BUTOXYPOLYPROPYLENE GYLCOL	Nov 1974	a	7.7
CARBETAMIDE	Aug 1991	a	1

CARBOXIN	Aug 1987	a	1
CARFENTRAZONE-ETHYL	Aug 1998	a	1
CETYL ALCOHOL	Nov 1974	a	7.1
CHAMOMILE OIL	Feb 2000	a	3.1
CHINA CLAY	Nov 1974	a	7.1
CHLORFLURENOL	Feb 1974	a	1.6
CHLORHEXIDINE	Nov 1974	a	7.8
CHLORIDAZON	May 1988	a	1
CHLOROXYLENOLS	Feb 1975	a	7.8
CITRONELLA OIL	Feb 2000	a	7.1
CLARY SAGE OIL	Feb 2000	a	7.1
CLOPIDOL	Nov 1974	d	2.3
COBALT NAPHTHENATE	-	d	7.1
COLOPHONY	Feb 1997	b	7.4
CROSPOVIDONE	Aug 1996	a	2
CULICINOMYCES CLAVOSPORUS	Nov 1982	a	5.1
CYCLAMIC ACID	Nov 1971	a	7.1
CYCLOHEXANE	Nov 1974	a	7.7
CYCLOHEXANOL ACETATE	-	a	7.7
CYROMAZINE	Nov 1980	a	2
DIAVERIDINE	Jun 1969	d	2.3
DICLAZURIL	Nov 2001	a	2.3
DIETHYL CARBONATE	-	a	7.1
DIFLUFENICAN	Feb 1987	a	1
DIKEGULAC-SODIUM	Mar 1980	a	1.6
DIMETHICONE	-	a	7.1
DIMETHYL ETHER	Nov 1988	d	4
d-PHENOTHRIN	Feb 1982	a	7.5, 1.2
DIPHENYLAMINE	Feb 1988	a	1
DIPROPYLENE GLYCOL MONOMETHYL ETHER	Nov 1987	a	4
DIURON	Nov 1987	a	1
DOCUSATE SODIUM (DIOCTYL SODIUM SULFOSUCCINATE)	Feb 1970	a	7.1
2,2-DPA	Nov 1989	a	1
EPSIPRANTEL	Nov 1991	a	2
ETHAMETSULFURON-METHYL	Nov 2000	a	1.1
ETHOPABATE	Jun 1969	d	2.3
ETHYL ACETATE	Nov 1974	a	7.1
ETHYL ALCOHOL	Nov 1974	a	7.1
ETHYLBUTYLACETYL-AMINOPROPRIONATE	Aug 2000	a	3.4
ETHYL BUTYRATE	-	a	7.1

ETHYL LACTATE	-	a	7.1
ETHYL METHACRYLATE	Nov 1974	a	7.1
FENFURAM	May 1977	a	1.3.1
FENHEXAMID	Feb 1999	a	1
FENOXYCARB	Feb 1988	a	1
FIR NEEDLE OIL (Canadian)	Feb 2000	a	7.1
FIR NEEDLE OIL (Siberian)	Feb 2000	a	7.1
FLUFENOXURON	Feb 1997	a	1
FLUMETSULAM	Feb 1992	a	1
FLUOMETURON	Aug 1989	a	1
FLUTOLANIL	Nov 2001	a	1.3
FLUROXYPYR	May 1986	a, c	1
FULLERS EARTH	Nov 1974	a	7.1
GERANIUM OIL	Feb 2000	a	7.1
GIBBERELLIC	Nov 1974	a	1.6
HELIOTHIS NUCLEAR POLYHEDROSIS VIRUS	May 1981	a	1.2
HEXAFLURON	Nov 1988	a	1
HEXYL ACETATE		a	7.7
HEXYTHIAZOX	Feb 1988	a	1
HUMAN OSTEOGENIC PROTEIN-1 (OP-1)	Aug 2001	b	6.2
HYDROPRENE	Feb 1988	a	1
HYDROXYPROPYL CELLULOSE	Nov 1982	a	7.1
ICODEXTRIN	Nov 2000	b	6
INDOLE-3-ACETIC ACID	Feb 1985	b	1.6
ISOPRENE ALCOHOL		a	7.1
IPRODIONE	Feb 1997	a	1
ISOSTEARYL ALCOHOL ETHOXYLATE	Nov 1999	a	5.1
JUNIPER BERRY OIL	Feb 2000	a	7.1
KAOLIN	Nov 1974	a	7.1
KRESOXIM-METHYL	Aug 1999	a	1
KUNZEA OIL	Feb 2000	a	7.1
LAURYL ALCOHOL 91-DODECANOL)	Nov 1974	a	7.1
LAVANDIN OIL	Feb 2000	a	7.1
LAVENDER OIL	Feb 2000	a	7.1
LEAD, METALLIC		a	7.1
LEMONGRASS OIL	Feb 2000	a	7.1
LEPIDOPTEROUS SEX PHEROMONES	Nov 1990	a	1
LIMONENE (DIPENTENE)	June 2002	a	7.1
LINSEED FATTY ACIDS	Aug 1990	a	2.1
LINURON	Feb 1990	a	1
LIQUORICE, DEGLYCYRRHISINISED	May 1999	a	7.1
MALEIC HYDRAZIDE	Nov 1992	a	1

MANGANESE DIOXIDE	May 1999	b	1
MESOLSULFURON-METHYL	Feb 2002	a	1.1
METARHIZIUM ANISOPLIAE	Feb 2000	b	4.2
METHOPRENE	Aug 1987	a	1
METHOXYFENOZIDE	Nov 2000	a	1
METHYL ACETATE		a	7.7
METHYL BENZOQUATE	Nov 1974	d	2.3
METHYL p-HYDROXYBENZOATE	Nov 1974	a	7.9
METSULFURONMETHYL	Nov 1985	a	1.1
NAPROPAMIDE	Aug 1987	a	1
NAPTHYL ACETAMIDE	Nov 1974	a	1.6
n-BUTYL BUTYRATE		a	7.1
n-BUTYL LACTATE		a	7.1
NEROLI OIL	Feb 2000	a	7.1
NICABAZIN	Jun 1969	d	2.3
NISIN	Jul 1987	d	7.1
NORFLURAZON	Nov 1983	a	1.1
NOVALURON	Nov 2000	a	1
OCTYL ALCOHOLS	Nov 1974	a	7.1
ORANGE OIL, SWEET	Aug 2000	a	7.1
OXABETRINIL	Feb 1987	a	1
OXYFLUORFEN	May 2001	a	1
PALMAROSA OIL	Feb 2000	a	7.1
PATCHOULI OIL	Feb 2000	a	7.1
PENCYCURON	Aug 1994	a	1
PEPPERMINT OIL	Feb 2000	a	7.1
PHENMEDIPHAM	May 1989	a	1.1
PHYTASE	Feb 1996	a	2.4
PICLORAM	Aug 1987	a	1
PICOLINAFEN	May 2000	a	1
PINUS SYLVESTRIS (PINE NEEDLE) OIL	Feb 2000	a	7.1
PIPERONYL BUTOXIDE	Aug 1991	a	7.5
POLOXALENE	Nov 1974	a	7.1
POLYHEDROSIS VIRUS OF HELICO ZEA OCCLUSION BODIES	Nov 1996	a	1
POLY (GNRF) OVALBUMIN	Feb 1990	a	2
PORCINE SOMATOTROPHIN	Nov 1991	c	2
PROCYMIDONE	Feb 1991	a	1.3
PROPYLENE GLYCOL	Nov 1974	a	7.1
2-PROPYLENE GLYCOL 1-MONOMETHYL ETHER	Nov 1987	a	4
POLY DIALLYL DIMETHYL AMMONIUM CHLORIDE (PolyDADMAC)	Nov 1997	a	4.1

POLYSORBATE 20	May 2001	a	1
PROPAMIDINE	Nov 1992	d	6.10
PROPYL ACETATES		a	7.1
PSEUDOMONAS FLUORESCENS	May 1985	a	1.8
PYRIMETHANIL	Feb 1996	a	1
PYRIPROXYFEN	Aug 1994	a	1
QUASSIA	Nov 1974	d	6, 2.1
QUINOXYFEN	Nov 2001	a	1.3
ROSEMARY OIL	Feb 2000	a	7.1
SAGE OIL (Spanish)	Feb 2000	a	7.1
SANDALWOOD OIL	Feb 2000	a	7.1
SEAWEED & UNFRACTIONED SEAWEED EXTRACTS	Feb 1985	d	1.5
SIMAZINE	Nov 1987	a	1.1
SOMATOTROPIN, EQUINE	Feb 1997	b	2
SUCRALFATE	Aug 1982	a	6.8
SULESOMAB	Jun 2002	b	6.1
SULFOSULFURON	Feb 1998	a	1
SULPHATED POLYSACCHARIDES		a	7.1
TANNIC ACID	Dec 1965	a	7.1
TANNIC ACID/BENZYL ALCOHOL PRODUCT	Nov 1993	a	7.1
TERBACIL	Aug 1987	a	1
THAUMATIN	Nov 1990	a	3.2
THIDIAZURON	Nov 1989	a	1
TRIASULFURON	Feb 1988	a	1
TRICHODERMA HARZIANUM	May 1996	a	1
(Z)-9-TRICOSENE	Aug 1991	a	1
TRIETHYLENE GLYCOL	Nov 1974	a	7.1
TRIFLOXYSULFURON	Feb 2002	a	1.1
TRIFLURALIN	Aug 1990	a	1
TRIFORINE	Aug 1987	a	1
UREA	Nov 1974	a	7.1
^{13}C-UREA	May 2001	a	6.1
VETIVER OIL	Feb 2000	a	7.1
VINYL ETHER	Nov 1987	b	6
VITAMIN K	Jul 1963	a	6.9, 2.8
XANTHOPHYLL (, -CAROTENE-3,3'-DIOL; LUTEIN; VEGETABLE LUTEIN; VEGETABLE LUTEOL; BO-XAN)	Nov 1974	a	7.1
YLANG YLANG OIL	Feb 2000	a	7.1
ZINC NAPHTHENATE		a	1.3

AGRICULTURAL/VETERINARY, INDUSTRIAL AND DOMESTIC CHEMICALS

4. OTHER OUTSTANDING MATTERS FROM PREVIOUS MEETINGS

4.1 PESTICIDES IN PAINT

PURPOSE

The Committee confirmed consideration of the entry in paragraph 5 of Appendix I (Uniform Paint Standard) in the SUSDP regarding pesticides in paint.

BACKGROUND

A clause in the Uniform Paint Standard prohibiting the manufacture, sale, supply or use of a paint containing an insecticide was recommended in 1994.

A recent inquiry regarding the inclusion of insect repellents in paint was considered at the June 2002 Meeting. While these were interpreted to fall into the definition of "insecticide", it raised the issue of a definition for this term.

The Committee agreed at the June 2002 Meeting to foreshadow an amendment to paragraph 5 of Appendix I so as to read "a person must not manufacture, sell, supply, or use paint containing a pesticide **except** a fungicide, bactericide or antifouling agent". The Secretariat was asked to seek comment from the XXXXXXXXXXXXXX and the XXXXXXXXXXXXXX on the proposed amendment.

DISCUSSION

The XXXXXXXXXXXXXX noted in pre-meeting comments that all paint products that contained a pesticide would be considered agricultural chemical products and would therefore require registration by the XXXXXXXXXXXXX. The XXXXXXXXXXXXXX supported the deletion of this prohibition in Appendix I that would allow individual products to be assessed on their merit by the XXXXXXXXXXXXX, rather than applying a blanket ban.

The XXXXXXXXXXXXXX indicated in pre-meeting comments that the amendment was a step in the right direction. The XXXXXXXXXXXXXX drew attention to the need to include "algicide" in addition to "fungicide, bactericide and antifouling agent" to the list of exclusions as algal growth was one of the major targets of paint film biocides.

The Committee concurred that algicide should be added to the foreshadowed amendment.

DECISION 2002/36 - 1.

The Committee agreed to amend paragraph 5, Appendix I to clarify that the current prohibition for the manufacture, sale, supply or use of paints containing a pesticide

excludes the use of a fungicide, algicide, bactericide or antifouling agent when used in paint. The Committee agreed that listing the exclusions was necessary to ensure that paints which legitimately incorporated a fungicide, algicide, bactericide or antifouling agent as a preservative or to achieve an antifungal, anti-algal, bactericidal or antifouling effect were not included in the Appendix entry.

Appendix I - Amendment

Paragraph 5 – amend to read:

5. A person must not manufacture, sell, supply, or use a paint containing a pesticide **except** a fungicide, algicide, bactericide or antifouling agent.

4.2 APPENDIX E, PART 1, STATEMENT A – NZ PIC NO.

PURPOSE

The Committee further considered Statement A of Appendix E in relation to a change to the NZ Poisons Information Centre (PIC) telephone number.

BACKGROUND

The Committee at the June 2002 Meeting was advised that the NZ PIC phone number, currently listed in Statement A as 03 4747000 was being updated to a 0800 (free-call) number, 0800 764 766. Both numbers would continue to operate in the immediate future (three years).

The Committee agreed to foreshadow the change and asked the Secretariat to include the proposed Appendix E Amendment in the pre-meeting gazette notice.

DISCUSSION

The Committee noted that no public comment was received and agreed to include the new telephone number, with a transition period up to May 2005. It was noted that old statement “a” would not require amendment as this would cease to be valid before the cessation of the old NZ PIC phone number.

DECISION 2002/36 - 2.

The Committee agreed to amend the Introduction of Appendix E to include the new PIC telephone number and details of the phase out of the old number to reflect the change in telephone number for New Zealand. The Committee also agreed to include a statement concerning the use of the appropriate number or in some cases, both numbers.

Appendix E, Introduction - Amendment

Amend by adding immediately after the heading "**Poisons Information Centre Telephone Numbers**":

Companies should use the poisons information centre telephone number(s) appropriate to the country(ies) of sale for the product, that is Australia or New Zealand or both. These are 13 1126 for Australia and 03 4747 000 for New Zealand. A new free-call number (0800 764 766) is being introduced in New Zealand. Use of the old number (03 4747 000) shall be phased out by May 2005.

Appendix E, Part 1 – Amendment

Statement "A" – amend statement to read:

A For advice, contact a Poisons Information Centre (Phone *eg Australia 13 1126; New Zealand 03 4747 000 [Not after May 2005] or 0800 764 766*) or a doctor (at once).

4.3 APPENDIX E, PART 2 - PHENOLS

PURPOSE

The Committee continued consideration of the first aid instructions for phenols.

BACKGROUND

The new standard first aid instructions (FAIs) were introduced at the February 2001 meeting of NDPSC. At this meeting, the old statements for phenols; a,c,j,s were translated as A,G3,E2,S3. That is, for the OLD statements:

(a) If poisoning occurs, contact a doctor or Poisons Information Centre. Phone *(eg Australia 13 1126; New Zealand 03 4747 000).*
(c) If swallowed, do NOT induce vomiting. Give a glass of water.
(j) (Cresols, Xylenols or Phenols 25 per cent or less) - If spilt on skin remove any contaminated clothing, wash thoroughly with soap and water, then methylated spirit. (Cresols, Xylenols or Phenols above 25 per cent) - If spilt on skin, remove any contaminated clothing, swab repeatedly with glycerin, PEG (polyethylene glycol) or PEG -methylated spirit mixture or if necessary methylated spirit alone.
(s) If in eyes, hold eyes open, flood with water for at least 15 minutes and see a doctor."

And for the NEW statements:

(A) For advice, contact a Poisons Information Centre (Phone *eg Australia 13 1126; New Zealand 03 4747 000*) or a doctor (at once).
(G3) If swallowed, do NOT induce vomiting.

(E2) If in eyes, hold eyelids apart and flush the eye continuously with running water. Continue flushing until advised to stop by the Poisons Information Centre or a doctor, or for at least 15 minutes.

(S3) If on skin, remove any contaminated clothing, wash skin thoroughly with soap and water, then methylated spirit if available. Contact the Poisons Information Centre or a doctor."

The new FAIs for phenols were brought to the attention of the Committee at the June 2002 Meeting by XXXXXXXXXXXXXX. XXXXXXXXXXXXXX suggested that these statements appeared not to be consistent with the old FAIs, particularly statement "j" which specified two different FAIs depending upon the concentration of phenols. XXXXXXXXXXXXXX proposed that statement S4 (If on skin, immediately remove any contaminated clothing, wash skin with methylated spirit or PEG (polyethylene glycol) 300 or 400 if available, then flush under running water until advised to stop by the Poisons Information Centre or a doctor.) apply to phenols above a specified concentration.

The Committee agreed that statement S4 should be included on the FAIs for more concentrated phenols and foreshadowed the amendment to Appendix E to allow for wider consultation.

DISCUSSION

The Committee noted the pre-meeting submission from the XXXXXXXXXXXXXX Poisons Information Centre which stated that it supported the inclusion of the first aid statement S4 for products containing more than 25% phenols.

The Committee noted the pre-meeting submission from the XXXXXXXXXXXXXX Poisons Service provided information concerning the treatments advised for dermal exposure of phenols. The need to specify a time limit for application of polyethylene glycol (PEG) or methylated spirits was also highlighted.

The Committee noted that XXXXXXXXXXXXXX were the only producers of phenols in Australia and they were not aware of any products with a concentration of >25% phenols currently available for sale.

A Member expressed concern that if the first aid instructions required washing with PEG/methylated spirits first before rinsing with water, that this may delay action if these substances were not readily available. The Committee noted that the first aid procedures applicable to occupational settings required the MSDS and any necessary antidotes to be available.

DECISION 2002/36 - 3.

The Committee concurred that the proposal from XXXXXXXXXXXXXX to include S4 in the first aid instructions for phenols above 25% was appropriate and in line with

treatment recommended by the International Program on Chemical Safety (IPCS) and Poisindex.

Appendix E Part 2 – Amendment

Phenols – amend entry to read:

Phenols		a,c,j,s
• 25 per cent and less	A,G3,E2,S3	
• above 25 per cent	A,G3,E2,S4	

4.4 CHLORINATING COMPOUNDS

PURPOSE

The Committee continued consideration of the scheduling of chlorinating compounds.

BACKGROUND

A class review of chlorinating compounds, undertaken by WA, was considered by the NDPSC at its August 1999 meeting, with a number of changes to the schedule classification and the format of entries foreshadowed as a result. The November 1999 Meeting agreed to requests from the XXXXXXXXXXXXXX and XXXXXXXXXXXXXX, to defer further consideration until the February 2000 meeting in order to allow more time to consider the implications.

The February 2000 Meeting received a submission from XXXXXXXXXXXXXX concerning the proposals, and further correspondence from the XXXXXXXXXXXXXX. That Meeting agreed to defer the consideration again, to the May 2000 Meeting, in order to allow more time for industry to consider the proposals and, in particular, to comment on the proposal for a class entry rather than individual substance entries.

The May 2000 Meeting again deferred consideration because of industry wishes for more consultation and discussion on the issues. This consultation and discussion was to occur through an informal meeting between selected NDPSC Members and a range of industry representatives. It was held on Monday 10 July 2000 at Sydney Airport and a report on the industry meeting was subsequently provided to Members. Participants at the meeting agreed that before the NDPSC proceeded with the proposed amendments, it would be preferable for industry to research whether any additional toxicology data could be provided to the Committee on the individual chlorinating compounds and the products in which they are present. This latter aspect would assist in determining cut-off concentrations. Notwithstanding this, the group agreed that a class entry to cover all chlorinating compounds would be undesirable and consideration should be given to separate entries being maintained for individual compounds in the SUSDP. This report was considered at the August 2000 Meeting, but further action was deferred to the November 2000 Meeting.

At the November 2000 Meeting XXXXXXXXXXXXXX and XXXXXXXXXXXXXX advised that they would provide further data and that discussions on labelling were under way between the XXXXXXXXXXXXX and the XXXXXXXXXXXXX. The Committee agreed to defer further consideration pending receipt and evaluation of this data.

The February 2002 Meeting noted that some information had been received from XXXXXXXXXXXXX, that the XXXXXXXXXXXXX had identified concerns with the proposed inclusion of isocyanurates and the hypochlorites in Schedule 6, and that the discussions between the XXXXXXXXXXXXX and the XXXXXXXXXXXXX had not progressed. The meeting confirmed that individual entries appeared to be the appropriate way forward and agreed that a firm proposal be circulated again, key stakeholders notified, and the proposal gazetted for consideration at the June 2002 meeting.

The June 2002 Meeting agreed to a final round of industry consultation for final consideration at the October 2002 Meeting.

DISCUSSION

The Committee noted that acute oral toxicity (LD_{50}) values in rats were available for various chlorinating compounds and that these may be divided into three broad groups:

Chlorinating Compound	**LD_{50} (mg/kg.bw)**
Sodium hypochlorite	8910
Dichloro isocyanuric acid Potassium dichloro isocyanurate Sodium dichloro isocyanurate	1173 1215 1671
Bromo chloro dimethyl-hydantoin Calcium hypochlorite Chlorine dioxide Dichloro-dimethyl hydantoin (10%) Trichloro isocyanuric acid	860 850 292 542 406

A Member proposed that by using the above values, sodium hypochlorite should be unscheduled, while all others should be included in Schedule 6 under CHLORINATING COMPOUNDS. It was also suggested that the cut off points for Schedule 5 should be set at 20% available chlorine for all substances. Dichloro isocyanuric acid would be separately scheduled in Schedule 6 with a cut off to Schedule 5 at 40% available chlorine.

A Member reported that the XXXXXXXXXXXXX had previously expressed concern over inclusion of sodium hypochlorite and the isocyanurates in Schedule 6. The issues

with sodium hypochlorite had been resolved while there had been no negative feedback received concerning the proposal for dichloro-isocyanurates.

The Committee recognised the lack of a national body for the manufacturers of XXXXXXXXXXXXX. The XXXXXXXXXXXXX was to develop a labelling proposal that would avoid the use of the signal heading POISION with the XXXXXXXXXXXXX, but the Committee noted that there had been a lack of progress on this project and a failure to present alternative risk management approach for consideration.

The Committee noted the XXXXXXXXXXXXX's concerns that the inclusion of POISON as a signal heading may lead to unscheduled yet potentially "ineffective" spa treatments being used, was not accepted as an argument for not properly labelling a poison. The Committee also noted that a similar argument could, and has been made for other domestic products eg cleaners, disinfectants and home garden/home vet products, and has not been accepted. The Committee saw this as an educational issue for the industry sector. Any other approach would need a change to the labelling and container requirements of Parts II and III of the SUSDP.

A Member noted that if pool chemicals were made Schedule 6, there may be issues with meeting the tactile requirements with a large container. The Committee also noted that while poison containers were widely available, it was difficult to source 1-2kg containers for solids, which the majority of spa chemicals would require. Another Member noted that a packaging manufacturer offered to supply such containers provided the cost of the mould was met.

The Committee agreed that for this item only, post-meeting submissions from all previous respondents, including the XXXXXXXXXXXXX, would be allowed at the next meeting as further public submission under Regulation 42ZCZ of the *Therapeutic Goods Regulations (1990)*.

A Member proposed a delayed implementation of the new scheduling amendments as pool and spa chemicals were seasonal products and product had already been manufactured, labelled and distributed for the next season. The Committee concurred that a delayed implementation would allow the manufacturers of these products to change their labelling without recalling and relabelling stock that has already been manufactured.

DECISION 2002/36 - 4.

The Committee agreed to implement the foreshadowed scheduling changes to chlorinating compounds as the acute toxicological profile associated with this class of compounds (chlorinating compounds) was appropriately included in Schedule 6.

The Committee agreed to delay the implementation date until 1st September, 2003 as these were seasonal products, which required a longer lead time for labelling changes.

Schedule 5 – New Entry

DICHLOROISOCYANURIC ACID containing 40 per cent or less of available chlorine, **except** in:

(a) liquid preparations containing not less than 2 per cent but not more than 4 per cent of available chlorine when labelled with the statements:

WARNING – Ensure adequate ventilation when using. Vapour may be harmful. May give off dangerous gas if mixed with other products;

(b) liquid preparations containing less than 2 per cent of available chlorine; or

(c) other preparations containing 4 per cent or less of available chlorine.

Schedule 5 – Amendments

CHLORINATING COMPOUNDS – amend entry to read:

CHLORINATING COMPOUNDS containing 20 per cent or less of available chlorine, **except**:

(a) when separately specified in these Schedules;

(b) sodium hypochlorite;

(c) liquid preparations containing not less than 2 per cent but not more than 4 per cent of available chlorine when labelled with the statements:

WARNING – Ensure adequate ventilation when using. Vapour may be harmful. May give off dangerous gas if mixed with other products;

(d) liquid preparations containing less than 2 per cent of available chlorine; or

(e) other preparations containing 4 per cent or less of available chlorine.

CALCIUM HYPOCHLORITE – delete entry.

CHLORINATED LIME – delete entry.

DICHLOROISOCYANURATES – delete entry.

SODIUM HYPOCHLORITE – delete entry.

TRICHLOROISOCYANURIC ACID – delete entry.

Schedule 6 – Amendment

BROMOCHLORODIMETHYLHYDANTOIN – delete entry.

Schedule 6 – New entries

CHLORINATING COMPOUNDS **except**:

(a) when included in Schedule 5;

(b) when separately specified in these Schedules;

(c) sodium hypochlorite;

(d) in liquid preparations containing not less than 2 per cent but not more than 4 per cent of available chlorine when labelled with the statements:

WARNING – Ensure adequate ventilation when using. Vapour may be harmful. May give off dangerous gas if mixed with other products;

(e) in liquid preparations containing less than 2 per cent of available chlorine; or

(f) in other preparations containing 4 per cent or less of available chlorine.

DICHLOROISOCYANURIC ACID **except**:

(a) when included in Schedule 5;

(b) in liquid preparations containing not less than 2 per cent but not more than 4 per cent of available chlorine when labelled with the statements:

WARNING – Ensure adequate ventilation when using. Vapour may be harmful. May give off dangerous gas if mixed with other products;

(c) in liquid preparations containing less than 2 per cent of available chlorine; or

(d) in other preparations containing 4 per cent or less of available chlorine.

Schedule 7 – Amendment

TRICHLOROISOCYANURIC ACID – delete entry.

4.5 LITHIUM IN PIGMENTS

PURPOSE

The Committee continued consideration of the scheduling of lithium when included in pigments.

BACKGROUND

Lithium salts were included in Schedule 4 at the July 1967 meeting of NDPSC, which was amended at the February 1968 meeting to exempt preparations (eg lithia water) containing 0.01% or less of lithium. An application for lithium in topical preparations was considered at the May 1985 meeting but lapsed due to lack of information. Over the period November 1998-November 2000, the entries were then harmonised with New Zealand including a new entry for dermal preparations (Schedule 2).

Lithium is found naturally in a variety of minerals including tourmaline, which may contain up to 2.5% lithium.

XXXXXXXXXXXXX sought an amendment to the lithium Schedule 2 entry to allow for pigments (eg tourmaline) containing lithium not to be scheduled.

At the June 2002 Meeting, the Committee foreshadowed an amendment to Schedules 2 and 4 and agreed to consult with industry on the cut-off limit to be placed on lithium when used as an excipient, prior to consideration at the October 2002 meeting.

DISCUSSION

The Committee noted that there had been no responses received as a result of the foreshadowed rescheduling, nor any additional information supplied concerning a proposed cut-off limit for lithium when used as an excipient.

The Committee felt it could not progress the foreshadowed change to the schedules at this stage as it lacked the necessary information and data to set an appropriate cut-off limit for lithium when used as an excipient.

OUTCOME

In the absence of any response, the Committee agreed to defer the matter to the February 2003 Meeting to allow the sponsor to submit a proposed cut-off limit for lithium when used as an excipient, along with any necessary data supporting their proposal. The Committee noted that the deadline for the submission of data to allow consideration at the February 2003 Meeting was 7th January, 2003.

4.6 INSULIN-LIKE GROWTH FACTORS

PURPOSE

The Committee continued consideration of the scheduling of insulin-like growth factors as a class entry.

BACKGROUND

Prior to the June 2002 Meeting, the Committee had considered a number of human and animal somatotropins (growth hormones) but had not considered any of the insulin-like growth factors (IGFs) or somatomedins. The IGFs are produced in the liver in response to the release of somatotropin, and have a wide range of anabolic and growth promoting actions including stimulation of cartilage growth, protein synthesis and mitosis.

At the June, 2002 meeting, the Committee agreed to include insulin-like growth factor I in Schedule 4 as its use required professional diagnosis and management of use and the Schedule 4 entry provided a barrier to diversion during manufacturing through licensing requirements. The Committee also agreed that the potential for abuse and diversion warranted inclusion of a generic entry for the insulin-like growth factors in Schedule 4 and an entry under Paragraph 5 of Appendix D to control illegal possession. Members agreed that these proposals be foreshadowed to allow for public consultation.

DISCUSSION

The Committee noted that no correspondence had been received concerning the foreshadowed generic entry for insulin-like growth factors in Schedule 4 and inclusion in Appendix D, paragraph 5.

DECISION 2002/36 - 5.

The Committee agreed, based on the potential for abuse and diversion, to include a generic entry for insulin-like growth factors in Schedule 4 and in Appendix D, paragraph 5 as foreshadowed at the June, 2002 Meeting. The Committee also agreed to include a new entry for somatomedins cross-referencing the new entry for insulin-like growth factors in the index of the SUSDP.

Schedule 4 – New entry

#INSULIN-LIKE GROWTH FACTORS **except** when separately specified in this Schedule.

Schedule 4 – Amendment

INSULIN-LIKE GROWTH FACTOR I – amend to read:

#INSULIN-LIKE GROWTH FACTOR I

Appendix D, Paragraph 5 – New entry

INSULIN-LIKE GROWTH FACTORS.

6. MATTERS REFERRED BY THE NATIONAL REGISTRATION AUTHORITY FOR AGRICULTURAL AND VETERINARY CHEMICALS

6.1 DIRECT-FED MICROBIALS

PURPOSE

The Committee considered the scheduling of direct fed microbials and the policy issues associated with these products.

BACKGROUND

Microbial fermentation products are fed to livestock both as nutritional supplements and to infect the animal's gastrointestinal tract with what are believed to be beneficial organisms.

There was no established nomenclature for these types of products. XXXXXXXXXXXXX uses the terminology *fermentation products* for non viable products based on the fermentation liquor; and *direct fed microbials* for organisms fed to animals to deliberately "infect" the animals with beneficial organisms. These two groups can be collectively referred to as Probiotics.

XXXXXXXXXXXXX Paragraph Removed XXXXXXXXXXXXX

In referring these products to the NDPSC, CPAS raised the issues of whether the Committee wished to see all products of this type, if the Committee wanted to deal with the use of organisms in this way as a group generic entry (either to exclude them from scheduling or include them in a schedule) or evaluate them as individual organisms. CPAS noted that similar products had been registered in the past without referral to the Therapeutic Goods Administration (TGA), and that some registrations pre-date the NRA.

There was also an expectation that the number of these types of products would be likely to increase as the products became more popular in their use.

DISCUSSION

The Committee discussed the ramifications of both scheduling these organisms as a generic entry and exempting them from scheduling and the need for any ongoing referral of these products to the NDPSC. In particular, the likely hazards related directly to the origin and nature of the products. That is, the principal toxicity for both "live" fermentation products were associated with the fermentation media and protein content, potential skin and eye irritants and in particular both skin and inhalation sensitisation. For those products including "live" organisms the additional issues of human pathogenicity and propensity for undesirable transfer of genetic material (eg antibiotic resistance) also needed consideration.

The Committee was of the view that it could not include a generic entry for these types of organisms in either Appendix A or Appendix B as the data available for this type of use in Australia was currently insufficient to draw common conclusions about these classes of products. Equally, the Committee did not believe that placing these products into Schedule 5 would add value from a safety perspective as any required first aid and safety directions and warning statements could be dealt with adequately as part of the NRA's registration process. Members agreed that the available information supported a continued unscheduled status for these products while not specifically permitting class entries in Appendices A or B.

The Committee then proceeded to consider the scheduling of products under items 6.1.1 and 6.1.2 within the agreed policy framework.

XXXXXXXXXXXXXX **Paragraphs Removed** XXXXXXXXXXXXXX

OUTCOME

The Committee agreed not to schedule direct-fed microbials and fermentation products for use as veterinary food additives at this time, based on their toxicological profile and history of use in food production for humans. To reassure the Members that there were no significantly different toxicity profiles emerging from new types of these products, the Committee agreed to inform the XXXXXXXXXXXXX to refer any new products containing either new organisms or the same organisms with different toxicity profiles, within the categories of direct-fed microbials and fermentation products to CPAS. Further, CPAS would provide the NDPSC with the evaluation reports for these products for review where relevant. This referral would be reviewed regularly.

6.2 FLUMIOXAZIN

OUTCOME

On the basis of the observed developmental and reproductive toxicity following both single and repeated exposure to flumioxazin, the Committee recommended that CPAS include warning statement 47 " **WARNING - This product contains flumioxazin which causes birth defects in certain laboratory animals. Women of child bearing age are advised not to mix, load or spray this product. They should keep out of crops being sprayed.**" in their labelling advice to the NRA.

DECISION 2002/36 - 6.

The Committee agreed that flumioxazin be included in Schedule 7 on the basis of the following irreversible effects:

- Reproductive and developmental toxicity after both single oral and repeated oral and dermal dosing;
- Chronic hepatotoxicity following repeated dosing; and
- Induction of porphyria and the potential for photodermatitis.

Schedule 7 – New entry

FLUMIOXAZIN.

6.3 BIFENAZATE

DECISION 2002/36 - 7.

The Committee agreed that on the basis of the low acute toxicity and lack of significant longer-term toxicity, bifenazate be exempt from the requirements of scheduling.

6.4 TETRACONAZOLE

DECISION 2002/36 - 8.

The Committee agreed that on the basis of the acute toxicity, supported by evidence of chronic hepatotoxicity, disruption to hormonal metabolism and marginal reproductive toxicity, tetraconazole be included in Schedule 6 with a cut-off to Schedule 5 at 20%.

Schedule 6 – New entry

TETRACONAZOLE **except** when included in Schedule 5.

Schedule 5 - New entry

TETRACONAZOLE in preparations containing 20 per cent or less of tetraconazole.

6.5 CLOTHIANIDIN

DECISION 2002/36 - 9.

The Committee agreed that clothianidin be included in schedule 6 on the basis of the high acute toxicity of the active in mice. Further, the difference in the acute oral toxicity in the rat for the active and the formulation did not allow establishment of a cut-off to a lower schedule.

Schedule 6 – New entry

CHLOTHIANIDIN.

6.6 MOXIDECTIN

DECISION 2002/36 - 10.

The Committee agreed that on the basis of the acute toxicity of the product and the potential for acute neurotoxicity following post treatment exposure with larger dogs, the product be included in Schedule 6.

Schedule 6 - Amendment

MOXIDECTIN – amend to read:

MOXIDECTIN for external use:

(a) for the treatment of cats and dogs in preparations containing 2.5 per cent or less of moxidectin when packed in single dose tubes; or

(b) for the treatment of animals in preparations containing 2 per cent or less of moxidectin.

6.7 MAGNESIUM FLUOROSILICATE/SULFUR/ROTENONE

OUTCOME

The Committee agreed:

- That the inclusion of magnesium fluorosilicate in the product was sufficient to place the product in Schedule 6 and that on the basis of the extrapolated toxicity profile XXXXXXXXXXXXX should be included in Schedule 6.
- On the basis of the acute toxicity, to foreshadow entries for rotenone, cubé and derris in Schedule 6 with an appropriate cut off to Schedule 5 and exempt, to be returned to the Committee for consideration at the June 2003 meeting. The Committee would consider establishing appropriate cut offs based on the toxicological data provided.

- That sulfur remain unscheduled.

FORESHADOWED

Schedule 6 - New entries

ROTENONE **except**:

(a) when included in Schedule 5; or

(b) in preparations containing (to be determined) per cent or less of rotenone.

CUBÉ **except**:

(a) when included in Schedule 5; or

(b) in preparations containing (to be determined) per cent or less of cubé.

DERRIS **except**:

(a) when included in Schedule 5; or

(b) in preparations containing (to be determined) per cent or less of derris.

Schedule 5 - New entries

ROTENONE in preparations containing (to be determined) per cent or less of rotenone **except** in preparations containing (to be determined) per cent or less of rotenone.

CUBÉ in preparations containing (to be determined) per cent or less of cubé **except** in preparations containing (to be determined) per cent or less of cubé.

DERRIS in preparation containing (to be determined) per cent or less of derris **except** in preparations containing (to be determined) per cent or less of derris.

6.8 EXTRACT OF LEMON EUCALYPTUS

OUTCOME

The Committee re-affirmed its opposition to the use of terms such as "natural" and "Safe on kids" where these may breach provisions of Part 1, Section 18 of the SUSDP.

The Committee agreed to resolve the issue of the nomenclature for the entry out-of-session.

DECISION 2002/36 - 11.

The Committee agreed that on the basis of the acute toxicity in rats and eye irritancy in rabbits, extract of lemon eucalyptus be included in Schedule 5 with an exemption from the requirements of scheduling for preparations containing 40% or less of extract of lemon eucalyptus.

Schedule 5 - New entry

EXTRACT OF LEMON EUCALYPTUS, being acid modified oil of lemon eucalyptus (*Corymbia citriodora*), **except** in preparations containing 40 per cent or less of extract of lemon eucalyptus.

6.9 CARBARYL

OUTCOME

Members confirmed that the existing scheduling for agricultural and veterinary uses of carbaryl was appropriate on the basis that the toxicity profile was appropriate for inclusion in Schedule 6, and Schedule 5 for preparations containing 10% or less of carbaryl.

Members did not support the removal of the Schedule 4 entry on the basis that a doctor's prescription should continue to be required for any human therapeutic use of carbaryl.

6.10 DIQUAT

DECISION 2002/36 - 12 .

The Committee agreed that on the basis of the acute oral toxicity in humans and the acute dermal and inhalational toxicity in experimental animals, diquat should be included in Schedule 7. The Committee also agreed that the acute toxicity profile of products containing 20% or less of diquat supported a cut-off to Schedule 6.

Schedule 7 - New entry

DIQUAT **except** when included in Schedule 6.

Schedule 6 - Amendment

DIQUAT – amend entry to read:

DIQUAT in preparations containing 20 per cent or less of diquat.

6.11 CODLING MOTH GRANULOSIS VIRUS

DECISION 2002/36 - 13.

The Committee concurred that the acute toxicity profile of CMGV was likely to be low and on this basis agreed to exempt CMGV from the requirements of scheduling.

8. ANTIBIOTICS FOR CONSIDERATION FOLLOWING RECOMMENDATIONS OF THE JOINT EXPERT TECHNICAL ADVISORY COMMITTEE ON ANTIBIOTIC RESISTANCE (JETACAR)

8.1 VIRGINIAMYCIN

This item was deferred to the February 2003 meeting pending the receipt of the final report from the XXXXXXXXXXXXXX.

8.2 ANTIBIOTICS IN PREPARATIONS FOR INTRA-MAMMARY INFUSION IN ANIMALS

PURPOSE

The Committee considered the scheduling of antibiotics for intra-mammary infusion in animals.

BACKGROUND

In 1999, the Joint Expert Advisory Committee on Antibiotic Resistance (JETACAR) recommended:

"That all antibiotics for use in humans and animals (including fish) be classified as S4 (prescription only)" (Recommendation 6).

The Commonwealth Government's response to the JETACAR Report accepted "the concept that all antibiotics for use in humans and animals (including fish) be classified as S4 (prescription only)". However, the Government's acceptance was qualified by highlighting that "… certain antibiotic products might be exempted from this scheduling class where the National Registration Authority (NRA), the Therapeutic Goods Administration (TGA) and the NDPSC assess the antibiotic products as having a low and acceptable risk of promoting antibiotic resistance".

The Committee agreed that the scheduling of intra-mammary antibiotics listed outside of Schedule 4 would be reviewed at the October 2002 meeting. This intention was included in the post- February 2002 meeting notice published in the Commonwealth of Australia Gazette No GN 18, 8 May 2002.

Benzylpenicillin including procaine penicillin was first listed in Schedule 6 in the late 1960's to early 70's for intra-mammary infusion and growth promotion purposes in

animals. In 1988, this entry was revised to only intra-mammary infusion in animals. The other antibiotics were first listed in S6 for intra-mammary infusion in animals as follows:

- Dihydrostreptomycin - 1981.
- Novobiocin – 1977.
- Phenoxymethylpenicillin and Phenethicillin - late 1960's to early 70's.
- Streptomycin – mid to late 1960's.

DISCUSSION

The Committee agreed to review these antibiotics for intra-mammary infusion in animals as a group, rather than individually.

The Committee noted a submission from XXXXXXXXXXXXXX, which indicated that it supported JETACAR Recommendation 6, and retention of veterinary intra-mammary antibiotics in Schedule 4. The submission did not contain any data for review.

The Committee noted a letter from the Chair of the EAGAR at the NHMRC which stated that it had no objections to the rescheduling of the antibiotics listed above used for intra-mammary infusion in animals in line with the Government Response ie all antibiotics for use in humans and animals are classified as S4.

The XXXXXXXXXXXXXX provided a listing of currently registered intra-mammary antibiotic products from its registered products database (CRIS) which showed that no registered intra-mammary antibiotic products were outside of S4.

The Committee noted that as there were no registered intra-mammary antibiotic products in Schedule 6, the deletion of these entries from Schedule 6 would have no regulatory impact.

DECISION 2002/36 - 14.

The Committee agreed to remove the entries for antibiotics for intra-mammary infusion in animals from Schedule 6 as no data had been submitted to support the premise that such products had a low and acceptable risk of promoting antibiotic resistance. In addition, there are no registered intra-mammary antibiotics included in Schedule 6 and removal of the entries from Schedule 6 is consistent with the Government Response to JETACAR.

Schedule 4 – Amendments

BENZYLPENICILLIN – amend entry to read:

BENZYLPENICILLIN.

DIHYDROSTREPTOMYCIN – amend entry to read:

DIHYDROSTREPTOMYCIN.

NOVOBIOCIN – amend entry to read:

NOVOBIOCIN.

PHENETHICILLIN – amend entry to read:

PHENETHICILLIN.

PHENOXYMETHYLPENICILLIN – amend entry to read:

PHENOXYMETHYLPENICILLIN.

PROCAINE PENICILLIN – amend entry to read:

PROCAINE PENICILLIN.

STREPTOMYCIN – amend entry to read:

STREPTOMYCIN.

Schedule 6 – Amendments

BENZYLPENICILLIN – delete entry.

DIHYDROSTREPTOMYCIN – delete entry.

NOVOBIOCIN – delete entry.

PHENETHICILLIN – delete entry.

PHENOXYMETHYLPENICILLIN – delete entry.

PROCAINE PENICILLIN – delete entry.

STREPTOMYCIN – delete entry.

8.3 FUTURE REVIEWS/TIMETABLE

PURPOSE

The Committee considered the timetable for assessing the scheduling of antibiotics under Recommendation 6 of the Report of the Joint Expert Technical Advisory Committee on Antibiotic Resistance (JETACAR).

BACKGROUND

At the May 2001 meeting, the Committee identified "priorities for review" which included:

- Ionophores
- Intra-mammary antibiotics
- Non-ionophore feed additives
- Ocular antibiotics
- Aquaculture and apiary

The November 2001 Meeting reviewed non-prescription antibiotics for human use and confirmed the existing S3 status for sulfacetamide for ophthalmic use and the existing S4 status for clindamycin. A proposed review of antibiotics available for use in caged birds and ornamental fish was postponed to a future meeting due to the lack of submissions.

The February 2002 Meeting confirmed the need to work closely with EAGAR in the decision making process for the scheduling of antibiotics.

The Committee was advised at the June 2002 Meeting that EAGAR had suggested that consideration of the remaining non-S4 antimicrobials should be tackled in the following order:

- Growth promoters not being reviewed under JETACAR recommendation 2.
- In feed antimicrobials for prophylactic uses not being reviewed under JETACAR recommendation 2.
- Intra-mammary antibiotics (EAGAR believed that very few were not in S4 now).
- Ionophores.
- Non-food animal agents.
- Human agents including topical agents.

Members noted at the June 2002 Meeting that human antibiotic agents not in Schedule 4 and the ionophore reviews had been completed, and that the non-food animal agents had been deferred due to lack of data. The Committee agreed that Intra-mammary antibiotics would be considered at the October 2002 Meeting, growth promotants not being reviewed under JETACAR recommendation 2 would be reviewed at the February 2003 Meeting, and in-feed antimicrobials for prophylactic uses not being reviewed under JETACAR recommendation 2, would be reviewed at the June 2003 Meeting.

DISCUSSION

The Committee was notified of a meeting between the Chair, the Secretary and a Member of the NDPSC with Industry, where Industry expressed concern about the review process.

Industry requested a timetable for the review to enable it to identify the substances for review and to give greater time to prepare submissions.

The Committee noted that the Secretariat had identified antibiotics outside Schedule 4 and simplified them by dividing them into small, manageable groups to be considered over 7 NDPSC Meetings commencing with this (October 2002) Meeting. If endorsed by the Committee, this timetable would become an outcome of the October 2002 Meeting and be gazetted for consideration at future NDPSC Meetings. This would allow transparency of the review process and sufficient time for Industry to respond.

Members agreed to consider each NRA review as it became available.

OUTCOME

The Committee endorsed the draft timetable proposed for the review of the scheduling of antibiotics to allow transparency of the review process and to enable Industry to respond to the reviews in a timely manner.

NDPSC REVIEW OF ANTIBIOTIC SCHEDULING - TIMETABLE

8.3.1 ANTIBIOTIC SUBSTANCES ALREADY GAZETTED FOR REVIEW

1. NDPSC 36 - October 2002 – Consideration of antibiotics for intramammary infusion in animals with a single entry in S6 but no corresponding NRA registrations outside of S4.

ANTIBIOTIC SUBSTANCE	Family	Schedule (outside S4)
benzylpenicillin	Penicillin	6 – intramammary infusion in animals
dihydrostreptomycin	Aminoglycoside	6 – intramammary infusion in animals
novobiocin	Miscellaneous	6 – intramammary infusion in animals
phenethicillin	Penicillin	6 – intramammary infusion in animals
phenoxymethylpenicillin	Penicillin	6 – intramammary infusion in animals
procaine penicillin	Penicillin	6 – intramammary infusion in animals
streptomycin	Aminoglycoside	6 – intramammary infusion in animals

2. NDPSC 37 - February 2003 – Consideration of growth promoters/ others scheduled outside S4 with no NRA registrations outside of S4.

ANTIBIOTIC SUBSTANCE	Family	Schedule (outside S4)
avoparcin	Glycopeptide	E – animal feeds
bacitracin	Polypeptide	6 & E – animal feeds
cuprimyxin	Miscellaneous	5 – treatment of animals (not listed in S4)
erythromycin	Macrolide	6 - intramammary infusion in animals & E – animal feeds
hygromycin	Aminoglycoside	6 – anthelmintic & E – animal feeds
nalidixic acid	Quinolone	6 – ornamental fish –no registrations
nisin/antibiotic substances	Polypeptide	E – no registrations
spiramycin	Macrolide	6 & E – animal feeds

8.3.2 SUBSTANCES TO BE INCLUDED IN THE POST-NDPSC 36 MEETING GAZETTE NOTICE

3. NDPSC 38 - June 2003 - Consideration of scheduling of antibiotics currently registered with the NRA but not listed in the SUSDP.

ANTIBIOTIC SUBSTANCE	Family	Products Labelled	No NRA Registrations
apramycin	Aminoglycoside	S4	2 – Powder – 50 & 100g/kg
cefadroxil	Cephalosporin	S4	3 – Tablets –1, 0.2, 0.05 g/tablet
penethamate hydriodide	Penicillin	S4	1 – 5g/vial IM Injection
thiostrepton	Polypeptide	S4	1 – Ointment - 2,500 units/mL
phthalylsulfathiazole	Sulfonamide	S4	2 – Solution & tablet – 250mg/5mL & 250mg/tablet.

4. NDPSC 39 - October 2003 – Consideration of growth promoters scheduled outside of S4 with corresponding registrations.

ANTIBIOTIC SUBSTANCE	Family	Schedule (outside S4)	No NRA Regs
avilamycin	Macrolide	E – animal feed	1 – broiler chickens
bambermycin (flavophospholipol)	Glycophospholipid	6 & E – animal feed	2 – various sp
olaquindox – not listed in S4	Quinoxaline	6 & E	10 - pigs

5. NDPSC 40 - February 2004 – Consideration of other antibiotics scheduled outside of S4 with corresponding NRA registrations.

ANTIBIOTIC SUBSTANCE	Family	Schedule (outside S4)	No NRA Registrations
diaveridine	DHFR Inhibitor	E (Appendix B)	1 (S6) – coccidiostat/poultry
neomycin	Aminoglycoside	6 – ocular use in animals	5 (E) – preservative in inactivated cat vaccine
roxarsone not listed in S4	Arsenical	7 (under arsenic)	3 – awaiting NRA advice
tiamulin	Miscellaneous	5 & E – animal feed	8 – pigs & chickens

6. NDPSC 41 - June 2004 – Consideration of sulfonamides scheduled outside of S4 with corresponding NRA registrations.

ANTIBIOTIC SUBSTANCE	Schedule (outside S4)	No NRA Registrations
sulfacetamide	3 – ophthalmic use – reviewed Nov '01 5 – caged birds & ornamental fish	No NRA registrations outside of S4
sulfadiazine	5 – caged birds & ornamental fish	2 - fish
sulfadimidine	5 – caged birds & ornamental fish	3 – birds & fish
sulfamerazine	5 – caged birds & ornamental fish	5 – fish
sulfaquinoxaline/sulfonamides	5 – coccidiostat & E	4 – coccidiostat/poultry
sulfathiazole	5 – caged birds & ornamental fish	1 - fish

7. NDPSC - October 2004 – Consideration of tetracyclines scheduled outside of S4 with corresponding NRA registrations.

ANTIBIOTIC SUBSTANCE	Schedule (outside S4)	No NRA Registrations
chlortetracycline	5 – ocular use & intramammary infusion in animals, caged birds & ornamental fish	1 – awaiting NRA advice
oxytetracycline	5 – ocular use & intramammary infusion in animals, caged birds & ornamental fish	4? – awaiting NRA advice
tetracycline	5 – ocular use & intramammary infusion in animals, caged birds & ornamental fish	9 – awaiting NRA advice

PHARMACEUTICALS

13. OTHER OUTSTANDING MATTERS FROM PREVIOUS MEETINGS

13.1 MELIA AZEDARACH

PURPOSE

The Committee considered the foreshadowed Appendix C entry for *Melia azedarach*.

BACKGROUND

The June 2002 meeting agreed to foreshadow the inclusion of *Melia azedarach* or its extracts or its derivatives in Appendix C of the SUSDP, on public health and safety grounds. Whilst the Committee was of the view that there was a need to restrict the use of *Melia azedarach* on safety grounds, it recommended that additional information be sought to help resolve the following issues:

- Is there a mechanism for ensuring that only the non-toxic variety is used in products, given that the toxic variety has been found to be botanically indistinguishable from the non-toxic variety?
- Is it safe to establish a concentration cut-off to accommodate existing products?
- What are the long-term effects of Melia azedarach in humans and animals given that its limonoids have been found to be highly cytotoxic?
- What is the appropriate approach for veterinary products, given that Melia azedarach has also been established to be highly toxic in animals?

DISCUSSION

The following responses to the pre-meeting gazette notice had been received.

- XXXXXXXXXXXXXX supported the NDPSC approach of determining whether there were any distinguishing mechanisms for determining toxic from non-toxic varieties, safety cut-off concentrations, and a differentiation in approach between the use and scheduling of the substance with regard to human therapeutic, agricultural and/or veterinary applications that may allow access where appropriate.
- XXXXXXXXXXXXXX stated that any restrictive measures on *Melia azedarach* should not be to the detriment of Listed or Registered medicines. The following points were raised:
    - XXXXXXXXXXXXXX had a number of products Listed on the ARTG containing extracts of the herb, *Melia azedarach*. The extracts were sourced from either the leaf or the fruit. A 'Practitioner Only' Listed medicine contained *Melia azedarach* in the form of a leaf extract, dry concentrated at 10:1 ratio in 50% Ethanol:Water. The herbal extract was prepared using an Indian produced

herb utilising an Indian extraction technique. The finished product contained 196.00 mg of the herb per tablet. The recommended dosage for the management of certain skin conditions for adults was 6 tablets per day. The product had been marketed for the past two years with no reports of adverse reactions.

- A 'Practitioner Only' Listed medicine contained *Melia azedarach* in the form of a fruit extract, dry concentrated at 4:1 ratio in 100% water. The herbal extract was prepared using a Chinese produced herb utilising Chinese extraction techniques. The finished product, an oral powder, contained 36.67 mg of the herb. The recommended dosage for adults was to take 12 grams of powder per day for the relief of pain and burning sensation associated with cystitis. The product had been marketed for the past XXXXXXXXXXXXX with no reports of adverse reactions.
- XXXXXXXXXXXXX had requested from its foreign suppliers toxicological and chemical data however, no information had been received as yet. Once this data was supplied, it would be passed on to the Committee, before decision was finalised. Unfortunately, no data (limonoid, toxicological, and long term safety data) could be furnished concerning the extracts used in the XXXXXXXXXXXXX formulae.
- XXXXXXXXXXXXX believed that *Melia azedarach* may require restriction for safety purposes. However, since the herb had been used for centuries in India and China, there should be a place for its use in Australia as well.

- XXXXXXXXXXXXX raised the following points:
  - The scientific studies the Committee had relied on in support of the proposal did not include a bibliography and the only indirect reference to such scientific studies was by reference to other considerations by the Committee in relation to the scheduling of *Azadirachta indica* (neem).
  - In relation to *M azedarach*, the committee appeared to have relied on other studies, including studies conducted in Australia, but these studies had not been specifically cited.
  - The TGA had obvious concerns with the supply of raw material (eg "wildcrafting"), and claimed it was the responsibility of Australian sponsors to ensure the correct identity of the received material. The key issue was whether such an approach was warranted given the history of use and recorded safety profile of the substance. XXXXXXXXXXXXX contended that a form of confirmation in the compositional guidelines was not warranted. It believed that in the event that confirmation was considered appropriate the possibility of a chemical analysis and/or botanical identification should be explored further in lieu of prohibition.
  - Regarding the establishment of an appropriate concentration cut-off to accommodate existing products, the Pharmacology of Chinese herbs stated that the LD_{50} of *M azedarach* in mice was 480 $\pm$ 63.4 mg/kg, and in rats 120 $\pm$ 38.5 mg/kg. It cautioned that patients taking the herb may develop gastrointestinal symptoms including nausea, vomiting and abdominal pain. Occasionally, blurred vision and skin eruption were reported. Contraindications included heart disease, acute tuberculosis, peptic ulcer, and liver diseases. Because of this, the

dose in Chinese Herbal Medicine (CHM) of 3-9 g of raw herb was set sufficiently low to ensure any adverse reactions did not occur.

- In traditional Chinese herbal medicine *Melia azedarach* had been used for literally hundreds of years (since 1186) for the treatment of parasitic diseases without any cause for concern. The traditional dosage limit was in recognition of the slightly toxic profile of the substance if consumed in large quantities.
- All XXXXXXXXXXXXXX l products were patent herbal medicines and used extensively in China for at least 100 years. They were manufactured from raw materials according to the Chinese Pharmacopoeia and in recent times to Australian accredited GMP standards.
- XXXXXXXXXXXXXX stated that the weight of scientific evidence advanced for public comment to support the proposal to prohibit *Melia azedarach* in Australia was completely outweighed by the safe history of traditional use in China and Australia.
- XXXXXXXXXXXXXX also noted with concern that the recognition of "traditional use" as defined in the *Therapeutic Good Act* appeared to be subject to progressive circumvention by the Regulator in favour of applying "western" scientific standards in terms of safety. Whilst such approach may be justified where the evidence clearly pointed to a safety issue, it appeared this approach was being invoked without any evidence of adverse reactions in the general population.

The Committee noted that there were 17 products listed on the ARTG containing *Melia azedarach* (of the *Meliaceae* family). The indications listed included liver detoxification, treatment for lice, and protection of capillaries. A number of the products were "grandfathered", with some containing 340 mg/capsule equiv to the dry fruit, and 135 mg/mL equiv to the dry leaf. No agricultural or veterinary products were listed on the PUBCRIS database.

A member stated that the meliatoxins isolated from the fruit of the Chinaberry tree had extreme acute oral toxicity of 6.4 mg/kg in pigs and the concern regarding the absence of a real mechanism by which the toxic and non-toxic variety of *Melia azedarach* could be differentiated was reiterated. The member also advised the Committee that other compounds were isolated from other parts of the plant which exhibited significant cytotoxicity.

The Committee noted with concern that the issues raised at the June 2002 meeting remained unresolved and that there was inadequate information available to assist in characterising the risks associated with *Melia azedarach* and assessing existing products containing its extracts or derivatives. Members noted the concerns raised in the pre-meeting public submissions received and a member also advised that the Traditional Chinese Medicine industry in Victoria had expressed concerns that inclusion of *Melia azedarach* and its extracts or derivatives in Appendix C would have detrimental effects on the industry.

A member queried the expression "Practitioner Only Listed medicine" used in XXXXXXXXXXXXXX 's submission and asked if it implied that there was some form

of professional or legally enforceable restrictions on this type of preparation. Members agreed that it would be useful if information was sought in terms of the implications of reflecting this classification on product labels and to determine whether there was any enforceable professional or legal control associated with products labelled as such.

The Committee noted that XXXXXXXXXXXXXX had requested from its foreign suppliers toxicological and chemical data relating to *Melia azedarach*, which it indicated would be forwarded to the Committee for consideration when available. In addition, a member advised that the Traditional Chinese Medicine industry in Victoria also undertook to provide data and stated that it would be appropriate for stakeholders to be given a reasonable opportunity to provide relevant data to the Committee.

OUTCOME

The Committee agreed to defer to the June 2003 meeting, further consideration of the foreshadowed inclusion of *Melia azedarach* and it extracts or derivatives in Appendix C of the SUSDP. To facilitate evaluation of data provided, the Committee agreed that submissions relating to *Melia azedarach* should be received by the Secretariat by COB 28 February 2003. The Committee further indicated that data written in a foreign language would also be accepted, provided that both the English translation and original documents were submitted together.

Furthermore, the Committee also agreed to ask the Office of Complementary Medicines (OCM) for its opinion on the potential hazards associated with Melia azedarach and products containing its extracts or derivatives listed on the ARTG.

13.2 AZADIRACHTA INDICA (NEEM)

PURPOSE

The Committee considered the scheduling of *Azadirachta indica* (neem).

BACKGROUND

XXXXXXXXXXXXXX had sought approval of a new TGAC, neem seed extract powder, and had submitted information and toxicology studies in support of the registration of XXXXXXXXXXXXXX. Azadirachtin acts as an insect repellent and feeding inhibitor, and causes insect growth disruption due to interference with hormone production. The product was proposed for use as an "in furrow" application to prevent XXXXXXXXXXXXX at the time of planting.

The February 2002 NDPSC meeting considered the scheduling of the proposed TGAC, neem seed extract powder, and azadirachtin, a limonoid component of neem (*Azadirachta indica*). The Committee also noted that the Complementary Medicines Evaluation Committee (CMEC) June 2001 meeting considered an application to include cold-pressed neem seed oil (neem oil is also known as margosa oil) as a new complementary medicine substance for use as a listable therapeutic agent. The CMEC recommended to the TGA

that cold-pressed neem (*Azadirachta indica*) seed oil was suitable for use in listable therapeutic goods, provided it was restricted to topical application on the skin only and that the following conditions were met:

- therapeutic goods containing the substance were supplied with label warnings that these were for external use only and should be kept out of the reach of children; and
- the containers of therapeutic goods containing this substance were fitted with child-resistant closures.

Based on the available data, the February 2002 NDPSC meeting agreed to include *Azadirachta indica* (Neem) or its extracts or its derivatives for agricultural or veterinary use in Schedule 7, and preparations for agricultural use containing 5% or less of total limonoids, when extracted from seed kernels using water, methanol or ethanol were included in Schedule 5. However, the Committee remained concerned over the acute toxicity of neem oil in children, the effects on male and female fertility, and the embryotoxicity of crude or unrefined extracts of neem. Consequently, the Committee concluded that use of neem extracts or derivatives in humans warranted restriction, and the Committee foreshadowed a proposal to include *Azadirachta indica* (neem) or its extracts or its derivatives in preparations for human use in Appendix C of the SUSDP, to be considered at the June 2002 meeting.

Following the February 2002 NDPSC meeting, a number of representations were received objecting to the proposed scheduling of *Azadirachta indica* (neem). Various persons and organisations claimed that they were not aware that the scheduling of Neem was under consideration and protested against the restrictive nature of the proposed scheduling action. As a consequence, the NDPSC at its June 2002 meeting agreed to defer any further consideration of the scheduling of Neem to its next meeting to be held on 15-17 October 2002, and annulled the decisions relating to *Azadirachta indica* (neem) made at the February 2002 meeting. In order to provide stakeholders with the opportunity to make a formal public submission to the NDPSC in accordance with statutory requirements, the Committee agreed to recommence the public consultation process for the consideration of scheduling of Neem at the October 2002 NDPSC meeting. Accordingly, the CMEC and Chemical Product Assessment Section (CPAS) evaluation and other relevant material were made publicly available through the NDPSC website.

There were no products containing azadirachtin, *Azadirachta indica* or neem listed on the ARTG or PUBCRIS at the time of the October 2002 meeting.

DISCUSSION

The Committee was provided with the following agenda papers:

- Extract from the February and June 2002 NDPSC ratified minutes
- Information paper on neem on NDPSC Website
- OCM Evaluation Report on Cold Pressed Neem Seed Oil (*Azadirachta indica* Juss)

- CPAS Evaluation Report on *Azadirachta indica*
- Evaluation reports/risk assessment of XXXXXXXXXXXXX (azadirachtin) technical
- Rural Industries Research and Development Corporation (RIRDC) feasibility study report entitled "Growing Neem in Australia"
- Published study entitled "Antifertility Effects of neem (Azadirachta indica) oil by single intrauterine administration: A novel method for contraception
- Australian Internet sites selling neem products and list of products available from local markets
- Range of products sold in Canberra local markets
- Extract from Poisindex Managements on Eucalyptus Oil
- June 2002 NDPSC pre-meeting public submissions (Attachment 1)
- October 2002 NDPSC pre-meeting public submissions (Attachment 1)
- EXTOXNET and US EPA website information relating to azadirachtin and clarified hydrophobic extract of neem oil
- OCM submission on Neem

The Committee noted the submission from the Office of Complementary (OCM), restating CMEC's recommendation to the TGA that cold-pressed neem (*Azadirachta indica*) seed oil was suitable for use in listable therapeutic goods, provided it was restricted to topical application on the skin only and that the following conditions were met:

- therapeutic goods containing the substance were supplied with label warnings that these goods were for external use only and should be kept out of the reach of children; and
- the containers of therapeutic goods containing this substance were fitted with child-resistant closures.

Following its recent reconsideration of this matter, CMEC concluded that "while the data do not provide conclusive evidence of the safety of neem oil when used by this route, they assist in supporting the contention that neem oil, in various forms and under various traditional names has a very long history of traditional medicinal use, including the use as a topically applied agent. Importantly, during a long history of traditional topical use of various preparations obtained from *Azadirachta indica*, including neem seed oil likely to be similar to that proposed for listing, no significant concerns as to its safety have emerged or have been reported by Ayurvedic practitioners".

The Committee noted that the XXXXXXXXXXXXX PIC and XXXXXXXXXXXXX had advised that they had no documented cases of neem poisoning, although the latter indicated that in many cases, the agent of poisoning may

not be recorded or coded into a category from which agents such as neem could be identified.

The Committee noted that some 50 public submissions were received and included with this item. A full listing and summary of these submissions is provided at Attachment 1. The following major points were raised by stake holders:

- Labelling of neem products as a "poison" or their inclusion in Schedule 7 or Appendix C would not be appropriate based on a wide body of evidence and open literature supporting their safety.
- Neem has over 4000 years history of safe and extensive use in traditional medicine including use by Ayurvedic practitioners in India. Neem oil and extracts from other parts of the neem tree for cosmetic and medicinal use should be exempt from scheduling.
- Neem oil should not be used for contraceptive purposes but used only topically and not taken orally or inserted into any body cavity. Labelling and supportive literature including directions on proper use of products should provide effective mechanisms for ensuring safe use of neem.
- All imported and locally produced neem oil should be screened for purity, cleanliness and grade and checked for aflatoxins. A maximum limit for aflatoxin content should be established.
- Neem oil has very low acute oral, dermal and inhalation toxicity.
- Neem is non-toxic on the grounds that the associated anti-reproductive effects are reversible and therefore beneficial in controlling population.
- Developing neem-based industries had significant economic advantages and provided a safe alternative for people intolerant of commercially produced products.
- A number of neem-derived preparations had been approved by the USEPA as an agricultural pesticide and neem-based pesticides were a safe and natural alternative to toxic synthetic chemicals.
- The reported incidences of neem poisoning in children were most likely caused by ingestion of neem oil contaminated with aflatoxins or ingestion of extracts from *Melia azedarach* confused as neem.
- Cold-pressed oil from Neem seed kernels should be used appropriately and restrictively as a Listable substance, and requiring warning statements on the label to address the concerns of use by pregnant women would be a reasonable approach. However, if the use of additional conditions and warning statements could be avoided by the determination of safety cut-off concentrations or similar distinguishing mechanisms, then this approach would be preferable.
- Neem oil should be scheduled similarly to essential oils, i.e. eucalyptus oil, and neem products for agricultural use should be scheduled and made to comply with all necessary requirements in force.

- Several respondents who claimed to have personally used neem oil and extracts from other parts of the tree including leaves and bark reported no consequential adverse effects. It was stated that neem had been used as a therapeutic agent for both topical and internal application as well as for cosmetic use in both humans and animals.
- There was insufficient evidence to support any regulatory action on neem and its extracts.

The Committee had a lengthy discussion and the following key issues were highlighted:

- The Committee's concerns relating to reproductive impairment and abortifacient action of some unknown component(s) in neem had remained unresolved. No new evidence or scientific comment was provided to clarify or repudiate these findings. Further, no evidence was provided to support the assertions made that aflatoxin or other contamination, and not neem itself, caused the reported acute toxic effects.
- The argument of long history of safe use of neem was based mainly on anecdotal evidence of traditional use. Whilst traditional use may be an indicator of safety where obvious symptoms of acute toxicity may be immediately associated with exposure, the Committee was not convinced that this provided a sound basis for conclusions regarding other types of toxicity. In particular, the Committee remained concerned about potential adverse effects where the consumer would not normally make a connection between exposure and subsequent symptoms. For example, the Committee considered it would be unlikely that the critical connection would be established between exposure to neem and adverse effects such as foetal resorption and antifertility effects, unless monitored closely by a medical practitioner. The Committee noted there was a wide body of anecdotal evidence on neem oil's traditional use as a spermicidal agent and abortifacient, supporting their concerns regarding reproductive toxicity. Members also noted that some submissions raised the argument that neem was beneficial in controlling population.
- Some submissions provided details of the extraction and processing of different neem seed extracts/preparations and of some components, which were useful in adding to the knowledge of the types of terpenoids present in neem oil extracts. However, the data provided did not clarify what preparations or components were likely to be toxic to the reproductive tract or those preparations or components which may have anti-androgenic and/or hormonal properties.
- The available information relating to dermal absorption of certain uncharacterised toxic component(s) of neem oil was still inadequate. There was sufficient evidence however to suggest that neem oil was absorbed intravaginally producing abortion in primates. Further, members were reminded that not all dermatological conditions were associated with intact skin surfaces. Parasitic skin conditions such as scabies were normally associated with skin injury that promoted significant systemic absorption of a wide range of substances through the epidermis.
- It was proposed that products containing cold-pressed neem seed oil should be labelled with WS 67 "Do not use if pregnant or likely to become pregnant". Members were of the view that the foetotoxicity associated with neem, i.e. foetal

resorption and implantation failure, was unlikely to be discovered by the consumer in the absence of close monitoring by a medical practitioner, and that it would be appropriate to require a suitable warning on product labels to alert consumers of these effects.

- The submissions did not provide adequate information relating to the level of neem oil/extract in various products, the pharmacological effects of such products when used orally and whether neem was subject to first-pass metabolism.
- 'Debitterised' neem oil is highly purified oil which is bitterless, odourless and colourless, and comprising mainly long-chain fatty acids and glycerides. Based on available evidence, 'debitterised' neem seed oil fed to rats at 10% of the diet did not affect reproductive parameters in a 3-generation study but produced minor parental effects, i.e. reduced body weight gains (Chinnasamy *et al*).
- The proposal to include aqueous or alcoholic extracts of neem seed oil for agricultural pesticidal use in Schedule 5 still appeared valid, based on available data. It was noted that there was no new data submitted relating to proposed uses vs exposure to alter the Committee's viewpoint. In addition, there was no relevant standard applicable to neem established either by the Food Standards Australia New Zealand (FSANZ) or the Therapeutic Goods Administration (TGA).
- Based on verbal advice obtained from XXXXXXXXXXXXXX, it appeared that neem extracts did not require testing for aflatoxins based on the FSANZ's Contaminants and Natural Toxicants Standard. In addition, the National Registration Authority's (NRA) existing Minimum Compositional Standard did not include a limit for aflatoxins.
- The Committee agreed to expressly restrict the use of products for human dermal therapeutic use to those containing only cold pressed neem seed oil, to ensure that no selective accumulation of toxic components occurred during processing of other extracts from the neem seed or other parts of the neem tree. Accordingly, given that cold-pressed neem seed oil contained approximately 96% vegetable oil, a cut-off for exemption of 1% cold-pressed neem seed oil was proposed on the basis that this should provide an adequate margin of safety against the reproductive toxicity.
- The United States Environmental Protection Agency (USEPA) exemption for clarified hydrophobic neem extracts and for some limonoids present in neem including azadirachtin and dihydroazadirachtin raised in submissions, appeared to be based on the need to establish tolerances for residues, which was not a consideration for scheduling.
- A similar approach to the scheduling of eucalyptus oil was proposed for neem oil and its derivatives. Although eucalyptus oil had been established to be acutely toxic, its toxicity and adverse effect profile was well-characterised. It was noted that the chemistry of eucalyptus oil was also well-characterised and its toxicity was clearly associated with specific identified components. Furthermore, eucalyptus oil did not have the unresolved issues of toxicity, as with neem and its extracts, hence it would be inappropriate to schedule these two substances similarly at this time.

Members noted the submission and proposal relating to *Cinnamomum camphora* and agreed to refer this to the Office of Complementary Medicines (OCM).

The Committee supported the establishment of Compositional Guidelines and testing of neem seed oil extracts for aflatoxins as a condition for listing/registration.

DECISION 2002/36 - 15.

In summary, the Committee agreed that *Azadirachta indica* (neem) or its extracts or its derivatives:

(i) in preparations for human internal use except 'debitterised neem seed oil' be included in Appendix C of the SUSDP;
(ii) be included in Schedule 6 (base Schedule);
(iii) when 'debitterised' be exempt from scheduling;
(iv) in preparations containing cold pressed neem seed oil for human dermal use, labelled with the recommended warning statements and fitted with a child resistant closure be exempt from scheduling;
(v) in preparations for human dermal use containing 1% or less of cold pressed neem seed oil be exempt from scheduling;
(vi) preparations when included in Schedule 6 should be labelled with Appendix F Warning Statement 67 (Do not use if pregnant or likely to become pregnant); and
(vii) extracted from seed kernels using water, methanol or ethanol contained in preparations for agricultural use containing 5 per cent or less of total limonoids be included in Schedule 5.

These decisions were based on the following rationale:

(i) There was clear evidence of reproductive toxicity and antiandrogenic effects in experimental animals, and acute toxicity in humans to warrant prohibition of all human internal use of neem products until sufficient evidence is available to characterise the substance(s) responsible for the toxicity.

(ii) A spectrum of toxicity including acute, reproductive and foetal toxicity was seen over a range of preparations and extracts containing neem which provided an overall toxicity profile appropriate for inclusion in Schedule 6 of the SUSDP for all uses other than internal human use.

(iii) The Committee agreed to exempt 'debitterised' neem seed oil from scheduling on the basis that highly purified neem oil containing only fatty acids and glycerides is unlikely to cause toxicity.

(iv) The Committee accepted CMEC's recommendation relating to products containing cold pressed neem seed oil for topical use on the skin, and was of the view that there was scope for exempting such products. However, the Committee has remained sufficiently concerned over the potential for dermal absorption and the possible reproductive and foetotoxic effects from dermal exposure, that it has

agreed to exempt such products only when they are labelled with "Do not use if pregnant or likely to become pregnant", in addition to CMEC's recommended label warnings and requirement for CRC on products.

(v) The reproductive toxicity of concern to the Committee was associated with the 4-5% non-lipid fraction of the cold pressed neem seed oil comprising approximately 95-96% vegetable oil. The Committee is confident that allowing an exemption for dermal products containing 1% or less of the cold pressed neem seed oil should provide an adequate safety margin against reproductive toxicity, based on the further 1:100 or greater dilution of the neat cold pressed neem seed oil in such products. Other extracts from the neem seed or other parts of the neem tree were not given a similar exemption to the cold pressed neem seed oil, due to concerns that the uncharacterised reproductive toxicants may be inadvertently concentrated during processing of such extracts. No adequate compositional and toxicological data on extracts and preparations other than cold pressed neem seed oil was available to the Committee to resolve this issue in a manner that minimised the potential hazard.

(vi) The Committee has agreed that *Azadirachta indica* (neem) or its extracts or its derivatives in Schedule 6 should be labelled with Appendix F Warning Statement 67, based on neem's demonstrated reproductive, antifertility and foetotoxic effects in experimental animals.

(vii) Based on the available acute toxicological data and in-furrow use which minimised operator exposure, the Committee agreed that it would be appropriate to include in Schedule 5 *Azadirachta indica* extracts, extracted from neem seed kernels using water, methanol or ethanol, in preparations containing 5 per cent or less of total limonoids, for agricultural use.

Appendix C – New entry

AZADIRACHTA INDICA (neem) or its extracts or its derivatives, in preparations for human internal use **except** 'debitterised neem seed oil'.

Schedule 6 - New entry

AZADIRACHTA INDICA (neem) or its extracts or its derivatives **except**:

(a) in preparations for human internal use;

(b) when included in Schedule 5;

(c) 'debitterised neem seed oil';

(d) in preparations for human dermal therapeutic use containing cold pressed neem seed oil, when in a container fitted with a child resistant closure and labelled with the statements:

" Not to be taken"

"Keep out of the reach of children"

"Do not use if pregnant or likely to become pregnant"; or

(e) in other preparations for dermal use containing 1 per cent or less of cold pressed neem seed oil.

Schedule 5 - New entry

AZADIRACHTA INDICA EXTRACTS (neem extracts), extracted from neem seed kernels using water, methanol or ethanol, in preparations containing 5 per cent or less of total limonoids, for agricultural use.

Appendix E, Part 2 – New entry

AZADIRACHTA INDICA (neem) or its extracts or its derivatives when included in Schedule 6.
Standard Statement …….A, E1

Appendix F, Part 3 – New entry

AZADIRACHTA INDICA (neem) or its extracts or its derivatives when included in Schedule 6.
Warning Statement …….67

Part 1, Interpretation – New entry

"**Debitterised neem seed oil**" means highly purified neem oil containing only fatty acids and glycerides of fatty acids.

13.3 FLUVOXAMINE AND VENLAFAXINE

PURPOSE

The Committee considered the foreshadowed inclusion of fluvoxamine and venlafaxine in Appendix K.

BACKGROUND

The February 2002 NDPSC Meeting considered the proposal to include the serotonin and nonadrenaline re-uptake inhibitor (SNRI) drugs, sibutramine and ziprasidone, in Appendix K of the SUSDP. To ensure consistency across the class, the Committee agreed to review all SNRI drugs for the need to include a sedation warning on the label at the June 2002 meeting. Subsequent literature searches undertaken yielded six compounds classified as SNRIs, i.e. venlafaxine, sibutramine, ziprasidone, duloxetine and

milnacipran, although duloxetine and milnacipran were not listed on the ARTG at the time.

The June 2002 meeting agreed to include ziprasidone in Appendix K of the SUSDP and foreshadowed the inclusion of fluvoxamine and venlafaxine in the same Appendix, which was to be confirmed at the October 2002 meeting.

DISCUSSION

Fluvoxamine

The Committee noted that a pre-meeting submission from XXXXXXXXXXXXXX had been received stating that the foreshadowed inclusion of fluvoxamine in Appendix K of the SUSDP was not warranted. XXXXXXXXXXXXXX requested reconsideration of the foreshadowed decision on the grounds that fluvoxamine:

- had a reported incidence of somnolence/drowsiness/sedation of less than 7% (6.4%) in worldwide clinical trial and drug safety monitoring.
- did not have a significant effect on psychomotor activity and therefore the ability to drive or operate machinery.
- had an equal if not lower incidence of somnolence compared with other selective serotonin re-uptake inhibitors (SSRI's) available for use in Australia.

The Committee noted the data provided by XXXXXXXXXXXXXX reported:

- a reduced incidence of somnolence compared with that recorded in the clinical studies used to support registration.
- that fluvoxamine did not have a significant effect on psychomotor activity and did not affect driving competence based on the findings of studies undertaken post registration.

Venlafaxine

The Committee noted that a pre-meeting submission from XXXXXXXXXXXXXX had been received stating that the addition of a mandatory warning statement to the label of dispensed medicines containing venlafaxine may serve only to exaggerate the possible risk, hence, discourage patients from continuing with effective therapy or unnecessarily curtail their ability to lead a normal lifestyle. In addition, XXXXXXXXXXXXXX stated that appropriate statements relating to somnolence were included in the Consumer Medicine Information (CMI). Subsequently, the company requested that the NDPSC not proceed with the foreshadowed decision to include venlafaxine in Appendix K of the SUSDP.

The Committee noted that the data provided by XXXXXXXXXXXXXX suggested that venlafaxine did not affect the driving ability of treated subjects who were tested on five driving parameters, i.e. the critical flicker fusion test, the choice reaction time test, the digital symbol substitution test, the trail-making test and the line analogue rating scale.

The Committee was advised that the Product Information (PI) for XXXXXXXXXXXXX which contains venlafaxine, listed hypersomnia, drowsiness, lethargy and sedation as potential adverse effects. It was indicated that this group of adverse effects was listed in the PI if the frequency was more than 3%. However, the sponsor for XXXXXXXXXXXXX suggested that the studies provided to the Committee clearly indicated that it could not be assumed that venlafaxine would necessarily impair the ability of a patient to function normally, eg. to make critical decisions or operate machinery.

Appendix K

A Member advised the Committee that based on anecdotal evidence, patients taking anti-depressant drugs commonly experienced somnolence, but the incidence of this adverse effect appeared to be considerably lower with venlafaxine and fluvoxamine. The Member also stated that the inclusion of venlafaxine and fluvoxamine in Appendix K of the SUSDP may not be warranted on the basis that a sedation warning was already included in the PI and CMI

Members were of the view that the inclusion of venlafaxine and fluvoxamine in Appendix K may not be warranted at this time, on the basis that both the CMI and the PI reflected a sedation warning. Furthermore, it was noted that the Australian Pharmaceutical Formulary (APF) 17th Edition, which is the Pharmacy Profession's Code of Conduct, had recommended that dispensed medicines containing venlafaxine and fluvoxamine be labelled with label 12, which stated: *"This medicine may affect mental alertness and/or coordination. If affected, do not drive a motor vehicle or operate machinery"*.

OUTCOME

The Committee agreed not to include venlafaxine and fluvoxamine in Appendix K of the SUSDP at this time. This decision was made on the grounds that the available evidence indicated that these substances had a low potential to cause sedation or affect motor skills at the recommended doses and furthermore, the inclusion of sedation warnings in the CMI and PI was considered sufficient.

13.5 PSEUDOEPHEDRINE

PURPOSE

The Committee considered the scheduling of pseudoephedrine – modified release, combination, undivided and other preparations – currently listed in S2.

BACKGROUND

The June 2002 meeting agreed to reschedule all OTC single-active immediate release preparations from S2 to S3. This decision was based on evidence that pharmacist intervention would help reduce the problem of diversion to the illicit drug trade while

maintaining access for legitimate users. In addition, pseudoephedrine was included in Appendix H of the SUSDP to maintain the status quo regarding advertising.

However, at the same meeting, the Committee considered the available information was insufficient to consider the scheduling of the remaining S2 formulations. Consequently, it was agreed that a review of the scheduling of the remaining pseudoephedrine-containing products in S2 be foreshadowed and in the interim, additional data would be sought from the jurisdictions and industry on formulation details, extractability of the pseudoephedrine from the formulation, and annual sales volume (no.of units) for each formulation over the last five years.

DISCUSSION

Additional data had been sought from June 2002 Meeting respondents. The following responses were received:

- XXXXXXXXXXXXXX provided formulation details of their products.
- XXXXXXXXXXXXXX supported the rescheduling of remaining S2 preparations to S3.
- XXXXXXXXXXXXXX supported the retention of modified release and other preparations in S2 on the basis that change to S3 would not improve the level of vigilance and would introduce significant operational barriers to practice. The XXXXXXXXXXXXXX noted that provision of pseudoephedrine in Schedule 2 was covered by the existing Code of Professional Conduct in relation to supply of excessive quantities and that a new Code for pseudoephedrine was being developed.
- XXXXXXXXXXXXXX supported the rescheduling of all OTC pseudoephedrine-containing products to S3, outlining the existing restrictions on sale in XXXXXXXXXXXXXX, claiming diversion of combination products was occurring and supporting exclusion from Appendix H.
- XXXXXXXXXXXXXX was opposed to the rescheduling of modified release, combination, undivided and other preparations in S2 to S3. XXXXXXXXXXXXXX requested that the Committee consider the actions taken to date by the industry and urged that a broadly based approach for managing the issue be adopted. An extensive and detailed code of conduct in relation to pseudoephedrine was provided.
- XXXXXXXXXXXXXX highlighted that any rescheduling would be premature due to self-regulatory strategies being put in place and stated that increased regulation would not offer significant improvements over the self-regulatory approach being actioned by the key stakeholders themselves. In addition, increased restriction inevitably means increased costs and delays for consumers. An extensive submission was provided covering a broad range of initiatives by XXXXXXXXXXXXXX to address the issue of diversion.
- XXXXXXXXXXXXXX supported the same scheduling for single-active and all pseudoephedrine-containing products including modified release preparations. The

company also provided information relating to the extractability of pseudoephedrine from various formulations including XXXXXXXXXXXXXX.

- XXXXXXXXXXXXXX stated that the existing scheduling of combination products was adequate and appropriate, and that further restrictions on these products were not warranted. They proposed that any product which presented the pseudoephedrine component in such a way that it could be readily separated from other active ingredients by simple dissolution or other simple physical means should be regarded in the same way as a single active ingredient conventional release product. XXXXXXXXXXXXXX further proposed that the term "combination" should only apply to 'compounded' products as per the existing definition in the SUSDP.
- XXXXXXXXXXXXXX stated that the proposal to change the current pseudoephedrine scheduling would obscure any quantitative assessment of the current status and cancel out the beneficial effects of the joint strategies implemented via industry and pharmacy bodies to address the issue of illicit diversion of pseudoephedrine.
- XXXXXXXXXXXXXX urged the Committee to consider a broader approach to the issue. It stated that the current self-regulatory approach taken by industry and pharmacy should be supported and given sufficient time to produce results.
- XXXXXXXXXXXXXX opposed any further restrictions on pseudoephedrine-containing products and considered the decision taken in June 2002 to reschedule single active ingredient products from S2 to S3 to be flawed.
- XXXXXXXXXXXXXX supported the retention of combination products in S2. It stated that further restrictions would create unrealistic workloads for pharmacists and create difficulty for legitimate patients to access the medication. This was said to lead to inappropriate medication and/or increased visits to the doctor.
- XXXXXXXXXXXXXX advised that only single entity preparations were being sought consistently from pharmacies.
- The XXXXXXXXXXXXXX advised that single-active and bilayer pseudoephedrine preparations, where pseudoephedrine could be physically separated from other components, were being sought and bought in the Territory, XXXXXXXXXXXXXX.

The Committee was advised that the Chair and the TGA Representative attended a meeting initiated by XXXXXXXXXXXXXX to discuss the proposed ASMI Code of Conduct designed to help prevent diversion of pseudoephedrine containing non-prescription medicines. It was noted that the Victorian team-based model involving the Victorian Police, Victoria Health and pharmacy peak bodies, adopted to develop a mechanism for dealing with the problem of diversion was widely supported at this meeting. The meeting noted the need for the proposed ASMI Code of Conduct to be cleared by the Australian Competition and Consumer Commission (ACCC) prior to implementation. The Chair advised that XXXXXXXXXXXXXX had undertaken to update the Committee on any progress towards the implementation of the proposed Code of Conduct.

The Committee recalled that at the June 2002 meeting, it was agreed that single-active immediate release preparations in S2 be rescheduled to S3, and that the scheduling of remaining preparations in S2, i.e. combination products including bilayer presentation, single-active modified release, undivided and compounded preparations, be reviewed. At the June 2002 Meeting, jurisdictional members were also asked to provide information on 'high-risk' pseudoephedrine products in S2 being targeted for diversion.

The XXXXXXXXXXXXXX member advised that following the June 2002 NDPSC meeting, a conference was convened by the Australian Bureau of Criminal Intelligence (ABCI), which was attended by various stakeholders including representatives from various jurisdictions and the industry, to address the issue of pharmaceuticals being diverted to the illicit drug trade. At the conference, the NSW Police Service and Australian Government Analytical Laboratories (AGAL) made a joint presentation on the outcome of preliminary investigations of various combination products to determine the ease of extraction and pseudoephedrine yield. The conference had concluded that further testing was required to investigate the entire range of OTC combination products. The Australian Bureau of Criminal Intelligence would coordinate this research and seek funding for testing of all OTC combination products containing pseudoephedrine. The member advised any information arising from this research would be provided at the February 2003 meeting.

The Committee was advised that preliminary information presented at the conference indicated that a 40% pseudoephedrine yield from products was still considered financially viable given the existing market price of amphetamines. However, the gel formulations appeared to inhibit the extraction of pseudoephedrine. A member suggested that the type of formulation and difficulty of extraction may not provide a sufficient deterrent to diversion and that this may not be an appropriate basis for scheduling.

The Committee noted the data provided by XXXXXXXXXXXXXX relating to the extractability of pseudoephedrine from OTC combination preparations. It was noted that pseudoephedrine HCl was readily extracted from XXXXXXXXXXXXXX tablets with good recovery using a method available on the internet. However, slow release preparations (XXXXXXXXXXXXXX) all formed a gum when extracted with toluene, necessitating the conversion of pseudoephedrine HCl to pseudoephedrine free base. This was followed by extraction of the free base with organic solvents, leading to a lower recovery of pseudoephedrine. With slow release preparations, it was stated that XXXXXXXXXXXXXX tablets only required crushing prior to extraction and XXXXXXXXXXXXXX tablets required the XXXXXXXXXXXXXX to be removed first by soaking in acetone. Members noted a discrepancy regarding anecdotal reports of extracting XXXXXXXXXXXXXX using other techniques in particular, the type of solvent used for removing the XXXXXXXXXXXXXX coating on the tablets.

A jurisdictional member advised that combination products continue to be found in clandestine laboratories although it was not clear if these were actually being converted in any quantity to amphetamines. XXXXXXXXXXXXXX reported a significant reduction in the sales of OTC single-active pseudoephedrine products following their rescheduling to S3, whereas the other jurisdictions advised that single-active and 'bilayer' preparations

such as XXXXXXXXXXXXXX were still consistently being targeted in pharmacies for purchase and subsequent diversion. In contrast, modified release single-active pseudoephedrine OTC preparations were not raised as a significant concern in the jurisdictions at the time.

Members agreed that the preliminary information available on the diversion and conversion of compounded and modified release pseudoephedrine preparations did not support an amendment to the existing scheduling of these products at this time. Accordingly, the Committee did not support further restrictions on these products at this time.

The Committee agreed that combination products including bilayer preparations where pseudoephedrine could be readily separated or extracted from other components in the formulation by simple dissolution or other physical means were not included in the definition for 'compounded' in the SUSDP. Members agreed that sponsors of such products be informed of the Committee's concerns regarding this and asked if they intended to reformulate such products.

Members agreed that the findings of the research to be conducted on all OTC preparations may assist in characterising the potential for products/formulations likely to be targeted for diversion and could be valuable in the Committee's consideration of the scheduling of remaining pseudoephedrine-containing preparations in S2. In addition, the Committee was strongly supportive of a national approach to address the problem of pseudoephedrine diversion and supported the proposed ASMI Code of Conduct.

The Committee agreed that it would actively consider the issue of pseudoephedrine diversion at each meeting and placed pseudoephedrine as a standing item on future agendas.

OUTCOME

The Committee considered that the preliminary information available did not support scheduling action on the compounded, undivided and modified release pseudoephedrine preparations in S2 at this meeting. However, the Committee remained concerned over the potential for the products left in S2 to be diverted to the illicit drug trade and it would be reconsidering the issue at the February 2003 meeting with further public consultation. The Committee was of the view that this would allow an opportunity for the Committee to be informed of the outcome of ongoing investigations to be conducted on all OTC pseudoephedrine products and for sponsors to indicate their plans for existing and future product lines.

The Committee agreed that previous submissions relating to this matter will be carried forward to the February 2003 meeting, and the persons who made the submissions will be eligible to comment on any decisions made at the February 2003 Meeting.

13.6 SODIUM PICOSULFATE AND MACROGOL 3350

PURPOSE

The Committee considered the foreshadowed inclusion of macrogol 3350 and sodium picosulfate in preparations for oral laxative use in Schedule 4 of the SUSDP.

BACKGROUND

The February 2002 NDPSC meeting considered the scheduling of sodium picosulfate due to concerns highlighted in the ADRAC Bulletin relating to low volume bowel cleansing products containing sodium picosulfate for use in bowel cleansing prior to colonoscopy. As a result, the Committee agreed to include sodium picosulfate in preparations for oral use for bowel cleansing prior to diagnostic, medical or surgical procedures, in Schedule 3 of the SUSDP.

The June 2002 meeting considered an application from XXXXXXXXXXXXX proposing the following:

(a) retain sodium phosphate and macrogol 3350 (polyethylene glycol - PEG) bowel cleansing preparations in Schedule 3;
(b) schedule sodium picolsulfate bowel cleansing preparations in Schedule 3;
(c) schedule any of these products for use a laxative as S4; and
(d) include all three products in Appendix H of the SUSDP.

The June 2002 meeting noted that there was no need to consider items a.) and b) as the proposed outcomes were already in place. However, the Committee considered the information available at the meeting relating to item c) inadequate to warrant a decision and agreed that there was a need to examine the safety/risk profile and abuse potential of sodium picosulfate and macrogol 3350 for laxative use. Consequently, the Committee agreed to foreshadow the inclusion of sodium picosulfate and macrogol 3350 for oral laxative use in Schedule 4, and seek information from affected sponsors. The Appendix H proposal was not supported on the basis that the proposed indication, for oral use for bowel cleansing purposes, specified in Schedule 3 of the SUSDP was not appropriate to be advertised.

DISCUSSION

The Committee noted the following pre-meeting submissions:

- XXXXXXXXXXXXX opposed the foreshadowed inclusion of macrogol 3350 for the treatment of constipation in S4. It provided data to support what XXXXXXXXXXXXX claimed as excellent safety profile of PEG in comparison to osmotic or stimulant laxatives, and indicated that it was not aware of a single report, anecdotal or otherwise, of its product being abused.

- XXXXXXXXXXXXXX did not support the rescheduling of sodium picosulfate to S4, based on its safety profile and stated that scheduling was not the appropriate mechanism for dealing with issues of deliberate misuse.
- XXXXXXXXXXXXXX submitted that XXXXXXXXXXXXXX used for bowel cleansing purposes should remain as S3, and supported the rescheduling of sodium picosulfate and macrogol 3350 for laxative use to S4.
- XXXXXXXXXXXXXX opposed the inclusion of sodium picosulfate in S4 based on the safety data provided to demonstrate the favourable safety record of sodium picosulfate for laxative use in Australia and overseas, and its low potential for abuse. It proposed that its current unscheduled status be retained and that PEG 3350 be cross-referenced to macrogol 3350 in the index of the SUSDP for clarity.

The Committee noted that the evaluation report for the sodium picosulfate and PEG submissions stated that:

- The evaluator considered that whilst consistency of scheduling of laxatives was desirable on commercial and safety grounds, PEG, having a different mode of action and less electrolyte disturbance may not have common safety concerns seen with other osmotic agents. The safety dataset evaluated did not raise any specific issues or safety concerns in terms of electrolyte disturbance, severe gastrointestinal disturbance or misuse and the evaluator would view that this agent should be retained as unscheduled.
- XXXXXXXXXXXXXX which produced a sodium picosulfate laxative preparation XXXXXXXXXXXXXX provided periodic safety update reports (PSUR), which likewise did not reveal any consistent or worrisome trends with regard to misuse, electrolyte disturbance or severe gastrointestinal disturbance. However, the PSUR did report cases of more severe gastrointestinal disturbances but these were seen in patients receiving large doses for bowel preparation. On this basis, the evaluator considered that there were no unexpected or newly emergent adverse events with extensive use of sodium picosulfate as a laxative at low doses, and considered that there was no compelling need to change the current (unscheduled) listing.

The Committee noted the advice that the July 2001 Medicines Evaluation Committee (MEC) meeting recommended that the indication of laxative use for XXXXXXXXXX be deleted from their labelling and product literature, on the rationale that use of bowel evacuants for treatment of constipation was inappropriate. In addition, MEC also recommended that the sponsors of both products be advised to either delete all doses for other indications for children under 9 years from the labelling and product literature, or justify their specific recommended doses.

The Committee noted that the Adverse Drug Reactions Section in the Therapeutic Goods Administration (TGA) had advised that all adverse reports associated with macrogol 3350 and sodium picosulfate had been in the context of their use in bowel cleansing.

A member strongly disagreed with XXXXXXXXXXXXXX statement that scheduling was not the appropriate mechanism for controlling deliberate misuse of drugs and poisons.

OUTCOME

The Committee agreed that the unscheduled status of macrogol 3350 and sodium picosulfate for laxative use remained appropriate on the basis that:

- there were no adverse event reports in Australia associated with laxative use of macrogol 3350 and sodium picosulfate; and
- there was no evidence associating laxative use of these substances with electrolyte disturbance, severe gastrointestinal disturbance or misuse.

13.7 POLYACRYLAMIDE

PURPOSE

The Committee considered the foreshadowed inclusion of polyacrylamide in preparations for injection for tissue augmentation or cosmetic use in Schedule 4 of the SUSDP.

BACKGROUND

The June 2002 Meeting agreed to include polylactic acid in preparations for injection for tissue augmentation or for cosmetic use in Schedule 4 of the SUSDP. At this Meeting, the Committee was also advised of a new product containing polyacrylamide XXXXXXXXXXXXXX was available for use as dermal filler. The Committee foreshadowed the inclusion of polyacrylamide in Schedule 4 of the SUSDP in order to ensure involvement of a medical practitioner and thereby minimising potential hazards in its use.

DISCUSSION

The Committee noted that pre-meeting submissions had been received from the following:

- XXXXXXXXXXXXXX objected to the scheduling of polyacrylamide as a means to restrict the procedure of injection for cosmetic or tissue augmentation. The company stated that there was nothing to suggest that polyacrylamide, marketed as XXXXXXXXXXXXXX elicited adverse effects whether used by a medical professional or otherwise.
- The XXXXXXXXXXXXXX supported the scheduling of polyacrylamide.

The Committee reaffirmed its view that inclusion in Schedule 4 of injectable substances used for tissue augmentation or implantation purposes to enhance appearance should be

administered by medical professionals. Members recalled the concerns associated with use of such products by non-medically trained individuals including the use of incorrect injection techniques and inappropriate infection control procedures. The Committee also agreed that an appropriate level of patient follow-up and monitoring was essential to reduce the potential for adverse effects and severe late complications.

The Committee also recalled the issue raised at the June 2002 Meeting that use of these types of products by unqualified and unskilled persons could result in an under-reporting of any adverse events and therefore limit the ability of the manufacturer and regulatory bodies to become familiar with the adverse events associated with the product remained relevant.

The Committee noted the point highlighted by XXXXXXXXXXXXXX that substances used similarly to polyacrylamide could be implanted via a small incision and would not be covered by the proposed Schedule 4 entry for polyacrylamide in preparations for injection. Members agreed that to clarify the intent of the Schedule 4 entries for substances used for tissue augmentation or cosmetic use, it would be appropriate to separately specify "in preparations for injection or implantation".

DECISION 2002/36 - 16.

The Committee agreed to include polyacrylamide in preparations for injection or implantation for tissue augmentation or cosmetic use in Schedule 4 of the SUSDP on the basis that minimisation of the potential public health hazard associated with use of the product requires:

- professional examination and counselling prior to use;
- medical supervision of technique, procedures and siting during use; and
- medical monitoring of post-procedural outcomes, adverse effects and long term sequellae.

Schedule 4 - New entry

POLYACRYLAMIDE in preparations for injection or implantation:

(a) for tissue augmentation; or

(b) for cosmetic use.

13.8 RANITIDINE, CIMETIDINE, FAMOTIDINE AND NIZATIDINE

PURPOSE

The Committee considered the foreshadowed amendments to the Appendix F, Part 3 entries of the SUSDP for ranitidine, cimetidine, famotidine and nizatidine.

BACKGROUND

The June 2002 Meeting considered a proposal from XXXXXXXXXXXXXX, and agreed to foreshadow the following amendments to the Appendix F, Part 3 entries for ranitidine, cimetidine, famotidine and nizatidine, and inclusion of a requirement for a new warning statement (WS) 96.

- Delete WS 35, 68 and 69 in Appendix F, Part 3 for cimetidine, famotidine, nizatidine and ranitidine.
- Delete WS 70 in Appendix F, Part 3 for famotidine, nizatidine and ranitidine, but retain WS 70 for cimetidine.
- Include a requirement for WS 96 in Appendix F, Part 3 for cimetidine, famotidine, nizatidine and ranitidine.

Appendix F, Part 1 - New entry

96. CAUTION – This preparation is for the relief of minor and temporary ailments and should be used strictly as directed. If symptoms persist or recur within two weeks of completing the course, consult a doctor.

DISCUSSION

The Committee noted that comments had been received from the Medicines Evaluation Committee (MEC) relating to the foreshadowed amendment for ranitidine. MEC stated that the amendments proposed were inconsistent with MEC's recommendation of 2 May 2002, and that the words "of completing the course" were inappropriate for OTC products, given that they are intended for use for symptomatic relief rather than as a course of treatment. MEC suggested the revision of the wording of the proposed WS 96 to the following:

> *CAUTION: This preparation is for the relief of minor and temporary ailments and should be used strictly as directed. If symptoms persist or recur within two weeks, consult a doctor.*

The Committee noted that comments had also been received from XXXXXXXXXXXXXX relating to the foreshadowed amendments. XXXXXXXXXXXXXX agreed with the Committee's view of providing a more meaningful and simplified approach to labelling of ranitidine packs, which conveyed the message on how to use the product appropriately and directed consumers to consult a doctor when appropriate. However, XXXXXXXXXXXXXX was of the view that the proposed WS 96 was still potentially confusing to consumers because like WS 68, it was unclear whether it referred to treatment for 2 continuous weeks or a total of 2 weeks, given the episodic nature of the condition. XXXXXXXXXXXXXX highlighted that the term "course" was relevant when applied to antibiotic preparations where consumers understood that it is necessary to complete an entire course but this was considered

inappropriate for ranitidine for the treatment of the symptoms of heartburn and dyspepsia. XXXXXXXXXXXXX proposed the following revision of WS 96:

> "*This preparation is for the relief of minor and temporary ailments and should be used strictly as directed. Consult a doctor if symptoms persist after 14 days of continuous use*".

XXXXXXXXXXXXX indicated that it did not oppose the deletion of WS 35, 68, 69 and 70 for nizatidine in S2. However, the company had proposed the following revision of WS 96:

> *"CAUTION – This preparation is for the relief of minor and temporary ailments and should used strictly as directed. If symptoms recur within two weeks, consult a doctor."*

A Member stated that the revised Warning Statement 96 proposed by MEC was consistent with the intent of the warning statement adopted by New Zealand for these substances. Members noted that these products were intended for short-term use only and that if symptoms persisted or recurred within 2 weeks of treatment, then it would be appropriate to seek medical advice.

DECISION 2002/36 - 17.

The Committee agreed to amend the new WS 96 as proposed by MEC. This decision was made on the basis that this statement should convey clear directions to consumers on how to use the products correctly to when it would be appropriate to seek medical advice.

Appendix F, Part 1 - New entry

96. CAUTION – This preparation is for the relief of minor and temporary ailments and should be used strictly as directed. If symptoms persist or recur within two weeks, consult a doctor.

Appendix F, Part 3 – Amendments

Cimetidine – amend to read:

Cimetidine when included in Schedule 3.

Warning Statement……70, 96

Famotidine – amend entry to read:

Famotidine when included in Schedule 2.

Warning Statement……96

Nizatidine – amend entry to read:

Nizatidine when included in Schedule 2.

Warning Statement……96

Ranitidine – amend to read:

Ranitidine when included in Schedule 2.

Warning Statement……96

13.9 HYDROCORTISONE/CLOTRIMAZOLE

PURPOSE

The Committee considered post-meeting comments from XXXXXXXXXXXXXX concerning the June 2002 Meeting decision not to include hydrocortisone for dermal use in Appendix H of the SUSDP.

BACKGROUND

The June 2002 meeting considered XXXXXXXXXXXXXX 's proposal to permit its Schedule 3 combination product, containing 1% w/w hydrocortisone and 1% w/w clotrimazole, to be advertised. However, the Committee was not convinced that advertising the combination product of hydrocortisone and clotrimazole directly to the public would provide health benefits, on the grounds that this combination product was not an appropriate first-line treatment. The Committee was of the view that advertising could promote an inappropriate message to the public that this combination product was an appropriate first-line medication for the treatment of skin conditions that could be successfully treated by single active products.

DISCUSSION

The Committee was informed that there was no provision within the legislation for the NDPSC to consider a post-meeting comment when no amendment was made to the SUSDP at the previous meeting. However, to facilitate further consideration of this matter, the Committee agreed to treat XXXXXXXXXXXXXX 's comments as a new submission.

The Committee noted that XXXXXXXXXXXXXX stated that the hydrocortisone and clotrimazole combination product offered the pharmacist an additional option when treating minor fungal infections and the decision to use a combination product rather than a single-active antifungal agent as first-line therapy may not necessarily be the outcome after the patient was counselled. The company stated that it intended to prepare advertising material that would preserve the quality use of this combination product by encouraging the patient to discuss their skin condition with their pharmacist.

Furthermore, XXXXXXXXXXXXXX indicated that the pharmacist would be encouraged to recommend that their patient seek the advice of their local doctor for more serious fungal skin infections and that the package leaflet was being assessed for readability to ensure that patients knew how to use the combination product correctly.

The Committee concurred with XXXXXXXXXXXXXX 's viewpoint that hydrocortisone/ clotrimazole combination had a long history of safe use as a Schedule 4 medication and more than 2 years of safe use as a *Pharmacist Only Medicine*. Members also noted XXXXXXXXXXXXXX's advice that to date, there were no reported adverse events associated with this combination in the ADRAC database.

The Committee also noted XXXXXXXXXXXXXX had highlighted that a product containing 0.5% hydrocortisone and 2% miconazole nitrate (XXXXXXXXXXXXXX 0.5%) for similar indications to XXXXXXXXXXXXXX 's combination product was available in pharmacies as a Schedule 2 medication and could be advertised to the public.

The Committee recalled that members were concerned that advertising combination corticosteroid and anti-fungal preparations could promote inappropriate use as a first-line treatment. A Member advised the Committee that in New Zealand, corticosteroid in combination with an anti-fungal agent was the first choice treatment for certain skin conditions. The Member highlighted the inherent difficulty in correctly diagnosing the presence of fungal infections in skin conditions, particularly at the early stage of infection and that referring a patient to a doctor may not necessarily reduce this risk significantly.

A Member raised a query concerning the possible lodgement of repetitious submissions by sponsors in an attempt to overturn an undesirable outcome. The Committee clarified that any subsequent submissions by a sponsor should contain additional information that was not previously considered by the Committee and that may be relevant to the initial decision.

DECISION 2002/36 - 18.

The Committee accepted that there may be a potential public health benefit from advertising hydrocortisone cream (1% or less) or in combination with an antifungal as a first-line treatment for certain skin conditions and agreed to amend the existing Appendix H entry for hydrocortisone accordingly. The Committee was of the view that increased consumer awareness of the OTC availability of such products would assist discussion with the pharmacist on the treatment options available for a range of minor skin conditions.

Appendix H - Amendment

Hydrocortisone – amend entry to read:

Hydrocortisone.

14. PROPOSED CHANGES/ADDITIONS TO THE STANDARD FOR THE UNIFORM SCHEDULING OF DRUGS AND POISONS.

14.1 SUSDP, PART 4

14.1.1 FLURBIPROFEN

PURPOSE

The Committee considered the scheduling of flurbiprofen lozenges.

BACKGROUND

Flurbiprofen is a propionic derivative NSAID, which is structurally related to ibuprofen. It is used in daily doses of 150 mg to 300 mg primarily for the chronic treatment of musculoskeletal and rheumatic conditions, for dysmennorhoea and post-operative pain. In Australia, flurbiprofen is available in lozenges for treatment of sore throats (S3) and in eye drops for treatment of intraoperative miosis (S4).

The November 1993 meeting agreed to include flurbiprofen in Schedule 4 of the SUSDP and subsequently, flurbiprofen in divided preparations for topical oral use containing 10 mg or less of flurbiprofen per dosage unit was rescheduled from S4 to S3 at the February 2000 meeting. The May 2000 meeting agreed to include flurbiprofen in Appendix H of the SUSDP.

DISCUSSION

XXXXXXXXXXXXXX submitted an application to reschedule its product, XXXXXXXXXXXXXX lozenges, containing 8.75mg flurbiprofen per dosage unit from Schedule 3 to Schedule 2. The company provided the following points in support of its proposal:

- The local post-marketing experience confirmed that no new safety issues were likely to occur when XXXXXXXXXXXXXX was used in the non-prescription setting.
- Concerns about potential overuse and possibility of systemic side effects following use of the product were unwarranted on the basis of the self-limiting nature of the condition and the low daily dose of flurbiprofen. In addition, the pack size (140-210 mg) would deliver less flurbiprofen than the daily dose used in the chronic setting (200-300 mg).
- There was more than three years of post-marketing experience since flurbiprofen lozenges were first available without prescription in February 1999, and there had been no safety concerns or evidence of abuse/misuse associated with the product over this period.
- Sore throat was a common ailment that was usually treated by self-medication in the first instance. The availability of XXXXXXXXXXXXXX in S2 would provide

consumers with an additional product for the treatment of sore throat with proven safety and efficacy.

The Committee noted from the evaluation report that:

- Flurbiprofen, when administered in the form of lozenges, was well absorbed but produced very low plasma concentrations because of the low unit dose of oral lozenges compared with internal oral dose forms. It had a very low to absent potential for abuse, drug interactions, or masking of serious disease states.
- The indication for use of flurbiprofen lozenges (symptomatic relief of sore throat) was suitable for self-identification and treatment without professional advice.
- Use in Australia and New Zealand as Pharmacist-only medicines had been associated with an excellent safety profile, and there was no expectation that a shift to Schedule 2 would result in any additional problems.
- There was reasonable marketing experience within Australia (about XXXXXXXXXXXXXX and XXXXXXXXXXXXXX lozenges) and overseas (XXXXXXXXXXXXXX lozenges). The spontaneous reporting rate of adverse events had been very low, with the exception of difficulties with the taste of the lozenges. Post-marketing surveillance suggested that the lozenge formulation was very safe in over the counter use.
- The evaluator recommended that, provided the NDPSC was comfortable with waiving the usual requirement for 2 years of local marketing before rescheduling was approved, XXXXXXXXXXXXXX lozenges containing flurbiprofen 8.75 mg be moved from Schedule 3 to Schedule 2.

The XXXXXXXXXXXXXX indicated in its pre-meeting comments that the appropriate schedule for flurbiprofen lozenges was S3, on the basis that the product was not appropriate for self-selection.

The Committee expressed concern with regard to the potential contraindications associated with flurbiprofen, particularly with its use in patients with asthma. Members noted that the proposed primary pack and consumer medicine information (CMI) leaflet provided by the sponsor for XXXXXXXXXXXXXX lozenges, clearly carried a warning relating to use of the product by asthma suffers.

DECISION 2002/36 - 19.

The Committee agreed to amend the SUSDP to include flurbiprofen for oral topical use containing 10mg or less of flurbiprofen per dosage unit in Schedule 2 of the SUSDP. This decision was made on the basis that the post-marketing safety data provided demonstrated that the product has a very low potential for causing adverse effects, there was no evidence of abuse or misuse and the product meets the requirements for inclusion in Schedule 2.

Schedule 2 - New entry

FLURBIPROFEN in divided preparations for topical oral use containing 10mg or less of flurbiprofen per dosage unit.

Schedule 3 – Amendment

FLURBIPROFEN – delete entry

Schedule 4 - Amendment

FLURBIPROFEN – amend entry to read:

FLURBIPROFEN **except** when included in Schedule 2.

Appendix H - Amendment

FLURBIPROFEN – delete entry

14.1.2 ACETYLCYSTEINE

PURPOSE

The Committee considered the scheduling of acetylcysteine in dietary supplements.

BACKGROUND

Acetylcysteine is the acetylated derivative of the amino acid, cysteine. Cysteine is commonly found in a wide variety of foods, and acetylcysteine is readily metabolised to this form. Acetylcysteine is a mucolytic agent used in the treatment of pulmonary diseases associated with increased viscosity of bronchial secretions. Acetylcysteine is effective and widely used in paracetamol poisoning and it was also recommended as a second line agent in acrylonitrile and methacrylonitrile poisonings. Acetylcysteine was included as an excipient in products such as protective antioxidant crème/lotion and non-sterile contact lens care preparations.

The August 2000 Meeting agreed to include carbocysteine in Schedule 2 of the SUSDP on the grounds of harmonisation. Subsequently, the November 2000 meeting included oral formulations containing acetylcysteine in Schedule 2 of the SUSDP on the same grounds, but retained injectable and inhalational formulations in Schedule 4. This meeting also noted the availability of many cysteine-based dietary supplements in Australia and that acetylcysteine was readily metabolised to this form.

DISCUSSION

XXXXXXXXXXXXXX submitted a proposal to exempt acetylcysteine from the requirements of scheduling when taken orally and used in preparations as an antioxidant

in “sports supplement” type products. The following points were raised in support of XXXXXXXXXXXXX 's proposal:

- XXXXXXXXXXXXX was planning to market an oral supplement XXXXXXXXXXXXX that utilised the increased glutathione production associated with acetylcysteine supplementation, containing 500 mg of N- acetylcysteine per tablet and with a maximum recommended daily dose of 2 tablets. This form of supplement had been on sale in the United States by XXXXXXXXXXXXX since 1999, and over XXXXXXXXXXXXX kg of this substance had been sold.
- Following a safety assessment of the toxicological data, the applicant believed there was no justification for the Schedule 2 restriction on acetylcysteine when used in XXXXXXXXXXXXX supplements as an antioxidant. It was stated that the concerns related to the safety of use of acetylcysteine in specific medical cases, i.e. diabetes and asthma, although not associated with its use as an XXXXXXXXXXXXX would be more appropriately addressed through label warnings.
- The rationale for the scheduling of oral forms of acetylcysteine appeared to be based on cough and cold medications in New Zealand, and did not appear to deliberately restrict its use in dietary supplements as an XXXXXXXXXXXXX. Therefore, use in dietary supplements for XXXXXXXXXXXXX properties should be exempt from scheduling.

The Committee noted the following points raised in the evaluation report:

- Intravenous acetylcysteine was indicated for paracetamol overdose while inhaled acetylcysteine was indicated for its mucolytic effects in conditions such as cystic fibrosis. Both products were Schedule 4 medicines. Oral acetylcysteine available in some cough and cold preparations was available under Schedule 2 and the oral dose of acetylcysteine proposed by the sponsor was 500mg bd.
- Oral acetylcysteine has approximately 10% bioavailability due to first-pass metabolism in the liver, with the major metabolites being cysteine and inorganic sulfite. The major biochemical actions of acetylcysteine are to replace glutathione levels and act as an antioxidant *in vitro*.
- High doses of IV acetylcysteine as used in paracetamol overdose were associated with nausea, vomiting and rarely, allergic and anaphylactic reactions. This could include bronchospasm, which was also associated with inhaled acetylcysteine.
- Animal LD_{50}s for acetylcysteine were approximately 6g/kg in rats, 1g/kg in dogs and 3g/kg in mice and it was suggested from the literature that a likely lethal human dose was 5-15g/kg (10-30 x 500mg tablets). Safety databases suggested no worrisome adverse event profiles with use as an oral supplement as available in the USA since 1992.
- Acetylcysteine may cross the placenta during pregnancy. Although data were inconclusive on this point, it was reasonable to include pregnancy as a contraindication to use of this substance.

- Higher oral doses of acetylcysteine (93g over a 3 day period) for paracetamol overdose had been associated with high incidences of nausea, vomiting and diarrhoea. Lower doses (as proposed) were associated with mostly mild gastrointestinal events usually not requiring treatment interruption.
- The antioxidant properties of oral acetylcysteine demonstrated largely *in vitro* may not translate into the human *in vivo* situation. There was evidence to suggest that in otherwise healthy individuals, doses as low as 1.2 g/day acetylcysteine might actually act as a pro-oxidant and lowered reduced glutathione and increased oxidised glutathione (Kleinveld *et al* Eur. J. Clin. Pharmacol. 1992;43:639-642).
- There was no data provided relating to the potential for overdose with oral acetylcysteine, although care would be needed if used to enhance sports performance and if made available for general sale as a sports supplement.
- Oral acetylcysteine up to 1g per day as proposed should not raise any significant safety concerns based on extensive over-the-counter use in the United States at this dosage level. The evaluator considered it reasonable to de-schedule this item with the following provisos:

    (a) An appropriate warning for non-use during pregnancy be included.
    (b) Mild nausea, vomiting or diarrhoea may occur and should be reported to a pharmacist or medical practitioner if this occurs.
    (c) The dosing regimen be strictly not exceeded (because of the unknown risk of misuse due to enhanced expectations).
    (d) Due to inconclusive evidence of *in vivo* antioxidant benefit in otherwise healthy humans, no claim for antioxidant or associated sports performance recovery should be made.

The Committee noted the evaluator's provisos but did not consider 'reverse scheduling' to be appropriate in this case.

The Committee noted that there were 2 existing products listed on the ARTG containing acetylcysteine as active ingredient. One product was XXXXXXXXXXXXX injection ampoule containing 2 g/10mL of acetylcysteine for use as antidote for paracetamol poisoning. The other was XXXXXXXXXXXXX inhalation vial containing 200 mg/mL (20%) for use as mucolytic in bronchopulmonary disease or as an adjunct to diagnostic bronchial studies, tracheostomy or anaesthesia. The Committee also noted that the recommended dosage listed in Martindale for acetylcysteine when used orally as a mucolytic was 600 mg daily in 1 to 3 divided doses for adults and adolescents over 14 years of age.

A Member noted that the Food Standards Code did not allow acetylcysteine as an additive to sports foods and that the anti-oxidant effect of acetylcysteine was yet to be proven in humans. Members also noted that whilst foods were exempt from the requirements of scheduling by virtue of the Appendix A entry, additives to food were not.

Members proposed to allow a cut-off in the Schedule 2 entry for acetylcysteine to exempt oral preparations with a recommended daily dose of 1g or less, based on acetylcysteine's

safety profile at this dosage level. The Committee recognised that there were other mechanisms in place which would regulate the use of acetylcysteine in foods or medicines, i.e. Food Standards Australia New Zealand (FSANZ) or the Therapeutic Goods Administration (TGA), respectively.

DECISION 2002/36 - 20.

The Committee agreed to amend the Schedule 2 entry for acetylcysteine to exempt oral preparations labelled with a recommended daily dose of 1g or less of acetylcysteine, on the basis of the safety data provided and long history of safe OTC use overseas at this dosage level.

Schedule 2 – Amendment

ACETYLCYSTEINE – amend entry to read:

ACETYLCYSTEINE in preparations for oral use **except** when labelled with a recommended daily dose of 1 g or less acetylcysteine.

Schedule 4 – Amendment

ACETYLCYSTEINE – amend entry to read:

ACETYLCYSTEINE **except**:

(a) when included in Schedule 2; or

(b) in preparations for oral use when labelled with a recommended daily dose of 1 g or less of acetylcysteine.

14.1.3 MACROGOL 3350, SODIUM PHOSPHATE AND SODIUM PICOSULFATE

PURPOSE

The Committee considered the proposed editorial amendment for macrogol 3350, sodium phosphate and sodium picosulfate.

BACKGROUND

An editorial amendment was proposed by the Secretariat to make the wording of the Schedule 3 entry for all substances for oral use for bowel cleansing purposes consistent. The following were the entries for macrogol 3350, sodium phosphate and sodium picosulfate in Schedule 3 of the SUSDP.

MACROGOL 3350 in preparations for oral use for bowel cleansing purposes.

SODIUM PHOSPHATE in oral preparations for bowel cleansing prior to diagnostic, medical and surgical procedures.

SODIUM PICOSULFATE in preparations for oral use for bowel cleansing prior to diagnostic medical and surgical procedures.

The existing entry in S3 for sodium phosphate specifying "in oral preparations for bowel cleansing prior to diagnostic, medical and surgical procedures " was harmonised with New Zealand.

DISCUSSION

The Committee was of the view that it would be appropriate to amend the entries for sodium phosphate and macrogol 3350 to be consistent with the entry for sodium picosulfate and to clarify the initial intent of the entries.

DECISION 2002/36 - 21.

The Committee considered the wording of the sodium picosulfate entry promoted clarity and clearly reflected the intent of the Committee. The Committee agreed to amend the entries for sodium phosphate and macrogol 3500 editorially to reflect the wording used in the sodium picosulfate entry.

Schedule 3 – Editorial Amendments

MACROGOL 3350 – correct entry to read:

MACROGOL 3350 in preparations for oral use for bowel cleansing prior to diagnostic medical and surgical procedures.

SODIUM PHOSPHATE – correct entry to read:

SODIUM PHOSPHATE in preparations for oral use for bowel cleansing prior to diagnostic medical and surgical procedures.

14.1.4 BUDESONIDE

PURPOSE

The Committee considered additional safety data submitted XXXXXXXXXXXXXX in support of a budesonide rescheduling proposal.

BACKGROUND

The February 2002 Meeting considered a proposal from XXXXXXXXXXXXXX to reschedule intranasal budesonide for the treatment of perennial allergic rhinitis (PAR) from S4 to S3. However, the Committee was of the view at the time that the following

issues needed to be resolved and asked that additional information be sought from the applicant:

- Potential for development of steroid-type side effects.
- Potential for development of local safety problems including nasal sepsis or perforation development.
- Data on rates of spontaneously reported Cushing's syndrome.

DISCUSSION

The Committee noted the additional information provided by XXXXXXXXXXXXXX addressing the Committee's concerns relating to the long-term safety of budesonide intranasal spray for PAR as a Schedule 3 product. The submission highlighted the following points:

- The company's Periodic Safety Update Reports (PSURs) for the period of April 1995-April 2001 covering all intranasal budesonide presentations did not raise any new safety issues or identify any areas for concern, and no cases relating to abuse or misuse of the substance was reported during post-marketing surveillance.
- The majority of local reactions were mild and transient. Reported adverse events were included in the consumer documentation, with recurrent epistaxis. The potential for nasal corticosteroids to cause septum perforation could not be fully discounted as contemporary use of intranasal steroids including XXXXXXXXXXXXX, had been associated with the occurrence of septal perforations in rhinitis patients. However, nasal septum perforation as a potential adverse effect was addressed in the consumer medicine information (CMI) leaflet.
- Only 1 case (non-serious) of Cushing's syndrome and 1 case (non-serious) of Cushingoid-like symptoms was reported during the 5-year post-marketing surveillance period, of which both had other potential causative factors reported (oral and inhaled steroid use).
- Intranasal budesonide was already regulated as S3 medication for the short-term prophylaxis and treatment of seasonal allergic rhinitis (SAR) for presentations that met the existing SUSDP criteria. In addition, evidence had shown that the majority of allergic rhinitis (AR) sufferers had been self-medicating with OTC preparations, including those with PAR.
- The proposed S3 intranasal budesonide presentation for PAR would cover the same age groups, presentations, maximum daily dose, maximum treatment duration and other warnings as those stated for SAR.
- It was proposed that a precaution similar to that put forward by the Sponsor of beclomethasone/fluticasone, i.e "should symptoms recur or become aggravated at any time during the course of treatment, the consumer should be directed to seek medical attention". Furthermore, intranasal budesonide used by patients to self-medicate both PAR and SAR should be controlled via the precautions/directions on the S3 labelling:

- To a maximum daily dose of 254 µg.
- Advice to down titrate to the lowest effective dose.
- Restricted to no more than 6-months treatment without medical advice.
- The patient will be advised to seek medical advice if:
  * symptoms persist for more than 7 days;
  * symptoms recur or become aggravated at other times; and
  * they develop specific adverse events.

- The existing intranasal budesonide product was reformulated to have a lower daily dose, thus decreasing the risk of side effects.
- XXXXXXXXXXXXXX also proposed that the product be allowed to be advertised under the existing Appendix H entry, if budesonide for PAR was approved as S3.

The Committee noted the following from the evaluation report:

- Long-term nasal biopsy studies and post-marketing data provided did not indicate any increased risk of mucosal atrophy and no issues relating to overdose or misuse of intranasal budesonide were noted in the PSURs.
- There were 2 cases of adrenal insufficiency and 7 cases of growth retardation from 1995 to 2001 in relation to XXXXXXXXXXXXX patient treatment days from international launch in 1986 to April 2002. In addition, there were 2 reported cases of Cushingoid features compounded by co-medication of inhaled and oral corticosteroids.
- In summary, the post-marketing data surveillance showed acceptably low local and systemic corticosteroid adverse events and no additional concerning or unexpected trends beyond those already recognised.
- The evaluator recommended that intranasal budesonide be listed in Schedule 3 to include the indication of perennial allergic rhinitis and that this indication be also allowed for in the current inclusion in Appendix H.

The Committee noted the pre-meeting submission from the XXXXXXXXXXXXX which stated that it was aware of on-going concerns particularly with possible growth suppression in children with long term use although no data was provided. The XXXXXXXXXXXXX proposed that a referral to a specialist be considered when treatment longer than 6 weeks was contemplated.

The Committee noted the pre-meeting submission from XXXXXXXXXXXXX which stated that Schedule 3 was appropriate for intranasal preparations for the treatment of allergic rhinitis. However, extending the S3 listing to allow use in children under 12 years of age was not supported.

The Committee noted that the current age limit of 12 years remained appropriate and that the existing Appendix H entry already allowed budesonide preparations included in Schedule 3 to be advertised, therefore no further action was required.

Members considered XXXXXXXXXXXXXX's proposal for a warning statement on the product label and noted that there were no entries in Appendix F for any of the intranasal corticosteroids. The Committee agreed that the warning statement proposed by XXXXXXXXXXXXXX ("If symptoms persist for more than 7 days, consult your doctor") be referred to the Medicines Evaluation Committee (MEC) for comment noting that this warning was already included in the Consumer Medicine Information (CMI) leaflet.

The Committee considered it appropriate to specify "for up to 6 months" in the schedule entry to clarify the intended short-term use of this product unless otherwise directed by a medical practitioner. Members noted that this approach was consistent with that adopted for other intranasal corticosteroids.

DECISION 2002/36 - 22.

The Committee agreed to amend the Schedule 3 entry for budesonide and extend the indications to include perennial allergic rhinitis (PAR). This decision was made on the basis of the submitted post-marketing safety data and that no safety issues were expected to arise from the short-term use of intranasal budesonide for the prophylaxis or treatment of allergic rhinitis.

Schedule 3 - Amendment

BUDESONIDE – amend entry to read:

BUDESONIDE in aqueous nasal sprays delivering 50 micrograms or less of budesonide per actuation when the maximum recommended daily dose is no greater than 400 micrograms and when packed in a primary pack containing 200 actuations or less, for the short-term prophylaxis or treatment of allergic rhinitis for up to 6 months in adults and children 12 years and over.

14.1.5 MOMETASONE

PURPOSE

The Committee considered the proposal to include mometasone for the treatment of allergic rhinitis (AR) in Schedule 3 of the SUSDP.

BACKGROUND

Mometasone is a topical glucocorticosteroid with local anti-inflammatory properties at doses that are not systemically active. In addition to its use in nasal sprays, it is also marketed for dermatological use in cream, ointment and lotion formulations and for the prophylactic treatment of asthma via inhaler.

Mometasone in aqueous nasal spray for the short-term prophylaxis or treatment of seasonal allergic rhinitis (SAR) in adults and children 12 years and over, was rescheduled

from S4 to S3 in November 1999. This was restricted to products delivering 50 µg or less of mometasone per actuation when the maximum recommended daily dose is no greater than 200 µg and when packed in a primary pack containing 200 actuations or less. The May 2000 Meeting agreed to include mometasone in Appendix H of the SUSDP.

DISCUSSION

XXXXXXXXXXXXXX submitted an application to extend the indications for mometasone in Schedule 3. The sponsor highlighted the following points in support of its proposal:

- The symptoms of AR are readily identifiable by both patients and parents, and proper use would be controlled through pharmacy supervision of sales. In most cases, it was likely that patients would have presented to a medical practitioner for an initial diagnosis.
- Mometasone furoate undergoes extensive first pass hepatic metabolism and has an extremely low systemic bioavailability following intranasal administration (≤0.1%). Therefore, the potential for systemic toxicity would be very low.
- Extensive trials assessing the efficacy and safety of mometasone furoate for the treatment of perennial allergic rhinitis (PAR) had been conducted in adults and children indicating that there had been no evidence of harmful effects when used for up to 12 months.
- There was no evidence of hypothalamic-pituitary-adrenal (HPA)-axis suppression, untoward side effects on the nasal mucosa or deleterious ocular effects following the long-term administration of intranasal mometasone in adults and adolescents (≥12 years). Similarly, in children aged 3-11 years, there was no evidence of HPA-axis suppression and growth retardation following treatment of AR with mometasone furoate for up to 12 months.
- Intranasal mometasone had been marketed internationally since 1997 and in Australia from 1999. Assessment of long-term safety studies and significant post-marketing experience revealed a low incidence of adverse events following prolonged treatment.
- Extensive clinical trials in children (3-11 years) had shown that intranasal mometasone was safe and effective treatment for AR when used for up to 12 months. This patient population did not have adequate access to intranasal preparations and the availability of mometasone as an S3 medicine for paediatric use would allow an effective, once-daily management of allergic rhinitis, under parental and pharmacist supervision.
- Additional data was provided informing that the US FDA had recently approved the use of intranasal mometasone furoate in children from 2 years of age for SAR and PAR.

The Committee noted the following points from the evaluation report:

- Local adverse events in adults and children predominated and were not substantially different to those seen with placebo or active comparators in the clinical trials dataset.
- Mometasone furoate did not show any evidence of misuse and showed a very low incidence of adverse events in extensive adult and paediatric use although the degree of exposure in children since marketing was not clearly discernible from the periodic safety update report (PSUR) provided.
- There was no evidence of HPA axis suppression or growth effects in children aged 3-11 years of age and the product had been available as a Schedule 4 medication for this age group since 1999. There were no reports of excess use or misuse in this younger age group, presumably because use in this age group would require supervision by a parent or carer.
- The evaluator recommended, based on the data provided, that the indication for use in adults and adolescents in Schedule 3 be extended to include PAR. In addition, the extension to include use in children aged 3-11 years was also recommended for inclusion in Schedule 3.

XXXXXXXXXXXXXX stated in its pre-meeting submission that it was aware of on-going concerns particularly with possible growth suppression in children with long term use and asked the Committee to consider its recommendation of referral to and review by a specialist where treatment of longer than 6 weeks was contemplated. However, no data to support this claim was submitted.

XXXXXXXXXXXXXX stated in its pre-meeting submission that it recommended Schedule 3 as the appropriate schedule for intranasal preparations for the treatment of allergic rhinitis, but extending the S3 listing to allow use in children under 12 years of age was not supported.

The Committee noted that whilst there was no evidence of HPA axis suppression in the cumulative PSUR summary provided to suggest adverse event profiles beyond those already recognised from the clinical studies, it did not provide a breakdown of the total sales volume for the 3-11 years age group vs adverse events noted. Such information is required to fully characterise the risk of adverse events in this age group. A similar difficulty was noted with the Australian data provided. The Committee agreed that the sponsor should be given the opportunity to clarify this matter.

A Member highlighted a concern that whilst diagnosis of SAR and PAR in adults and adolescents could be adequately managed by a pharmacist, diagnosis in children aged 3-11 years may be difficult. The member stated that it may be more appropriate for a small child to be fully assessed by a medical professional for diagnosis of AR in the first instance and to be followed by advice on treatment options, if appropriate.

Other members shared the same concerns and suggested that advice should be sought on the suitability of intranasal mometasone as S3 medication for AR in the 3-11 age group. The Committee agreed to seek expert advice on the matter from the Medicines Evaluation

Committee (MEC), Australian Drug Evaluation Committee (ADEC), Australian Society for Clinical Immunology and Allergy, and Australian Paediatric Endocrinology Group, particularly in relation to the following issues:

- The need for initial diagnosis or assessment by a medical professional before administration of intranasal mometasone in children <12 years of age for the prophylaxis or treatment of AR.
- Potential for growth suppression with long-term use given the chronicity of AR.
- Is there a need for on-going management of treatment by a medical practitioner?

The Committee considered it appropriate to specify "for up to 6 months" in the schedule entry to clarify the intended short-term use of this product unless otherwise directed by a medical practitioner. Members noted that this approach was consistent with that adopted for other intranasal corticosteroids.

OUTCOME

The inclusion in Schedule 3 of intranasal mometasone for the short-term prophylaxis and treatment of AR in children aged 3-11 years was deferred to a future meeting pending expert advice.

The Committee was of the view that there was sufficient data to reassure members of the suitability of intranasal mometasone for the short-term prophylaxis or treatment of allergic rhinitis in adults and children over 12 years. However, the Committee was not fully assured of the appropriateness of intranasal mometasone for AR as a Schedule 3 medication for the 3-11 years age group.

DECISION 2002/36 - 23.

The Committee agreed to extend the indication for mometasone in Schedule 3 to include for the short term prophylaxis or treatment of perennial allergic rhinitis in adults and children over 12 years. This decision was based on the adequate safety data provided which showed that intranasal mometasone for such indication has a good safety profile and very low potential for adverse effects when used at the recommended dosage.

Schedule 3 - Amendment

MOMETASONE – amend entry to read:

MOMETASONE in aqueous nasal sprays delivering 50 micrograms or less of mometasone per actuation when the maximum recommended daily dose is no greater than 200 micrograms and when packed in a primary pack containing 200 actuations or less, for the short-term prophylaxis or treatment of allergic rhinitis for up to 6 months in adults and children 12 years and over.

14.1.6 IBUPROFEN

PURPOSE

The Committee considered a proposal to exempt ibuprofen in preparations for topical use from the requirements of scheduling.

BACKGROUND

Ibuprofen, a propionic acid derivative, is a non-steroidal anti-inflammatory drug (NSAID). Ibuprofen is used in the management of mild to moderate pain and inflammation in conditions such as dysmenorrhoea, headache including migraine, post-operative pain, dental pain, musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis including juvenile idiopathic arthritis, peri-articular disorders such as bursitis and tenosynovitis, and soft-tissue disorders such as sprains and strains. It is also used to reduce fever. Its anti-inflammatory properties may be weaker than those of some other NSAIDs.

XXXXXXXXXXXXXX containing 5% ibuprofen (50 mg/g) was approved by the Medicines Evaluation Committee (MEC) in mid- 2001, and marketed since January 2002 as a Schedule 2 medicine. XXXXXXXXXXXXXX marketed by XXXXXXXXXXXXXX, has been available for more than 18 months in New Zealand and 6 months in Australia. However, other ibuprofen gels, which are of identical formulation to XXXXXXXXXXXXXX have been marketed in the UK, Ireland, Spain, Belgium and France, since 1991.

DISCUSSION

XXXXXXXXXXXXXX submitted an application to exempt ibuprofen for dermal use from scheduling. This proposal was intended to accommodate the product XXXXXXXXXXXXX. The sponsor provided the following justification for its proposal:

- Other NSAIDs with similar toxicity profiles were exempt from scheduling (i.e. diclofenac and piroxicam).
- Internal preparations of ibuprofen have a comparable or better risk/benefit ratio compared to internal NSAID formats. In addition, external preparations containing ibuprofen had a comparable risk/benefit ratio to diclofenac and piroxicam.
- There was no evidence of increased risk to consumers through the availability of external preparations of ibuprofen as unscheduled medicines.
- Topical ibuprofen preparations had been available as unscheduled medicines in overseas markets for considerable time where the overall incidence of adverse events was low and associated mainly with local skin reactions which were minor and transient.

The Committee noted from the evaluation report of the company's submission:

- Ibuprofen has a very low systemic bioavailability when administered topically and causes very few adverse effects. It had a very low to absent potential for abuse.
- The indication for topical administration of ibuprofen was suitable for self-identification and treatment without professional advice.
- Topical piroxicam and diclofenac products had been exempt from scheduling for approximately 2 years with no significant safety issues arising during that time. It would be unlikely that exempting topical ibuprofen from scheduling would cause any additional clinical problems, as it was used for the same indication as diclofenac and piroxicam.
- The requirement for 2 years local clinical use could be waived as there was a long marketing history of oral ibuprofen in Australia (first introduced in XXXXXXXXXXXXXX and the international post-marketing experience with an identical formula was considerable (XXXXXXXXXXXXXX sold in the UK with only 60 adverse events reported).
- The evaluator supported XXXXXXXXXXXXXX's proposal and recommended that ibuprofen be exempted from scheduling for topical use.

The Committee noted that ibuprofen has a very good safety record, has low systemic bioavailability when used topically (approximately 5%) and the clinical trials showed few adverse events when used topically. The Committee also noted a lack of potentially serious adverse events following overseas post-marketing experience with topical ibuprofen.

The Committee recognised that as a topical product, ibuprofen had a low potential for abuse and misuse, and noted that the product information (PI) included contraindications concerning use in the presence of asthma or allergies. Furthermore, the Committee acknowledged that ibuprofen was indicated for the treatment of minor ailments that could be diagnosed and treated by consumers safely without the need for counselling by a pharmacist. This supported the proposal for the product to become exempt from scheduling.

DECISION 2002/36 - 24.

The Committee agreed to exempt ibuprofen for external use from the requirements of scheduling on the basis of available safety data. Noting that ibuprofen for external use was for minor ailments, that were easily diagnosed and treated by consumers, without the need for pharmacist advice.

Schedule 2 - Amendment

IBUPROFEN – amend entry to read:

IBUPROFEN in preparations for oral use when labelled with a recommended daily dose of not more than 1200mg of ibuprofen:

(a) in divided preparations in packs of 100 or less dosage units each containing 200mg or less of ibuprofen; or

(b) in liquid preparations when sold in the manufacturer's original pack each containing 4 grams or less of ibuprofen.

Schedule 4 - Amendment

IBUPROFEN – amend entry to read:

IBUPROFEN **except**:

(a) when included in Schedule 2; or

(b) in preparations for dermal use.

14.1.7 OXEDRINE

PURPOSE

The Committee considered the scheduling of oxedrine.

BACKGROUND

Oxedrine (syn. synephrine) is a sympathomimetic amine occurring naturally in some Citrus species including *Citrus aurantium*, *Citrus sinensis* and *Citrus limon*, and in some cacti, e.g. *Coryphantha macromeris* and *Dolichotele* spp. Oxedrine has a similar pharmacology to ephedrine but is devoid of central nervous system (CNS) effects. The vasoconstrictor effect of synephrine is known to be due to activation of α-adrenoceptors.

The February 2002 meeting noted that there was a significant number of products being sold on the Internet containing *Citrus aurantium* and extracts from various parts of the bitter orange plant. Products containing oxedrine available on the Internet include supplements stated to support metabolism, burn body fat, and aid weight loss. Accordingly, the February 2002 meeting agreed to refer the matter to OCM for investigation, as it appeared that such products were illegally supplied as therapeutic goods.

DISCUSSION

The NDPSC noted the Minute received from OCM highlighted the following:

- There were approximately 1000 complementary products listed on the ARTG containing three herbal species, i.e. *Citrus aurantium, Citrus sinensis* and *Citrus limon*, that were reported to contain synephrine from various parts of the plant.

- It was not always clear from the literature which plant part(s) contained synephrine, and/or whether the synephrine was removed during preparations of the final medicinal product (degree of extraction).
- *Citrus aurantium*, *Citrus sinensis* and *Citrus limon* were considered suitable for use in Listed *medicines*.
- A comprehensive estimate of the concentration of synephrine in the products *per se* had not been made, but for indicative purposes, the possible amount of synephrine in the recommended daily dose ranges from 2 μg to over 31 mg. The amount of synephrine in individual products will depend, *inter alia*, on the plant part used, the degree of concentration in the extract and the amount of herbal material used in the product formulation.
- It should be noted that these herbs are also eaten as foods.

The Committee noted the following pre-meeting comments received:

- XXXXXXXXXXXXXX indicated an interest in the scheduling of oxedrine should there be any impact on complementary medicines. XXXXXXXXXXXXX provided a paper entitled "Determination of synephrine from Chinese medicinal drugs originating from *Citrus* species by ion-pair high performance liquid chromatography".
- XXXXXXXXXXXXXX stated that it was appropriate for oxedrine to be considered in the context of the current scheduling of phenylephrine (S4 – in preparations for injection and in preparations for human ophthalmic use containing 5 % or more of phenylephrine).
- XXXXXXXXXXXXXX had advised that according to published research the synephrine content in Chinese raw herb is approx. 0.56%, and that 3-10 g. of *Citrus aurantium* contained between 5-20 mg of synephrine. The common dosage of *Citrus aurantium* was stated to be between 3-10 g, although for some specific purposes dosages of up to 15 g were being used. XXXXXXXXXXXXXX had indicated that there were at present a large number of listed Chinese medicine products that may be affected by the proposed scheduling of oxedrine and the Committee had been urged to take these aspects into consideration.
- XXXXXXXXXXXXXX had stated that based on studies provided, a 10:1 extract of the plant material could contain up to nearly 6% synephrine (if 10:1 extract, hypothetically approx. 10X native content) and that typical extracts contain from 3% (Pellati et al, personal experience), but the concentration was increasing with demand. The submission had argued that *Citrus aurantium* fruit rind and extracts had a genuine place in Listed medicines and that extracts not complying with the legislated interpretation of a 'herbal substance' should be controlled at the TGA Compliance Branch interface, not by the SUSDP. In addition, it was stated that any SUSDP recommendation should not be based on the original plant material (e.g. orange oil, culinary orange peel), and the entry be phrased in such a way that it avoided netting TCM formulations and extracts compliant with the TG Act interpretation of 'herbal substance'.

The Committee was informed that the 31st edition of Martindale stated that oxedrine as the tartrate was given in the treatment of hypotensive states in doses of about 100 mg three times a daily by mouth. Additionally, it was noted that one weight loss product available on the Internet called XXXXXXXXXXXXX could potentially contain up to 240 mg or more of synephrine (extract equivalent to 6000 mg of dried fruit with assumption that the product contained a standardised extract containing 4% synephrine) per tablet, with a recommended dose of 2 tablets per day.

The Committee noted that a published literature entitled "Antiobesity and cardiovascular toxic effects of *Citrus aurantium* extracts in the rat: a preliminary report" (Gioacchino Calapai *et al*.), reported that acute administration through venous infusion of doses of a *C. aurantium* fruit extract (1.25-5 mg/kg) elevated the mean arterial pressure by way of arterial vasoconstriction. It was stated that the changes to blood arterial pressure were not observed after repeated oral administration (2.5-20 mg/kg, p.o. of 4% and 6% standardised fruit extracts). However, the paper had stated that whilst repeated administration (up to 15 consecutive days) of *C. aurantium* fruit extracts had produced a reduction in food consumption in the treated rats, significant pathological changes in electrical activity of the myocardium had been observed. It concluded that since it was not possible to exclude the appearance of cardiovascular toxicity after treatment with *C. aurantium* extracts in humans, their utilisation as antiobesity herbal medicine was in need of further study. The Committee noted that based on this data, it would appear that one dose of a 25 mg tablet of synephrine could have potential adverse implications for a 10-year old child. The Committee also noted that oxedrine was linked to cardiovascular toxicity following abuse of oxedrine tablets in Australia (Chierchia S *et al*. Circulation 1985; 69:8-14). On this basis it was suggested that oxedrine be appropriately included in Schedule 4 with a suitable cut-off.

Members noted that the TGA Library had conducted a literature review on oxedrine. However, members were of the view that there was limited information available at the time, from which a clear basis for a safe cut-off to exempt both oral and topical preparations containing synephrine for therapeutic use could be established. It was noted in the preliminary report that a concentration as low as 2.5 mg synephrine could potentially affect cardiovascular parameters and the products listed on the ARTG were reported by OCM to likely contain approximately 2 μg to over 31.24 mg of synephrine.

The Committee noted that oxedrine has a similar pharmacology to ephedrine but is devoid of central nervous system (CNS) effects and the vasoconstrictor effect of synephrine is known to be due to activation of α-adrenoceptors. Members raised the point that oxedrine was widely available on the Internet as a weight loss agent, and that there was an increasing amount of oxedrine being added to extracts, i.e. some extracts were noted to contain up to 40% oxedrine.

A member questioned whether there were benefits to be gained in scheduling oxedrine and if such action would address the issue of supply of illegal therapeutic goods.

The Committee noted the possible broad implications of any scheduling action. However, the Committee was of the view that scheduling oxedrine would primarily be

based on the grounds of public health and safety, given the potential adverse effects and contraindications associated with sympathomimetic-type substances and cardiovascular toxicity associated with oxedrine. It was proposed that the Committee defer its consideration of the scheduling of oxedrine to the February 2003 meeting and seek additional information from stakeholders.

OUTCOME

The Committee considered the information available at the meeting inadequate to assist in establishing a basis for a safe cut-off to exempt products containing oxedrine, based on the oxedrine content and proposed uses. The Committee agreed to defer further consideration to the February 2003 meeting and seek additional information relating to the following:

- extent to which oxedrine is being used as an active ingredient;
- purposes for which oxedrine is being used;
- oxedrine dose vs. risk of toxicity including cardiovascular effects; and
- pharmacology of oxedrine.

14.1.8 HYOSCINE BUTYLBROMIDE

PURPOSE

The Committee considered the Appendix H entry in the SUSDP for hyoscine butylbromide.

DISCUSSION

The Committee noted the advice from XXXXXXXXXXXXXX stating that hyoscine butylbromide was still listed in Appendix H of the SUSDP although the only existing entry for this substance was in Schedule 2. Members noted that the entry for hyoscine butylbromide in Appendix H was deleted at the June 2002 meeting and the corresponding amendment was included in SUSDP 17 Amendment 2.

OUTCOME

The Committee agreed that there was no further action required.

14.1.9 IODINE

PURPOSE

The Committee reviewed the existing entry for iodine in Schedule 2.

BACKGROUND

The Trans-Tasman Harmonisation Working Party (TTHWP) Recommendation 40/7 to harmonise the scheduling of iodine with New Zealand was considered at the February 2001 NDPSC meeting when the Committee agreed to foreshadow amendment of the Schedule 2 entry for iodine. This was confirmed at the May 2001 meeting and exempted products containing 300µg or less of iodine per recommended daily dose (no labelling requirement), while products containing >300µg per recommended daily dose were included in Schedule 2 with Appendix F requirements. The previous entry exempted all iodine products from scheduling, provided they were labelled with the required warning statements.

DISCUSSION

The Committee noted the correspondence received from XXXXXXXXXXXXXX and XXXXXXXXXXXXXX, seeking clarification as to whether the exempt status of iodine products containing more than 300µg of iodine but labelled with the appropriate warning statements was inadvertently removed at the May 2001 meeting.

The Committee noted that the TTHWP Meeting 7 background papers for iodine included an Australian Register of Therapeutic Goods (ARTG) search for iodine products in Nov 2000 which yielded a total of 235 registrations. In addition, there were many "listed" complementary medicines (multi-vitamin and mineral) which contained ingredients such as fucus vesiculosis, kelp or potassium iodide (with notations on equiv content of iodine), and that a number of these products contained over 100µg of iodine per tablet or capsule. However, it was stated that it was not possible to determine the approved daily doses for these products at the time. The Committee noted that it was the intention of the TTHWP for complementary medicines containing 300µg or more of iodine per recommended daily dose to be relabelled as Schedule 2, or reformulated to bring them within the 300µg per day limit for iodine.

The Committee confirmed its original decision to place a cut off of 300µg per daily dose for the scheduling of iodine, based on the upper limit of the recommended daily intake (RDI) for iodine (RDI: 100-300µg) and harmonisation with the current New Zealand scheduling for iodine.

OUTCOME

The Committee confirmed that the reverse scheduling entry in Schedule 2 was removed to facilitate Trans-Tasman harmonisation (TTH) and that the current scheduling of iodine was intended as written. The Committee also confirmed that products containing more than 300µg of iodine per daily dose and products containing natural sources of iodine (eg kelp) had been considered in making this decision.

14.2 SUSDP, PART 5

14.2.1 APPENDIX H

No further items were considered.

15. MATTERS REFERRED BY THE AUSTRALIAN DRUG EVALUATION COMMITTEE (ADEC)

15.1 NEW SUBSTANCES

15.1.1 RILUZOLE

DECISION 2002/36 - 25.

The Committee agreed to include riluzole in Schedule 4 of the SUSDP on the grounds that the condition being treated required professional diagnosis, management and monitoring of the indicated condition and any side effects.

Schedule 4 - New entry

RILUZOLE.

15.1.2 ERTAPENEM

DECISION 2002/36 - 26.

The Committee agreed to include ertapenem in Schedule 4 of the SUSDP on the grounds that the condition being treated required professional diagnosis, management and monitoring of the indicated condition and any side effects.

Schedule 4 - New entry

ERTAPENEM.

15.1.3 VALGANCICLOVIR

DECISION 2002/36 - 27.

The Committee agreed to include valganciclovir in Schedule 4 of the SUSDP on the grounds that the condition being treated required professional diagnosis, management and monitoring of the indicated condition and any side effects.

Schedule 4 - New entry

VALGANCICLOVIR.

15.1.4 TENOFOVIR

DECISION 2002/36 - 28.

The Committee agreed to include tenofovir in Schedule 4 of the SUSDP on the grounds that the condition being treated required professional diagnosis, management and monitoring of the indicated condition and any side effects.

Schedule 4 - New entry

TENOFOVIR.

15.1.5 PARECOXIB

DECISION 2002/36 - 29.

The Committee agreed to include parecoxib in Schedule 4 of the SUSDP on the grounds that the condition being treated required professional diagnosis, management and monitoring of the indicated condition and any side effects.

Schedule 4 - New entry

PARECOXIB.

15.1.6 AGALSIDASE ALFA

DECISION 2002/36 - 30.

The Committee agreed to include agalsidase alfa in Schedule 4 of the SUSDP on the grounds that the condition being treated required professional diagnosis, management and monitoring of the indicated condition and any side effects.

Schedule 4 - New entry

AGALSIDASE ALFA.

15.1.7 OMALIZUMAB

DECISION 2002/36 - 31.

The Committee agreed to include omalizumab in Schedule 4 of the SUSDP as a new class of treatment for the condition on the grounds that the condition required professional diagnosis for appropriate use and professional management and monitoring of the indicated condition and any side effects.

Schedule 4 - New entry

OMALIZUMAB.

15.1.8 THIS ITEM WAS WITHDRAWN.

15.1.9 EFLORNITHINE

DECISION 2002/36 - 32.

The Committee agreed to include eflornithine in Schedule 4 of the SUSDP on the grounds that the new chemical required medical management and monitoring for side effects.

Schedule 4 - New entry

EFLORNITHINE.

15.1.10 VORICONAZOLE

DECISION 2002/36 - 33.

The Committee agreed to include voriconazole in Schedule 4 of the SUSDP on the grounds that the condition being treated required professional diagnosis, management and monitoring of the indicated condition and any side effects.

Schedule 4 - New entry

VORICONAZOLE.

15.1.11 RASBURICASE

DECISION 2002/36 - 34.

The Committee agreed to include rasburicase in Schedule 4 of the SUSDP on the grounds that the condition being treated required professional diagnosis, management and monitoring of the indicated condition and any side effects.

Schedule 4 - New entry

RASBURICASE.

15.1.12 BIMATOPROST

DECISION 2002/36 - 35.

The Committee agreed to include bimatoprost in Schedule 4 of the SUSDP on the grounds that the condition being treated required professional diagnosis, management and monitoring of the indicated condition and any side effects.

Schedule 4 - New entry

BIMATOPROST.

15.2 FOR INFORMATION (SUBSTANCES ALREADY SCHEDULED)

15.2.1 ARTEMETHER/LUMEFANTRINE

16. OTHER MATTERS FOR CONSIDERATION

16.1 COLLOIDAL SILVER

PURPOSE

The Committee considered the scheduling of colloidal silver.

BACKGROUND

The February 1998 meeting considered the scheduling of colloidal silver following the discovery of a person, who was not medically trained, freely dispensing preparations containing 59% colloidal silver in the ACT. This meeting was of the view that both scheduling and TGA avenues for control of this substance should be explored. Advice on this matter was sought from MEC following the February 1998 NDPSC meeting. The May 1998 meeting continued its discussions relating to colloidal silver and agreed that scheduling the substance was not the appropriate mechanism for dealing with the issue at the time. In addition, the Committee was of the opinion that even if the substance was left unscheduled, its safety and eligibility for listing would have to be established first, if products for therapeutic use were to be legitimately marketed in Australia.

The February 1999 meeting noted the CMEC advice stating that there were no legitimate uses of colloidal silver at the time, and that the Surveillance Section of the TGA would be requested to investigate the illegal availability of colloidal silver products because of their significant toxicity. CMEC stated that the term "colloidal silver" was being used in a broad sense to cover a number of different types of preparations in which silver particles or ions were suspended in a liquid medium. The February 1999 meeting also agreed to further discuss the issue of colloidal silver under the trans-Tasman harmonisation process, on the basis that silver was scheduled in NZ at the time.

The May 2001 NDPSC meeting considered the TTHWP Recommendation 34/7 and agreed to amend the S2 entry for silver salts to read:

SILVER for therapeutic use **except**:

(a) in chewing gum containing 5 mg or less of silver per dosage unit when labelled with the statement “Overuse may stain skin or mouth”;

(b) in solutions for human oral use containing 0.3 per cent or less of silver when labelled with the statement “Overuse may stain skin or mouth”; or

(c) in other preparations containing 1 per cent or less of silver."

DISCUSSION

The Committee noted the Minute received from the Office of Complementary Medicines (OCM) providing a brief update of the situation relating to colloidal silver and proposed changes to the Regulations. It advised that:

- The CMEC December 2001 meeting again recommended that action be taken by the TGA in regard to the safety risk posed by products containing colloidal silver, including liaison with the NDPSC, as and if required.
- The Surveillance Section of the TGA advised that it remained unable to take any action against colloidal silver products regardless of whether therapeutic claims were made about such products or not. This was because colloidal silver used to treat drinking water; and equipment, or substances, for use in the purification or treatment of drinking water were excluded goods and excluded from the scope of the *Therapeutic Goods Act 1989*. To address this, it would be necessary to amend the Therapeutic Goods (Excluded Goods) Order, (the Order).
- Increasingly, therapeutic claims were being made about colloidal silver products, which were inappropriately presented as medicines, rather than as water treatment products. At the time, there were no colloidal silver products approved for supply as medicines in Australia.
- The TGA proposed to amend the Order so that equipment, or substances, for use in the purification or treatment of drinking water were included within the scope of therapeutic goods legislation where therapeutic claims were made about such equipment or substances.
- Before progressing any amendment to the Order, it was considered appropriate to consult with relevant stakeholders, including relevant organisations involved in water treatment and purification to ensure that an amendment would not have unforseen implications.
- Following completion of this consultation and subject to the issues raised in this consultation, the TGA would gazette an amendment to the Order such that equipment, or substances, for use in the purification or treatment of drinking water were included in the scope of the *Therapeutic Goods Act 1989*, if therapeutic claims were made about such substances or equipment.

The Committee noted the following responses to the pre-meeting gazette notice were received:

- XXXXXXXXXXXXXX indicated that it was under the impression that colloidal silver for therapeutic use was already covered under the existing S2 entry for silver.
- XXXXXXXXXXXXXX recommended that there should be greater control through regulation of colloidal silver containing products and devices to extract colloidal silver.

Members noted that there was evidence of chronic toxicity associated with prolonged use of some silver containing products, i.e. anti-smoking pills and lozenges. However, members recalled that the toxicology of silver and its salts was reviewed at the August 1992 NDPSC meeting and agreed that such toxicology data should be provided to the February 2003 meeting for information.

OUTCOME

The Committee noted the advice relating to the proposed amendments to the Therapeutic Goods (Excluded Goods) Order to regulate the supply and availability of colloidal silver being illegally marketed as therapeutic goods and agreed that there was no need to amend the existing S2 entry at this time, which should apply to products making therapeutic claims.

16.2 SALVIA DIVINORUM

PURPOSE

The Committee considered *Salvia divinorum* and its active ingredient salvinorin A.

BACKGROUND

Salvia divinorum is a member of the mint family and contains a range of diterpenes including salvinorin A, its primary psychoactive substance. It has been reported that salvinorin A is a highly active naturally occurring hallucinogen whose mechanism of pharmacological action is not clear. Inhalation of 200 to 500 μg (2.9-7.1 μg/kg for a 70 kg adult) of salvinorin A produces psychoactive effects in humans (Seibert DJ, 1994, *Salvia divinorum* and Salvinorum A: new pharmacologic findings. *J Ethnopharmacol* 43: 53-56). Traditionally, the leaves of *Salvia divinorum* were consumed by the Mazatec Indians of Mexico during spiritual rituals for its vision-inducing effects. The leaves were either chewed and ingested or taken as an aqueous infusion.

Salvia divinorum is being widely promoted as a “legal” hallucinogen on overseas internet sites increasing interest in its use as a recreational drug. Contemporary use of *Salvia divinorum* as a recreational hallucinogen includes smoking the dry leaves, chewing leaves in a quid or ingesting liquid extracts in tincture form.

The November 2001 NDPSC Meeting agreed to include *Salvia divinorum* and salvinorin A in Schedule 9 of the SUSDP, on the basis of high potential for abuse, and potential risk to public health and safety. The Schedule 9 amendment was included in SUSDP 16 Amendment No 4, which came into effect in State and Territory law on 1 June 2002.

DISCUSSION

The Committee was informed that the Therapeutic Goods Administration had received representations on *Salvia divinorum* from the media, who quoted extensively from a paper written by XXXXXXXXXXXXXX. XXXXXXXXXXXXXX was advised by the

Secretariat that consideration of his paper would not be within the formal processes required for consideration of scheduling proposals but nonetheless, the Chair of NDPSC had requested that his paper be provided to the October 2002 Meeting. The Secretariat also indicated that XXXXXXXXXXXXXX had not responded to a previous invitation to make a formal submission to the Committee with regard to the scheduling of *Salvia divinorum* and salvinorin A.

The Committee noted XXXXXXXXXXXXXX 's paper and in particular the following points:

- *Salvia divinorum* and salvinorin A became prohibited substances in Australia on 1 June 2002, whilst remaining freely available elsewhere in the world.
- Inadequate public consultation and lack of evidence to support the decision to include *Salvia divinorum* and Salvinorin A in Schedule 9 of the SUSDP.
- The scheduling of *Salvia divinorum* would place a heavy financial and regulatory burden on Australian researchers.
- The systematic chemical name for salvinorin A appearing in Schedule 9 the SUSDP is in error.

Members highlighted that there is considerable published literature on *Salvia divinorum* and salvinorin A, which indicates that the herb is being used as a recreational hallucinogen and supports the Committee's previous decision to include *Salvia divinorum* and salvinorin A in Schedule 9 of the SUSDP. In particular, it was noted that a case study (Hanes KR, 2001, Antidepressant Effects of the Herb *Salvia divinorum*: A Case Report. *J Clin Psychopharmacol* 21; 634-635) stated that:

"Ms G volunteered that she also benefited from occasional intoxicating oral doses of *Salvia divinorum*, consisting of from 8-16 leaves of the herb (approximately 2 to 4 grams), claiming that this herb had engendered a kind of 'psychospiritual' awakening, characterized by the discovery of the depth of her sense of self, greater self-confidence, increased feelings of intuitive wisdom and 'connectedness to nature'."

Members noted that XXXXXXXXXXXXXX had claimed inclusion of *Salvia divinorum* and salvinorin A in Schedule 9 would inhibit further Australian research into the therapeutic potential of the herb. It was pointed out that all Jurisdictions had provisions within their legislation whereby Schedule 9 substances could be made available when required for medical research, or for analytical, teaching or training purposes with approval of Commonwealth and/or State or Territory Health Authorities. A Member advised that XXXXXXXXXXXXXX is currently working under the auspices of a Department of XXXXXXXXXXXXXX that holds a permit to obtain and possess but not to resell any substance in Schedule 9, including *Salvia divinorum*.

The Committee was advised that the chemical name for salvinorin A specified in S9 of the SUSDP appeared to be incorrect. Members were informed that the Chemical

Abstract Service (CAS) Registry No for salvinorin A was 83729-01-5 and the name listed in the 9th Chemical Index was:

2H-Naphtho[2,1-c]pyran-7-carboxylic acid, 9-(acetyloxy)-2- (3-furanyl)dodecahydro-6a, 10b-dimethyl-4, 10-dioxo-, methyl ester, (2S, 4aR, 6aR, 7R, 9S, 10aS, 10bR)-(9CI)

The Committee agreed to adopt the elements of the CA Index name for salvinorin A with appropriate modification to conform to SUSDP naming conventions.

OUTCOME

The Committee agreed to make an editorial amendment to the systematic name for salvinorin A in Schedule 9 of the SUSDP to reflect the nomenclature specified in the CAS Registry.

Schedule 9 – Editorial amendment

8-METHOXYCARBONYL-4A,8A-DIMETHYL-6-ACETOXY- 5-KETO-3,4,4B,7,9,10,10A-SEPTAHYDRO-3-(4-FURANYL)- 2,1-NAPHTHO[4,3-E]PYRONE *(SALVINORIN A) – correct entry to read:

METHYL (2*S*, 4a*R*, 6a*R*, 7*R*, 9*S*, 10a*S*, 10b*R*)-9-ACETOXY-6a,10b-DIMETHYL-4,10-DIOXO-DODECAHYDRO-2-(3-FURYL)-2*H*-NAPHTHO[2,1-c]PYRAN-7-CARBOXYLATE *(SALVINORIN A).

Secretariat Note: The Secretariat has become aware that Congressman Joe Baca introduced a bill (HR 5607) into the United States (US) House of Representatives on 10 October 2002. The "*Hallucinogen Control Act of 2002* - Amends the *Controlled Substances Act* to add any material, compound mixture, or preparation which contains salvinorin A or *Salvia divinorum* to Schedule I (drugs or other substances with a high potential for abuse, with no currently accepted medical use in treatment in the US, and with respect to which there is a lack of accepted safety for use under medical supervision) unless specifically exempted or listed in another schedule."

16.3 IRON COMPOUNDS

PURPOSE

The Committee considered a request for clarification relating to the Schedule 2 entry for iron oxides when present as an excipient.

BACKGROUND

The Schedule 2 Iron Compounds entry in SUSDP 17 excludes iron oxides when present as an excipient, up to 1 per cent in individual preparations or up to 10 mg per dosage unit in divided preparations.

DISCUSSION

The Committee recalled that the 10 mg limit for iron oxides when present as an excipient in divided preparations specified in the Schedule 2 entry for iron compounds was adopted at the November 1995 Meeting to accommodate existing products and on the basis that iron oxides have very low bioavailability.

The Committee noted that the TGA sought clarification as to whether the 10mg limit for iron oxides as an excipient applied to the equivalent iron content as derived from the excipient, or to the iron oxide compound.

The Committee noted the correspondence received from XXXXXXXXXXXXXX also requesting an interpretation of the Schedule 2 limit specification for iron oxides when present as an excipient. XXXXXXXXXXXXXX asked whether the limit stated for iron oxides meant that:

- *a sponsor cannot have more than 10 mg of iron arising from iron oxides when used as excipients; or*

- *a sponsor cannot have more than 10 mg of iron oxide as excipients?*

XXXXXXXXXXXXXX had stated that different types of iron oxide may contain different levels of elemental iron and that the elemental component of iron oxides is generally of low availability. XXXXXXXXXXXXXX also requested the Committee to state the criteria used for the setting of the 10mg limit for iron oxide.

The Committee confirmed that the limit had been established to exempt known divided products containing iron oxide as an excipient, based on previous data reviewed by the Committee indicating that iron oxides were generally of low bioavailability.

OUTCOME

The Committee confirmed that the exemption in the Schedule 2 entry for use of iron oxide (any form or type) as an excipient applies to any preparation containing less than:

- 10mg of total iron oxides (not the equivalent iron content) when present as an excipient in divided preparations, or

- 1% of total iron oxides (not the equivalent iron content) in undivided preparations when present as an excipient.

In addition, an exempt preparation may also contain other salts of iron present as an active as specified in paragraphs (a) and (b) of the entry.

Accordingly, the Committee agreed that iron compound preparations for human internal use which contained iron oxides above these limits automatically fell into Schedule 2.

17. MATTERS REFERRED BY THE MEDICINES EVALUATION COMMITTEE (MEC)

17.1 RANITIDINE

PURPOSE

The Committee considered the scheduling of ranitidine.

BACKGROUND

Ranitidine is a selective H2-receptor antagonist that is active in reducing gastric secretions. It is used for symptomatic relief of heartburn, dyspepsia and hyperacidity and for the treatment of gastric, peptic and duodenal ulcers. At the November 2000 Meeting, the Committee agreed to reschedule ranitidine from Schedule 3 to Schedule 2 of the SUSDP for the relief of symptoms of gastro-oesophageal reflux in packs containing not more than 14 days supply.

DISCUSSION

The Committee considered the Medicines Evaluation Committee (MEC) report on a new product containing 300mg/dose for the relief of symptoms of gastro oesophageal reflux. The Committee noted that this was intended to be taken as a single dose when required (no more than one dose in 24 hours) for those patients who regularly did not obtain relief of their gastro-oesophageal reflux with one 150mg tablet. In addition, the MEC had imposed a requirement for the sponsor to clearly state on the labelling that the new formulation containing 300mg ranitidine was only for those patients who habitually needed to take two 150mg tablets to relieve their symptoms.

The Committee noted the maximum recommended daily dose of one 300mg ranitidine tablet was still within the maximum recommended daily dose specified for the 150mg ranitidine formulation for the relief of symptoms of gastro-oesophageal reflux, i.e. 2 x 150mg. Further, the ADEC (Australian Drug Evaluation Committee) had supported the efficacy and safety of a single night-time dose of 300mg ranitidine in the treatment of duodenal ulcer, benign gastric ulcer and sever reflux oesophagitis. Members agreed that a 300mg ranitidine product would be included in the existing Schedule 2 entry provided only 14 doses were provided per pack.

OUTCOME

The Committee agreed that the existing scheduling for ranitidine remained appropriate on the basis that the maximum pack size for the new double-strength ranitidine (300mg per dose) provided only 14 doses per pack.

18. MATTERS REFERRED BY THE MEDICINES CLASSIFICATION COMMITTEE (MCC) OF NEW ZEALAND

18.1 ACICLOVIR

PURPOSE

The Committee considered the recommendations of NZ MCC on the harmonisation of aciclovir.

BACKGROUND

Aciclovir, when converted to the triphosphate, is a potent and selective inhibitor of Herpes simplex virus (HSV) and other herpes viruses. It is a prototype of a group of antiviral agents that are phosphorylated intraceullularly by a viral kinase to become inhibitors of viral DNA synthesis.

The November 2001 NDPSC Meeting considered an application from XXXXXXXXXXXXX to exempt XXXXXXXXXXXXX containing 5%w/w aciclovir from the requirements of scheduling when sold in a small pack size of 2g. The Committee agreed to exempt preparations containing 5 per cent or less of aciclovir for the treatment of *Herpes labialis* in packs containing 10g or less, on the grounds that *Herpes labialis* was a short term and self-limiting condition, appropriate for self-diagnosis and management by consumers. In addition, the product was simple to use and increased access to such a product would be beneficial to public health.

It was recommended to NZ MOH that it adopt similar scheduling and NZ considered rescheduling of aciclovir at the May 2002 MCC Meeting.

DISCUSSION

The Committee noted MCC's decision to reject NDPSC's recommendation on the grounds that MCC considered that the larger pack size did not fit the criterion of short term use and increased the risk of inappropriate use.

The Committee also noted scheduling of topical aciclovir for the treatment of herpes labialis:

- General sale when in packs of 5% or less and containing 3 grams or less; and
- Pharmacy-only medicine when in packs containing more than 3 grams.

OUTCOME

Scheduling of aciclovir would remain unharmonised and that aciclovir be placed on the 2 year review list of unharmonised substances.

18.2 DEXTROMETHORPHAN

PURPOSE

The Committee considered the recommendations of NZ MCC on the harmonisation of dextromethorphan.

BACKGROUND

Dextromethorphan is an effective antitussive agent for treating uncomplicated, non-productive coughs and the recommended daily dose should not exceed 120 milligrams.

The July 2000 TTHWP meeting recommended that NZ and Australia adopt the SUSDP 15 Schedule 2 entry for dextromethorphan with additional restriction on the pack size of 600 mg or less of dextromethorphan (TTHWP Recommendation 13/6), based on the abuse potential of the substance. The Schedule 2 entry in SUSDP 15 for dextromethorphan is:

DEXTROMETHORPHAN

(a) in divided preparations containing 30 mg or less of dextromethorphan per dosage unit and with a recommended dose not exceeding 30 mg of dextromethorphan; or

(b) in undivided preparations containing 0.3 per cent or less of dextromethorphan, with a recommended dose not exceeding 30 mg of dextromethorphan.

The February 2001 NDPSC meeting endorsed TTHWP Recommendation 13/6 and recommended that NZ-MCC consider adopting this recommendation to harmonise. However, the NDPSC omitted to take further action in order to adopt TTHWP Recommendation 13/6, so the Schedule 2 entry for dextromethorphan had remained unchanged to this time.

The May 2002 MCC meeting considered the February 2001 NDPSC meeting recommendation that MCC consider deleting the Part III entry for dextromethorphan in NZ and replace it with the entry proposed under TTHWP Recommendation 13/6.

DISCUSSION

The Committee noted that NZ-MCC did not agree to adopt TTHWP Recommendation 13/6 on the grounds that there was no evidence of abuse of general sale products containing dextromethorphan in New Zealand. MCC therefore recommended that the NZ classification of dextromethorphan remained appropriate and that the NDPSC be informed of this decision including the rationale.

OUTCOME

The Committee agreed to reconsider TTHWP Recommendation 13/6 at the February 2003 NDPSC meeting following public consultation.

18.3 LOCAL ANAESTHETICS

PURPOSE

The Committee considered the recommendations of NZ MCC on the harmonisation of 3-aminobenzoic acid ethyl ester methanesulphonate and orthocaine.

BACKGROUND

In continuing its refinement of the various scheduling entries for local anaesthetics, which arose from NZ's use of a generic statement for all local anaesthetics, the July 2000 TTHWP meeting recommended that NZ MOH include 3-aminobenzoic acid ethyl ester methanesulphonate and orthocaine in Part I of their Schedule.

The February 2001 NDPSC Meeting endorsed TTHWP's recommendation on harmonisation grounds.

NZ considered TTHWP's recommendation at the May 2002 MCC Meeting.

DISCUSSION

The Committee noted MCC's decision to reject TTHWP's recommendation. MCC could find no reference in Martindale for these two local anaesthetics and recommended that the NDPSC delete them from scheduling if they are not contained in any products in Australia.

OUTCOME

The Committee agreed that if there are no products marketed in Australia, 3-aminobenzoic acid ethyl ester methanesulphonate and orthocaine be gazetted for consideration at the February 2003 Meeting for deletion from the SUSDP.

18.4 BENZAMINE

PURPOSE

The Committee considered the recommendations of NZ MCC on the harmonisation of benzamine.

BACKGROUND

In continuing its refinement of the various scheduling entries for local anaesthetics, which arose from NZ's use of a generic statement for all local anaesthetics, the July 2000

TTHWP Meeting recommended that NDPSC delete the Schedule 2 entry and retain the Schedule 4 entry for benzamine. TTHWP also recommended that NZ MOH adopt benzamine into Part I, subject to there being no general sales products containing the substance.

The February 2001 NDPSC Meeting agreed to TTHWP's recommendation.

NZ considered TTHWP's recommendation at the May 2002 MCC Meeting.

DISCUSSION

The Committee noted MCC's decision to reject TTHWP's recommendation as benzamine was not scheduled in NZ, had no reference in Martindale and was not contained in any products in either New Zealand or Australia.

The Committee also noted MCC's recommendation that NDPSC delete benzamine from the SUSDP.

OUTCOME

The Committee agreed that benzamine be gazetted for consideration at the February 2003 Meeting for deletion from scheduling, if there are no products in Australia.

18.5 BENZOCAINE

PURPOSE

The Committee considered the recommendations of NZ MCC on the harmonisation of benzocaine.

BACKGROUND

In continuing its refinement of the various scheduling entries for local anaesthetics, which arose from NZ's use of a generic statement for all local anaesthetics, the July 2000 TTHWP meeting recommended that the NDPSC amend the Schedule 4 and Schedule 2 entries for benzocaine. TTHWP also recommended that NZ MOH adopt equivalent schedule entries.

The February 2001 NDPSC Meeting agreed with TTHWP's recommendation based on previous deliberations concerning local anaesthetics and the fact that there were a number of products in Australia for which a generic entry was not appropriate.

NZ considered TTHWP's recommendation at the May 2002 NZ MCC meeting.

DISCUSSION

The Committee noted MCC's decision to amend the pharmacy-only schedule entry to impose an upper limit of 10% for external products and to amend the prescription entry to accommodate the change.

The Committee also noted MCC's concern about the pharmacy-only classification of oral products containing up to 200 mg of benzocaine and their request for further information on this matter including details of products available in Australia.

OUTCOME

The Committee agreed that the NDPSC Secretariat provide MCC with the requested information.

18.6 DIMETHISOQUIN (QUINOSOCAINE) AND PRAMOXINE (PRAMOCAINE)

PURPOSE

The Committee considered the recommendations of NZ MCC on the harmonisation of dimethisoquin (quinisocaine) and pramoxine (pramocaine).

BACKGROUND

The July 2000 TTHWP recommended that NDPSC delete the Schedule 4 and Schedule 2 entries for local anaesthetics, dimethisoquin and pramoxine, and replace them with Schedule 4 entries using INN nomenclature quinisocaine and pramocaine. TTHWP also recommended that NZ MOH adopt the equivalent schedule entries.

The February 2001 NDPSC Meeting agreed with TTHWP's recommendation based on previous deliberations concerning local anaesthetics and the fact that there were no affected products in Australia.

NZ considered the rescheduling of dimethisoquin and pramoxine at the May 2002 MCC Meeting.

DISCUSSION

The Committee noted that MCC agreed to TTHWP's recommendation to adopt quinisocaine and pramocaine as prescription medicines on the grounds that there would be no regulatory impact.

OUTCOME

New Zealand is harmonised with Australia.

18.7 LIGNOCAINE

PURPOSE

The Committee considered the recommendations of NZ MCC on the harmonisation of lignocaine.

BACKGROUND

In continuing its refinement of the various scheduling entries for local anaesthetics, which arose from NZ's use of a generic statement for all local anaesthetics, the July 2000 TTHWP meeting recommended that the NDPSC amend the Schedule 4 and Schedule 2 entries for lignocaine and that the entry should be expressed in terms of total local anaesthetic substances. TTHWP recommended the adoption of the INN (AAN) nomenclature of lidocaine (lignocaine). TTHWP also recommended that NZ MOH adopt equivalent scheduling entries.

The February 2001 NDPSC Meeting agreed with TTHWP's recommendation based on previous deliberations concerning local anaesthetics and the regulatory impact. NDPSC also considered it appropriate that the entries be expressed in terms of total local anaesthetic substances. The AAN nomenclature only was adopted.

NZ considered the rescheduling of lignocaine at the May 2002 MCC Meeting.

DISCUSSION

The Committee noted MCC's decision to amend the pharmacy-only schedule entry to impose an upper limit of 10% for external products and to amend the prescription entry to accommodate the change.

The Committee also noted MCC's concern about the pharmacy-only classification of oral products containing up to 200 mg of lignocaine and their request for further information on this matter including details of products available in Australia.

OUTCOME

The Committee agreed that the NDPSC Secretariat provide MCC with the requested information.

18.8 IBUPROFEN

PURPOSE

The Committee considered the recommendations of NZ MCC on the harmonisation of ibuprofen.

BACKGROUND

Ibuprofen, a propionic acid derivative, is a non-steroidal anti-inflammatory drug (NSAID) and its anti-inflammatory properties may be weaker than those of some other

NSAIDS. Ibuprofen is used in the management of mild to moderate pain and inflammation in conditions such as dysmenorrhoea, headache including migraine, postoperative pain, dental pain, musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis and rheumatoid arthritis including juvenile idiopathic arthritis, peri-articular disorders such as bursitis and tenosynovitis and soft-tissue disorders such as sprains and strains. It is also used to reduce fever.

The November 2000 TTHWP recommended that NZ MOH adopt the revised wording of the SUSDP 15 Amendment 2 that sets an upper daily dose for divided and undivided preparations and relaxes the concentration requirements for ibuprofen liquid preparations, but retains a 4g total content of ibuprofen in these packs.

The February 2001 NDPSC Meeting endorsed the TTHWP's recommendation.

NZ considered the TTHWP's recommendation at the May 2002 MCC Meeting.

DISCUSSION

The Committee noted that MCC agreed to TTHWP's recommendation.

The Committee also noted MCC's request that NDPSC limit the concentration of liquid ibuprofen permitted in pharmacy-only medicines.

OUTCOME

The Committee agreed that ibuprofen be gazetted for consideration at the February 2003 Meeting.

18.9 SELENIUM

PURPOSE

The Committee considered the recommendations of NZ MCC on the harmonisation of selenium.

BACKGROUND

Selenium sulfide has antifungal and anti-seborrhoeic properties and has been used as a 2.5% shampoo for the treatment of dandruff (pityriasis capitis) and seborrhoeic dermatitis of the scalp. It is also used as a 2.5% lotion in the treatment of pityriasis versicolor.

The July 2000 TTHWP Meeting considered the scheduling of selenium sulfide in preparations for topical use containing more than 2.5 per cent. TTHWP recommended that NZ MOH shift the Part III entry for selenium for external use in medicines containing more than 2.5% to Part I. The recommendation was made on the basis that prolonged use on broken skin has resulted in systemic toxicity.

The February 2001 NDPSC Meeting endorsed TTHWP's recommendation.

NZ considered TTHWP's recommendation at the May 2002 MCC Meeting.

DISCUSSION

The Committee noted MCC's decision to reject NDPSC's recommendation to reclassify selenium on the grounds that it would make external products more restrictive than internal products.

The Committee also noted MCC's recommendation that NDPSC harmonise with New Zealand on the scheduling of selenium.

OUTCOME

The Committee agreed that selenium be gazetted for consideration at the February 2003 NDPSC Meeting.

18.10 NIZATIDINE

PURPOSE

The Committee considered the recommendations of NZ MCC on the harmonisation of nizitadine.

BACKGROUND

Nizatidine is a potent, selective, competitive, and fully reversible inhibitor of the histamine H_2-receptor. It acts by inhibiting basal and nocturnal gastric-acid secretion for up to 12 hours, and is indicated for the treatment and maintenance of duodenal ulcers, treatment of benign gastric ulcers and treatment of oesophagitis (including erosive and ulcerative oesophagitis and associated heartburn due to reflux).

The August 2001 NDPSC Meeting considered an application from XXXXXXXXXXXXX requesting the rescheduling of nizatidine 150mg capsule from Schedule 3 to Schedule 2 for the relief of symptoms of gastro-oesophageal reflux with a maximum 14-day supply.

NDPSC approved the rescheduling based on the pharmacological and toxicological profile, clear indications appropriate for self-diagnosis, a history of safe use and well-characterised drug interactions. The Committee also agreed that in view of the possibility of significant side effects and drug/drug interactions, proximate access to professional advice and counselling remained appropriate. NDPSC recommended to NZ MOH to consider a similar scheduling outcome.

NZ considered NDPSC's recommendation at the May 2002 MCC Meeting.

DISCUSSION

The Committee noted MCC's decision to reject the NDPSC recommendation on the grounds that there were no nizatidine products marketed in New Zealand and that nizatidine had never been available over the counter.

The Committee also noted MCC's recommendation that NDPSC remove the OTC classification if there are no nizatidine OTC products marketed in Australia.

OUTCOME

The Committee agreed that the current nizatidine scheduling be retained as there is an OTC product marketed in Australia.

18.11 SILVER SULFADIAZINE

PURPOSE

The Committee considered the recommendations of NZ MCC on the harmonisation of silver sulfadiazine.

BACKGROUND

Silver sulfadiazine is a sulfonamide used in conjunction with debridement, as a 1% cream for the prevention and treatment of infection in severe burns. It has also been used in other skin conditions, such as leg ulcers, where infection may prevent healing and for the prophylaxis of infection in skin grafting. It has also been applied to the eyes in the treatment of superficial Aspergillus infections.

The November 2001 NDPSC Meeting, in its continuing discussion on the implementation for the JETACAR Recommendation 6, considered the rescheduling of silver sulfadiazine (SSDZ). That meeting noted that resistance still remained a potential problem for SSDZ and, in the absence of data in support of relaxing the scheduling of SSDZ, it was agreed that it remained appropriately scheduled in Schedule 4. The NDPSC recommended that New Zealand consider adopting a similar outcome.

NZ considered NDPSC's recommendation at the May 2002 MCC Meeting.

DISCUSSION

The Committee noted MCC's decision to reject the NDPSC recommendation on the grounds that pack sizes of 50g or less remained appropriately scheduled as a pharmacy-only medicine in New Zealand.

The Committee also noted MCC's recommended that NDPSC consider adopting a similar classification.

OUTCOME

The Committee agreed to gazette silver sulfadiazine for consideration at the February 2003 Meeting.

18.12 SOLANACEOUS ALKALOIDS

PURPOSE

The Committee considered the recommendations of NZ MCC on the harmonisation of solanaceous plants and alkaloids.

BACKGROUND

The naturally occurring muscarinic receptor antagonists are the alkaloids of the belladonna plants. The most important of these are atropine and hyoscine (scopolamine). The belladonna drugs are widely distributed in nature, especially in related plants of the family Solanaceae such as *atropa belladonna* and *duboisia leichardtii*. *Atropa belladonna* yields mainly the alkaloid atropine (dl-hyoscyamine). The same alkaloid is found in *datura stramonium* (total alkaloidal content of stramonium preparations is usually calculated based on hyoscyamine - Martindale) and *duboisia myoporoides*. The alkaloid hyoscine is found chiefly in the shrub *hyocyamus niger* (henbane). *Datura* leaf also contains hyoscine ~ 0.25-0.55%, traces only of hyoscyamine and atropine. *Duboisia leichardtii* leaves contain up to 5% tropane alkaloids, including hyoscyamine (10-80%) and hyoscine (6-46%).

The November 1987 NDPSC Meeting raised concerns that the dose limit for undivided preparations adopted by the July 1987 NDPSC Meeting were too high compared to the dose limit for divided preparations, by a factor of 10.

The July 2000 TTHWP Meeting agreed to recommend a reduced dose limit for undivided preparations containing solanaceous alkaloids of 0.025%.

To achieve consistency across the schedule entries for solanaceous alkaloids, the February 2001 NDPSC Meeting agreed to adopt the TTHWP recommendation. However, the August 2001 NDPSC Meeting noted that the solanaceous plant and alkaloid amendments in SUSDP 16/1 were interlocked in such a way that it was difficult to identify which entries need to be revised, without available data to provide a basis for determining the appropriate cut-offs. Accordingly, that meeting recommended the solanaceous alkaloid related entries be withdrawn from Amendment 1 or disallowed from the amendment where possible by the jurisdiction.

The November 2001 NDPSC Meeting agreed that the existing Schedule 4 entries in SUSDP 16/1 remained appropriate. That meeting also agreed to adopt principles for inclusion of preparations containing solaneceous plants and alkaloids (excluding hyoscine hydrobromide) in Schedule 2. This decision was based on the grounds that the products listed in the ARTG for OTC use containing solanaceous plants and alkaloids were

considered to be within currently established dose levels and supported by long history of use and post-marketing clinical experience.

The November 2001 NDPSC Meeting recommended that New Zealand adopt similar scheduling.

NZ considered NDPSC's recommendation at the May 2002 MCC Meeting.

OUTCOME

The Committee noted that MCC have harmonised with Australia on the nomenclature and classification levels for solanaceous plants and alkaloids, except for hyoscine butylbromide.

The Committee also noted that MCC have agreed that OTC hyoscine butylbromide tablets should retain their current restricted medicine classification.

22. AMENDMENTS TO THE SUSDP

22.1 EDITORIAL CHANGES AND ERRATA

22.1.1 CICLOPIROX

PURPOSE

The Committee considered the wording of the Schedule 2 entry for ciclopirox.

BACKGROUND

The February 2002 agreed to include in Schedule 2 ciclopirox in preparations for dermal use containing less than 2 % of ciclopirox.

DISCUSSION

The Committee noted that the existing entry used the reverse of the usual form of wording and considered the proposal to adopt the wording “CICLOPIROX in preparations for dermal use containing 2 % or less of ciclopirox”, for consistency with other schedule entries.

The Committee noted that there was only one product listed on the ARTG for supply in Australia (XXXXXXXXXXXXXX ciclopirox 80mg/g topical solution bottle) containing ciclopirox for topical use. The Committee agreed that this amendment would have no regulatory impact on existing products and would reflect the intent of the original scheduling decision.

OUTCOME

The Committee agreed to amend the wording for the concentration limit in Schedule 2 for ciclopirox to "2% or less of ciclopirox". This was on the basis that this amendment expressed the true intent of the original scheduling decision, is consistent with the form of words used for other schedule entries and would have no regulatory impact.

Schedule 2 - Editorial Amendment

CICLOPIROX – correct entry to read:

CICLOPIROX in preparations for dermal use containing 2 per cent or less of ciclopirox.

ATTACHMENT 1 - NEEM

A. EXTRACTS FROM NEEM SUBMISSIONS MADE TO THE NDPSC JUNE 2002 MEETING:

- XXXXXXXXXXXXXX opposed the proposal to list Neem Oil as Schedule 7 Dangerous Poison, on the basis that neem oil was widely used as wetting agent, plant nutrient and insect deterrent/repellent. In addition, the submission highlighted that the US Department of Agriculture did not classify neem as a 'dangerous poison'.
- XXXXXXXXXXXXXX did not support the proposal to schedule neem oil as a 'poison'. It had stated that the US had registered the product for personal and agricultural use without scheduling it as a 'poison', and that the product had untold proven beneficial effects for plants, animals and humans.
- XXXXXXXXXXXXXX opposed the proposal to include neem oil or its derivatives in Appendix C, Schedule 5 or Schedule 7 of the SUSDP, on the basis of widespread use in human therapeutic and cosmetic products, and organic horticultural industry.
- XXXXXXXXXXXXXX opposed the proposal to include neem and neem products in Schedule 7.
- XXXXXXXXXXXXXX had opposed the proposed inclusion of neem oil in Schedule 7, based on 'safe' personal use of neem oil, which also had 'proven' benefits as natural garden pesticide and treatment for head-lice.
- XXXXXXXXXXXXXX had indicated that neem was being used in cosmetic products worldwide although the concentration used in cosmetic products had not been established. XXXXXXXXXXXXXX urged the Committee not to restrict neem oil and its extracts from use in cosmetic products unless there was evidence to support restriction.
- XXXXXXXXXXXXXX opposed the considered restriction or banning of neem for human use, based on the wealth of anecdotal evidence to demonstrate neem's beneficial effects on the skin and as natural alternative for people with skin sensitivities who could not use commercially produced products.
- XXXXXXXXXXXXXX opposed the proposal to include neem and its derivatives in Schedule 7, based on neem's long history of 'safe' use in India and South East Asia, and anecdotal evidence demonstrating the benefits of using neem products to treat skin ailments.
- XXXXXXXXXXXXXX opposed the proposed listing of neem oil as a Schedule 7 poison, due to the lack of evidence to support the proposed restriction, whereas most scientific literature available supported the idea that neem oil was safe to humans.
- XXXXXXXXXXXXXX indicated that as organic producers and exporters, they were concerned that neem and its derivatives were being considered for scheduling thereby ruling out their use in agricultural applications. The submission highlighted that neem and its products were being used widely and safely in populous nations such as India with no consequential adverse health effects.

- XXXXXXXXXXXXXX opposed the proposed inclusion of neem and its derivatives in Appendix C, on the basis that the CMEC evaluation did not find any compelling evidence of toxicity arising from topical use. In addition, it was indicated that most instances of toxicity, particularly in children and infants, were associated with internal ingestion of some forms of neem oil, for which a dose level was not established. XXXXXXXXXXXXXX also stated that given the long history of safe use of neem in the Indian subcontinent for therapeutic, pesticidal and agricultural application, it questioned the extent to which the toxicology evaluation comprehensively differentiated between the toxicity profiles of different forms of neem, i.e. flowers, fruits, bark, leaf and seed powders, oils or extracts, to justify their inclusion in Appendix C.
- XXXXXXXXXXXXXX did not support the classification of neem oil as a 'poison', based on personal experience with neem oil products such as pet shampoo and kennel spray, where no consequential adverse health effect on the treated animals was seen.
- XXXXXXXXXXXXXX opposed any scheduling action on neem oil for cosmetic and natural medicine use in humans, but was not against regulating neem for use in agriculture. The submission had highlighted that *Azadirachta indica* A. Juss had been allowed to be used by Ayurvedic medicine therapists/practitioners, and had been used safely in humans for at least 5000 years.
- XXXXXXXXXXXXXX did not support the proposal to restrict the use of neem, as the plant was essential for natural pest control.
- XXXXXXXXXXXXXX requested that neem oil not be scheduled when used in cosmetics and medicinal products for humans, but agreed that agricultural use of neem must comply with all the necessary requirements in force. The submission also stated that neem oil and neem extracts were allowed to be used by Ayurvedic therapists and practitioners, and were safe for use in cosmetics and medicinals.
- XXXXXXXXXXXXXX objected the proposed inclusion of neem and other neem derivatives in Schedule 5 and Schedule 7, based on evidence demonstrating the value of neem in the protection of human, animal and horticultural health. In addition, it was stated that there was ample evidence to support that neem was not toxic to mammals, birds or reptiles.
- XXXXXXXXXXXXXX opposed any actions by the NDPSC to negate or override the recommendations made by the CMEC relating to neem for topical use in listable goods. XXXXXXXXXXXXXX had indicated that it had a major interest in the use of neem for external treatment and control of head lice.
- XXXXXXXXXXXXXX requested that no pre-emptive action be taken to restrict the use or availability of neem oil without substantial scientific basis, on the basis of neem's long history of use as a natural product.
- XXXXXXXXXXXXXX opposed the proposal to include neem and its extracts in Schedule 7, based on personal experience with products derived from various parts of the neem tree for therapeutic, cosmetic and pesticidal use, and no consequential adverse health effects.

- XXXXXXXXXXXXXX opposed any restriction on neem and its derivatives, on the basis that neem provided a safer and ecologically sound alternative to toxic and synthetic pesticides. The submission also urged that a similar system to the US be adopted in Australia, where approvals/registration for any new substance, extract or herbal powder are 'fast-tracked' on the grounds of environmental merit.
- XXXXXXXXXXXXXX opposed the proposal to schedule neem and/or its derivatives as a 'poison', based on personal experience with neem products, and long history of safe use worldwide. The submission had also stated that it had been marketing neem oil for the last 5 years with no health or safety problems encountered, and that neem oil had been registered in the USA for personal and agricultural use.
- XXXXXXXXXXXXXX opposed the scheduling of *Azadirachta indica* as a 'poison', on the grounds that its extracts were non-toxic to humans and animals and given the wide body of scientific evidence available to support its safety. The submission also highlighted that *Azadirachta indica* was not registered as a 'poison' in many countries including the US, and was being used widely in India for human health purposes in the last 4000 years.
- XXXXXXXXXXXXXX had opposed the proposal to schedule neem on the basis that it had been registered as 'non-poisonous' in other countries including the USA, and neem in its various forms had been used for human health purposes in India for a known period of 4000 years. The submission also highlighted the benefits of using neem to compliment chemical free practices on a broader scale, and as a non-toxic alternative to other known toxic chemicals.
- XXXXXXXXXXXXXX opposed the proposal to label neem and its derivatives with "poison", on the basis of having personally used neem products with no detrimental health effects experienced, and that such products had a long history of safe use worldwide.
- XXXXXXXXXXXXXX did not support the scheduling of neem seed oil as a 'poison' on the basis of publicly available evidence including research data from CSIRO and Queensland's Dept. of Agriculture, indicating that neem oil by itself was not toxic to humans or animals. In addition, it was stated that neem products were proven to be safe all over the world, and that the US EPA found no toxic dosage levels for neem seed oil could be established in the tests conducted. Furthermore, the submission highlighted that alcohol extracts of neem seeds produced no external irritation in rabbits and no toxic effects on mice, when taken internally, even in very large amounts.

  Secretary's Note: XXXXXXXXXXXXXX had included an extract of the US EPA's report supporting its finding that azadirachtin and clarified hydrophobic extract of neem oil was suitable for exemption from the requirement of a tolerance on all raw agricultural commodities when used as a botanical fungicide, insecticide and miticide (no symptoms were recorded, even the highest dosage used to establish an LD_{50} for azadirachtin). Information derived from the EPA website specified that *" When the natural neem oil is removed from the seeds and treated with alcohol, virtually all of the azadirachtin and*

related substances separate from the oil itself. The remaining oil - without the azadirachtin - is called Clarified Hydrophobic Extract of Neem Oil". This process suggested the removal of triterpenoid compounds which were present in the unrefined oil. However, no data on the process described by the USEPA was available to give an indication of the chemical profile of the components removed, before and after treatment with alcohol. The USEPA had classified azadirachtin and clarified hydrophobic extract of neem oil as active ingredients for use on food and non-food plants, although it also classified the clarified extract as a mild sensitiser. It had stated that based on results of toxicity tests, risks to human health were not expected from these active ingredients when used according to label directions (the Committee had not reviewed any data on pure azadirachtin).

- XXXXXXXXXXXXXX was opposed to any restrictions placed on the neem plant and oil, on the grounds of long history of safe use in India, and that access to chemical-free alternatives for the management of insect and disease would provide safer options.
- XXXXXXXXXXXXXX had opposed the proposal to include neem oil in Schedule 7, on the basis that no evidence of ill effects had resulted from his ingestion of neem leaves as a health food, and from using neem oil on animals and plants, as a pesticide and organic fertiliser.
- XXXXXXXXXXXXXX did not support the listing of neem oil as a Schedule 7 poison when used as a pesticide on organic produce.
- XXXXXXXXXXXXXX opposed the inclusion of neem or its extracts in Schedule 7 and that they should be allowed unrestricted use in organic farming, given that it was harmless to both humans and animals. In addition, the submission stated that neem oil and its extract, azadirachtin, was extremely effective in controlling insects and pests in grapevines, olive trees and other edible crops.
- XXXXXXXXXXXXXX opposed any restrictions placed on natural products.
- XXXXXXXXXXXXXX opposed the inclusion of neem oil and its derivatives in Schedule 7.
- XXXXXXXXXXXXXX proposed that unrestricted access to neem products should remain unchanged due to the lack of sufficient evidence to demonstrate that neem and its derivatives were unsafe. The submission had stated that both the fruit and leaves of the neem tree had been used for both culinary and medicinal purposes, and that the US Environmental Authority had given full chemical clearance for use of neem in 1993, and >10 other countries had allowed it to be marketed actively.
- XXXXXXXXXXXXXX – opposed the proposal to schedule *Azadirachta indica* (neem) or its derivatives as a poison, on the basis that no evidence had been found to suggest that pure neem may be poisonous to humans when used in the appropriate manner. XXXXXXXXXXXXXX had stated that all its neem extracts had been tested by the Australian Quarantine and Inspection Service (AQIS) for the presence of aflatoxins where there was no acceptable level allowed. In addition, the submission

also indicated that XXXXXXXXXXXXXX listed Neem as an accepted product for use in organic farming, which complied with their stringent guidelines for Organic Farming. Anecdotal evidence of the health benefits of taking neem orally on a daily basis had also been quoted.

> **Secretary's Note**: The Australian Organic Standard for neem extracts had specified that "…botanical pesticides must be part of a biorational pest management program, and cannot be the primary method of pest control in the Organic Management Plan".

- XXXXXXXXXXXXXX opposed the scheduling of neem products given his first-hand experience with such products, and on the basis of long history of safe use in both humans and animals worldwide.
- XXXXXXXXXXXXXX see October 2002 pre-meeting comments.
- XXXXXXXXXXXXXX see October 2002 pre-meeting comments.
- XXXXXXXXXXXXXX objected the proposed inclusion of neem oil in Schedule 7 and believed that after centuries of use, a proposed scheduling of neem should have a wide review and proper inquiry.

B. OCTOBER 2002 PRE-MEETING NEEM SUBMISSIONS RECEIVED:

- XXXXXXXXXXXXXX objected the inclusion of cold pressed neem oil in Schedule 7 and proposed that it be included in Schedule 5 of the SUSDP. The proposal was made on the grounds that there was a wide body of evidence available to support the suitability of cold pressed neem oil for inclusion in Schedule 5 of the SUSDP, according to the criteria listed for Schedule 5 in the Guidelines for Classification of Drugs and Poisons. In addition, the submission also proposed that appropriate packaging, label warnings, safety directions and child-resistant packaging be used for products containing neem oil.

  > **Secretary's Note**: An addendum to XXXXXXXXXXXXXX 's first submission had been provided, giving details of the production process of the cold-pressed neem oil (raw material supplied by XXXXXXXXXXXXXX), as well as information relating to the assay of azadirachtin (by HPLC) and aflatoxin (by TLC) content of XXXXXXXXXXXXXX 's cold-pressed neem oil. There was no data provided on other components/impurities present in XXXXXXXXXX 's cold-pressed neem oil other than azadirachtin A, and there was no further 'clean-up' or processing specified following the extraction of cold-pressed oil obtained by mechanical pressing/crushing of seed kernels, except for 2 stages of filtration.

- Victorian PIC stated that it was not aware of any documented cases of neem poisoning.
- XXXXXXXXXXXXXX indicated that in about 80% of emergency department presentations in Victoria, no cases of neem poisoning were found. However, the submission had further stated that in many cases, the agent of poisoning may had

been recorded or coded into a category from which agents such as neem could not be identified.

- XXXXXXXXXXXXXX did not agree with the proposed inclusion of neem oil extracts in Schedule 5 and 7 due to the lack of conclusive evidence to demonstrate acute toxicity to humans, and on the basis of long history of safe use as human therapeutic in India. The submission also highlighted the following points:
    - The neem tree is native to the Indian sub-continent, where it had been used as part of Ayurvedic medicine for at least 4000 years.
    - There appeared to be some confusion in the CPAS report which claimed that azadirachtin and related compounds called limonoids were all bitter principles. The components of neem remained not fully identified and the toxicology studies conducted with 'debitterised neem oil" did not identify exactly what was removed to eliminate the unpleasant odour and smell.
    - The acute toxicity studies conducted on cold-pressed neem oil from XXXXXXXXXXXXXX suggested that the acute oral LD_{50} (rats) >5000 mg/kg, acute dermal LD_{50} (rats) >2000 mg/kg and the inhalation LD_{50} (rats – 4 hour) > 2.11 mg/L. For a 10-kg child, these levels were equivalent to an oral dose of 50 grams or 60 mL of cold-pressed oil, and a dermal dose of 20 g (SG = 0.84 mg/mL) or 24 mL of cold –pressed neem oil.
    - *Melia azedarach* is a poisonous plant and should be included in Appendix C and prohibited from sale, supply and use. The submission also highlighted the considerable confusion between *Melia Azadirachta* (neem) and *Melia azedarach* (chinaberry).
    - Both cold-pressed neem oil and clarified hydrophobic neem were approved biopesticides in the USA and were not considered a risk to human health by the Office of Pesticides Programs.

      Secretary's Note: Cold-pressed neem oil by itself did not appear to be approved by the US EPA. Information obtained from the US EPA website suggested that only azadirachtin (including dihydroazadirachtin) and clarified hydrophobic extract of neem oil were approved for use in agriculture.

    - Did not agree with CMEC's recommendation to require child-resistant closures (CRCs) on all containers containing neem oil, regardless of concentration and volume. It was stated that eucalyptus oil, which was much more acutely toxic than neem oil, did not require CRCs for preparations containing 25 % per cent or less of eucalyptus oil or for containers greater than 2 litres. The submission also recommended that if CRCs were to be considered necessary for neem oil, a similar restriction should be applied to eucalyptus oil.
    - For the proposed use of neem oil as head lice treatment, a 200 mL bottle of head lice shampoo, containing 2% neem oil, would actually contain a maximum of 4 mL of cold-pressed neem oil. A 10-kg child would have to consume 15 x 200 mL bottle of head lice shampoo to achieve a dose level of 5000 mg/kg of neem oil. The company had argued that the reported Margosa

oil poisoning in infants and children following large doses of Margosa oil had been exclusive to Malaysia (occurred during the 1970s) and had not been reported elsewhere. This alone supported the contention that Margosa oil in Malaysia was contaminated with either aflatoxin or chinaberry.

- XXXXXXXXXXXXXX believed that neem and its products should not be scheduled on the basis of long history of safe use. The submission also recognised the potential problem of aflatoxin contamination and suggested that best farm practices should be used when growing, harvesting, storage and processing the crop. An extract from EXTOXNET on the toxicological profile of technical grade azadirachtin was also provided as well as information from other websites, e.g. New Crops and the USEPA.

  Secretary's Note: The EXTOXNET extract indicated that products containing azadirachtin must bear the signal word "Caution" or "Warning" on the label, although no rationale for this requirement was stated. In addition, the purity of the technical grade azadirachtin was not specified.

- XXXXXXXXXXXXXX objected the proposal to include neem in Schedule 5 or 7, on the basis that neem was a medicinal and non-toxic species and that reversible infertility did not legally represent toxification, i.e. mere suppression of a biological process. The submissions(s) highlighted that Neem had a history of safe use in India. In addition, the submission(s) also recommended priority listing of Camphor laurel (*Cinnamomum camphora*) due to toxicity concerns.
- XXXXXXXXXXXXXX stated its position that no neem seed oil or extracts/derivatives, nor the leaf, nor any other part or product from the Neem tree should be scheduled at this stage, as there was a wealth of studies and reports alluding to its safety and beneficial properties. The company indicated that neem was becoming widely used overseas and it was not aware of any country that considered or listed neem, in any of its forms, as a dangerous chemical. XXXXXXXXXXXXXX advised that various parts of the neem tree were being used for specific formulations, depending on the chemical characteristics of the extracts. XXXXXXXXXXXXXX supplied the following information on their products:
  - The leaf in powdered form and leaf extracts (or tincture) were being used in the majority of XXXXXXXXXXXXXX products, as the leaf did not contain azadirachtin (not for use in controlling insects), and the leaf was well regarded for its beneficial use on the human skin.
  - Powdered bark of the tree did not contain azadirachtin and was being used mainly for its traditional beneficial effects on the human skin.
  - Another component of neem being used was pure 'cold-pressed neem seed oil' which contained azadirachtin, and regarded worldwide as the main and specific ingredient responsible for insect control.
  - The following additional information had been provided including comments on the information available on the NDPSC website on neem:

    ⇒ There was no evidence that neem oil penetrated the skin and caused toxicological concern in animal or man. Toxicological data was

included to demonstrate that the unexpected toxicological manifestations associated with neem were largely due to unexpected contaminants such as aflatoxins.

⇒ XXXXXXXXXXXXX supported testing of neem products and full certification to international standards, i.e. OECD Guidelines for Testing of Chemicals, Section 4, Number 403 adopted 12th May, 1981. Triple-filtered, certified 100% pure Neem Seed Oil – Aflatoxin free, with no extractions or additives, should be approved for use, and be used as the standard in toxicity studies. In the case of the Leaf Extract it was imperative that the extraction method be carefully and accurately recorded.

⇒ The use of the toxicological information relating to XXXXXXXXXXXXX (in studies on whole neem seed polar solvent extracts), containing 12% azadirachtin (natural pure seed oil contains 0.05-0.06% azadirachtin), for the scheduling of neem in its natural state was inappropriate.

⇒ Studies relating to the methanolic extract of Neem Seed Kernel, with a reputed 12% azadirachtin content, did not realistically reflect the typical exposure of humans and animals to neem in its agricultural use.

⇒ Azadirachtin was present in neem oil but not in the leaf. The leaf, which may be shown to be toxic in unrealistic quantities when ingested, could be demonstrated to be of great benefit in certain applications when taken at the appropriate dose. Its use in agriculture was very minor, if at all.

⇒ The Registry of Toxic Effects of Chemical Substances (RTECS) gave the LD_{50} for Neem Oil as 14,000 mg/kg – bw in rats. However, without any evidence in support, the NDPSC had equated this to approximately 280- 560 mg/kg of the bitter principles. XXXXXXXXXXXXX did not believe that estimations were appropriate for this serious review of Neem.

⇒ The NDPSC's comments in respect to human death (children) following a dose of as low as 5 mL were considered not scientifically based, as it was not established whether the ingested oils were 100% pure cold-pressed Neem Seed Oil free from aflatoxins and additives. In addition, of further concern was the inference that Neem was being mistaken for an extract of the Chinaberry Tree, which was known to be toxic.

⇒ Another paper had reported 13 cases of Neem oil poisoning in children between the ages of 21 days and 4 years. No valid reason could be drawn as to why Neem oil should be administered to a 21-day-old healthy baby. XXXXXXXXXXXXX a cautioned against acceptance of this type of anecdotal evidence without proper validation.

⇒ XXXXXXXXXXXXX was not recommending that neem oil should be used as a contraceptive and made no comment regarding it's

abortifacient/embryocidal effects. In the event where Neem Seed Oil was approved for use other than in agriculture, it would be recommended that it only be used topically and that it should not be taken orally or inserted into any body cavity.

⇒ The NDPSC's concern that there was insufficient data to establish an ADI for various Neem derivatives was noted. This was due to the different ways in which the different parts of neem were being processed and it was suggested that the unadulterated and aflatoxin-free pure neem seed oil be examined initially, followed by the establishment of an ADI.

⇒ A minimum requirement for aflatoxin content should be established for all imported and locally produced Neem seed oil, with a certificate stating that the product was aflatoxin free.

⇒ XXXXXXXXXXXXX concurred that proper control of Neem and its derivatives was the best way forward and specific instructions for its use should be included on product labels and product information sheets.

⇒ It was proposed that the first principle for better control and administration of Neem in Australia should take into account its intended uses, i.e. agriculture, medicinal and pharmaceutical, cosmetic - beauty aids and veterinary.

Secretary's Note: The submission included data from toxicological studies which were stated to comply with the OECD Guidelines for Testing of Chemicals (Section 4, No. 403, adopted 12th May, 1981) and GLP. The chemical components of the test substance (neem oil) used in these studies were not identified except that it contained 1500-1600 ppm of azadirachtin. No long- term toxicity studies were conducted/submitted. The acute oral LD50 of neem oil stated is>5000 mg/kg bw (rat), acute dermal LD50 is >2000 mg/kg bw (rat) and acute inhalation LC50 is >2.11$\pm$0.06 mg/L of air (rat).

- XXXXXXXXXXXXX opposed the inclusion of *Azadirachta indica* (Neem) in Appendix C and urged careful consideration of the following issues:
  - *Azadirachta indica* was one of the world's most respected natural plant products and was used in natural treatments in India for over 4000 years.
  - The use of *Azadirachta indica* was not restricted to the level proposed by the NDPSC anywhere else in the world. The proposed inclusion in Appendix C would isolate Australia from access to this valuable natural product.
  - RIRDC recently completed a review of Neem's potential as a new crop in Australia due to the expanding demand throughout the world. Neem was being promoted as an alternative crop for Australian farmers and the proposed scheduling would put an end to all research projects currently being undertaken.

- A search on the Internet revealed approx. 1200 Australian companies actively involved in the promotion of products containing Neem, and a large number of these companies would be unaware of the scheduling proposal.
- The CMEC had recently evaluated *Azadirachta indica* and recommended to the TGA that the substance was suitable for topical use in complementary medicines with label safety directions.

- XXXXXXXXXXXXXX opposed the scheduling of neem seed oil as 'dangerous poison', on the basis that this was misleading and discouraged the use of a safe alternative. This was made on the basis of the long history of safe use in India and other countries.
- XXXXXXXXXXXXXX opposed the proposal to schedule neem in Australia as neem had a long history of use in Indian Ayurvedic medicine and modern research confirmed its medicinal value. The company urged the Committee to consider the seriousness of a "blanket" ban and take a considered view, particularly in regard to dermal application. Furthermore, the submission also stated its concerns regarding the lack of adequate notification and limited opportunity to participate more fully in the process.
- XXXXXXXXXXXXXX proposed that appropriate measures be put in place to ensure that imported neem products into Australia were screened for purity, cleanliness and grade. It stated that labelling neem leaf tea and neem leaf oil with "poison" was not acceptable.
- XXXXXXXXXXXXXX rejected the proposed scheduling of neem derivatives on the following grounds: the recommendation lacked scientific validity, the NDPSC did not take into account a broad range of matters specified under Section 52E, and the data presented was inconsistent with broader epidemiological data and did not support the conclusion that neem derivatives posed a genuine public health. In addition, it was stated that the proposed scheduling of neem on the basis of unsubstantiated data would necessitate a re-assessment of a broad range of common household/garden products that were exempt or classified as S5. XXXXXXXXXXXXXX supported the following:
    - adoption of uniform standards for neem oil/derivatives;
    - ensure that neem derivatives were certified to be 'aflatoxin free';
    - warning statements advising to 'keep out of reach of children' and 'do not swallow' should be placed on labels of neem containers; and
    - further research should be conducted into the safety, efficacy and toxicity of neem derivatives compared to other substances used for similar purposes.

- XXXXXXXXXXXXXX advised that its sister company would be evaluating in the next 8 months the spectrum of toxicological activity of neem. The evaluation was said to include chemical composition including any overlap, efficacy testing, stability, toxicity testing and environmental testing. XXXXXXXXXXXXXX had asked that

any scheduling of neem be suspended until the NDPSC had access to the results of this evaluation.

- XXXXXXXXXXXXXX considered the scheduling of neem oil as a poison erroneous and an unnecessary move at a time when countries around the world were moving towards encouraging the use of this valuable bio-resource for their agriculture and health programmes. XXXXXXXXXXXXXX had asked that the decision to schedule neem be postponed and invited the NDPSC Secretariat to attend the 7th World Conference on Neem, to be held in November 2002, to obtain the latest scientific information on neem. The submission highlighted the following points:
    - Neem is only mildly toxic and is less toxic than table salt (LD50 for Azadirachtin is 5000 mg/kg vs 3000 mg/kg for table salt).
    - Neem is efficacious for a wide range of diseases including rheumatism, joint pains, skin diseases, etc.
    - The reported infant mortality associated with consumption of neem oil may have been caused by contaminated oil. The neem seed kernel oil produced by India for international markets was generally accompanied by laboratory certification to confirm that it was free of aflatoxin.
    - The contraceptive action of neem may have been confused with infertility.
    - Neem had a long history of use in the Indian sub-continent.
    - The dosage of neem formulations was between 3-5 mL per liter of water and 200 litres of water is sprayed over 1 hectare. Neem did not have the toxicity and problems associated with synthetic pesticides including environmental pollution, health hazards due to high residual levels, indiscriminate destruction of insects and the potential for development of resistance by insects.
    - Neem oil was unlikely to be abused, given its bitter taste and unpleasant smell.
    - Neem had a wide range of proposed uses, i.e. human and animal health, agriculture, cosmetic and toiletries, and food storage.

- XXXXXXXXXXXXXX maintained its position regarding the scheduling of *Azadirachta indica* put to the NDPSC at its June 2002 meeting. XXXXXXXXXXXXXX believed that it was a sensible approach to ensure that cold-pressed oil from Neem seed kernels was used appropriately and restrictively as a Listable substance. It was stated that if additional warning statements were required to address concerns of use by pregnant women, XXXXXXXXXXXXXX would not see this as an unreasonable approach. However, if the use of additional conditions and warning statements could be avoided by the determination of safety cut-off concentrations or similar distinguishing mechanisms, then this would be the preferable.