Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

National Drugs and Poisons Schedule Committee

Record of Reasons

53rd Meeting
17-18 June 2008

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GLOSSARY

ABBREVIATION	*NAME*
AAN	Australian Approved Name
AC	Active Constituent
ACCC	Australian Competition and Consumer Commission
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
APMF	Australian Paint Manufacturers Federation
APVMA	Australian Pesticides and Veterinary Medicines Authority
AQIS	Australian Quarantine and Inspection Service
ARfD	Acute Reference Dose
ASCC	Australian Safety and Compensation Council
ASMI	Australian Self-Medication Industry
ARTG	Australian Register of Therapeutic Goods
BAN	British Approved Name
CAS	Chemical Abstract Service
CHC	Complementary Healthcare Council of Australia
CMEC	Complementary Medicine Evaluation Committee
CMI	Consumer Medicine Information

COAG	Councils Of Australian Governments
CPAS	Chemical Product Assessment Section
CRC	Child-Resistant Closure
CRIH	Chemical Review and International Harmonisation
CTFAA	Cosmetic, Toiletry & Fragrance Association of Australia
DAP	Drafting Advisory Panel
DSEB	Drug Safety and Evaluation Branch
EAGAR	Expert Advisory Group on Antimicrobial Resistance
ECRP	Existing Chemicals Review Program
EPA	Environment Protection Authority
ERMA	Environmental Risk Management Authority
FAISD	First Aid Instructions and Safety Directions
FOI	Freedom of Information
FSANZ	Food Standards Australia New Zealand
FWP	Fluorides Working Party
GHS	Globally Harmonised System for Classification and Labelling of Chemicals.
GIT	Gastro-intestinal tract
GP	General Practitioner
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 per cent 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 per cent 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
NPMB	Non-Prescription Medicines Branch
NZ	New Zealand
OCM	Office of Complementary Medicines
OCS	Office of Chemical Safety
ODBT	Office of Devices, Blood and Tissues
OOS	Out of Session
OTC	Over the Counter
PACIA	Plastics And Chemicals Industries Association
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
PSA	Pharmaceutical Society of Australia
QCPP	Quality Care Pharmacy Program
QUM	Quality Use of Medicines
RFI	Restricted Flow Insert
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
SVT	First aid for the solvent prevails
TCM	Traditional Chinese Medicine
TGA	Therapeutic Goods Administration
TGC	Therapeutic Goods Committee
TGO	Therapeutic Goods Order
TTHWP	Trans-Tasman Harmonisation Working Party
TTMRA	Trans-Tasman Mutual Recognition Agreement
UK	United Kingdom
UPS	Uniform Paint Standard
USA	United States of America
USFDA	United States Food and Drug Administration

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 INTERPRETATION OF AEROSOL CONCENTRATION IN THE SUSDP

PURPOSE

The Committee noted the inclusion of the interpretation of aerosol concentration in the SUSDP as a standing item on the agenda to remind the Committee that the implementation date for part of the June 2007 Decision (to Part 2 Paragraph 8(2)), regarding a specific labelling requirement for aerosols to express concentration as mass of the poison per stated mass of the preparation, was 1 January 2009.

2.2 SUSDP, PART 2

Item deleted.

2.3 SUSDP, PART 3

Item deleted.

2.4 SUSDP, PART 5

2.4.1 APPENDIX I (THE UNIFORM PAINT STANDARD - UPS) INCLUDING LEAD IN PAINTS OR TINTERS

PURPOSE

The Committee considered a review of Appendix I including a proposal to ban lead in paints and tinters at ≥ 0.1 per cent lead.

BACKGROUND

Prior to the October 2007 NDPSC meeting, NICNAS published a Priority Existing Chemical (PEC) assessment report *Lead in Industrial Surface Coatings and Inks* (http://www.nicnas.gov.au/Publications/CAR/PEC/PEC29.asp). Recommendation (2)(b) was that the Committee consider reviewing Appendix I in relation to the declared lead compounds for surface coatings.

The October 2007 NDPSC Meeting agreed that, as industrial use of paint fell within the Australian Safety and Compensation Council's (ASCC) jurisdiction, the various references to industrial use in Appendix I were in need of review. The Committee agreed

to foreshadow a review of Appendix I for the February 2008 NDPSC meeting. The February 2008 NDPSC Meeting noted progress to date on the review, including a workplan drafted and agreed by XXXXX and XXXXX. The Members also noted that no pre-meeting comment had been received regarding this issue.

DISCUSSION - SUBMISSIONS

How Appendix I, the Uniform Paint Standard (UPS) works

Appendix I is currently applied in 2 ways:

- 1) Part 2, Paragraph 16 references the First, Second and Third Schedule substances in Appendix I to allow reduced packaging and labelling requirements for paints/tinters than otherwise required by scheduling (these substances in paints/tinters still remain scheduled poisons, facilitating jurisdictional enforcement). Part 2, Paragraph 16 also requires application of the First, Second and Third Schedule specific labelling requirements set out in the Appendix F, Part 3 paint entry.
- 2) Appendix I also provides regulations (mostly prohibitions) for adoption by States and Territories. These regulations stand alone and there are no provisions elsewhere in the SUSDP which make these regulations a requirement of scheduling compliance. As such, the application of the regulations depends entirely on how the States and Territories implement them and would probably not be beholden to the SUSDP controls (e.g. the SUSDP's labelling exemptions for industrial use and the general exemptions through Appendix A may not apply).

XXXXX were requested to comment on how XXXXX implement the Appendix I regulations. XXXXX were also asked whether there may be benefit in considering a new paragraph in Part 3 which might allow all of Appendix I to be picked up if the SUSDP were to be adopted by reference, such as:

- **41a.** (1) A person must not possess or use a paint unless compliant with the provisions set out under Appendix I (Uniform Paint Standard).

The Committee noted the following from XXXXX responses (these responses had not been informed by the information in the XXXXX comment discussed latter):

QUEENSLAND (QLD)

- Appendix I is adopted under QLD *Public Health Regulation 2005* and given force by the *Public Health Act 2005*. The Act states:
  - ***60.*** *Person must comply with standard*

    (1) A person manufacturing, selling, supplying or using paint must comply with the standard.

    (2) In this section "prescribed" means prescribed under a regulation, "standard" means the prescribed part of the SUSDP dealing with paint, compiled by the

Australian Health Ministers' Advisory Council (AHMAC) and published by the Commonwealth.
(Note: QLD was aware the AHMAC reference needed to be changed)

– *The regulation states:*

18A Paint – Act, s 60. For the Act, section 60(2), definition standard, the prescribed part of the SUSDP dealing with paint is Appendix I (Uniform Paint Standard).

- XXXXX asserted that an additional provision in SUSDP Part 3 was unnecessary, but would not hurt either, as XXXXX did not (yet) adopt Part 3. XXXXX also discussed the Appendix I review with XXXXX and advised that responses tended to support that a full review of Appendix I was probably unnecessary at this stage, given that the review was originally proposed because of concerns with lead paint and the National Industrial Chemical Notification Assessment Scheme (NICNAS) Priority Existing Chemical (PEC) review of lead, rather than wholesale problems with Appendix I itself.
- XXXXX suggested that once XXXXX recommendations were received (below), the Committee could finalise its position on lead and make any necessary amendments. Further issues with Appendix I (if any) could then be addressed individually, rather than by pursuing a complete review of Appendix I.

NORTHERN TERRITORY (NT)

- NT adopt Appendix I in Regulation 13 of the *Poisons and Dangerous Drugs Regulations*:
  – ***13.*** *Appendix I: paint standards*

    (1) Appendix I applies in relation to the manufacture, supply and use of paint.

    (2) A person must not contravene Appendix I.
- XXXXX asserted that a separate paragraph in Part 3 would offer no benefit.

TASMANIA (TAS)

- Appendix I is picked up by the *Tasmanian Public Health Act 1997,* and is issued as guidelines where it is a legal requirement to comply with these guidelines. At this time XXXXX would not pick up the proposed Part 3 paragraph as the above arrangements would give the same effect.

SOUTH AUSTRALIA (SA)

- Appendix I, Appendix A and Appendix C are incorporated into the *Controlled Substances (Poisons) Regulations 1996* (regulation 5) (without any modifications). Lead compounds in paints (zinc-based > 0.2 per cent, others > 0.1 per cent) are classified as Schedule 6 poisons. This enables enforcement of certain offences under the *Controlled Substances Act 1984* i.e. it is an offence to use, sell, supply or purchase

a poison for a purpose prohibited by the regulations (including the current Appendix I).

- There is no specific exemption under this legislation for industrial/manufacturing use (except for the SUSDP's labelling exemption). Therefore it would be expected that the requirements of Appendix I apply in both domestic and industrial settings. However, the SA Department of Health – Public Health Division (as administrators of this legislation) did not typically investigate occupational exposure because it was expected that industrial use was adequately regulated by Safework SA and ASCC.
- SUSDP Part 3 is not adopted so a new paragraph would not take effect in SA. However, the wording of a new paragraph should be consistent with Appendix I i.e. prohibition of manufacture, sell, supply and use rather than possession and use. Opinion should be sought by jurisdictions that strike out Appendix I to determine whether reference to it in Part 3 of the SUSDP would be valid.
- XXXXX also identified a number of related issues:
  - Agrees with NICNAS that lead in paints and inks posed a potential health risk and supported consideration and consultation on the amendment of Appendix I or Appendix C to mirror NICNAS's recommendations.
  - NICNAS reported that all lead compounds for industrial use are imported. Therefore the point of import would appear to be the most effective stage on which to focus regulatory activity e.g. Australian Inventory of Chemical Substances (AICS) annotation and consideration of declared lead compounds and lead compound-containing paints as prohibited imports under Customs legislation.
  - The responsibility for addressing occupational exposure from industrial use of lead compounds in surface coatings and inks lies with ASCC and they are in a position to be able to minimise risk.
  - Part 4 of Appendix I should be amended to update the Australian Standards for toys to the current version AS/NZS ISO 8124.3:2003.
  - It appears that there is no regulation of the lead and cadmium content of surface coatings/clay of ceramic ware that comes into contact with food (with the potential for leaching) that is manufactured in Australia. XXXXX suggested that the Committee consider reviewing this issue (see item 8.2).

VICTORIA (VIC)

- Appendix I is not adopted into the *Victorian Drugs, Poisons and Controlled Substances Act 1981*. The suggested Paragraph in Part 3 would not influence that situation. It may be preferable to work through the Appendix I review to identify the problems with the use of particular substances in paints, then work out how best to regulate those uses.

- Advised that it was not clear that any Victorian department picked up Appendix I, however Consumer Affairs Victoria did take responsibility for product safety. In October 2007, Consumer Affairs Victoria issued a Product Safety Fact sheet *Children's toys containing lead.* An 18 month ban order was issued, effective from 25 September 2007, for all children's toys that do not comply with AS/NZS 8124.3:2003. Consumer Affairs Victoria also has bans on chopsticks and candle wicks containing lead.
- Appendix I is also not adopted as part of agvet legislation in Victoria. The Victorian Workcover Authority has advised that the UPS was not called up by Victorian occupational health and safety or dangerous goods legislation. A separate Victorian Department of Primary Industries (DPI) Order covered the use of tributyl tin in anti-fouling marine paint.

Members additionally noted the following advice tabled at the Meeting

WESTERN AUSTRALIA(WA)

- Regulation 33A in the WA Poisons Act picks up Appendix I and also references back to Part 1 of the SUSDP.

NSW

- Does not adopt Appendix I. NSW has its own provisions regarding paints of a type similar to those in Appendix I, but these do not mirror the Appendix I regulations.

ACT

- A bill has been tabled to adopt the current Appendix I (except that the bill would pick up the new Australian Standard for childrens toys).

Terms of reference

The February 2008 NDPSC Meeting agreed that the review's terms of reference should be finalised. XXXXX had subsequently clarified that, except for lead compounds, NICNAS had not undertaken PEC assessments of the chemicals listed in Appendix I and therefore XXXXX had restricted XXXXX review to lead compounds (see below). The Secretariat therefore proceeded on the basis of a background paper for the June 2008 NDPSC Meeting (with input from XXXXX) rather than a separate review paper.

Conflict between the Schedules and Appendix I

The February 2008 NDPSC Meeting agreed that while reviewing substances in the First, Second or Third Schedules of Appendix I, any schedule entries for these substances should also be examined to ensure that there would be no conflict. The Secretariat advised that:

- This was examined by the November 1999 and February 2000 NDPSC Meetings:
  - At the time the only scheduling cut-offs exempting paint with less than the Appendix I limit were for ethylene glycol monoalkyl ethers, toluene and xylene.

Paints / tinters containing more than the Appendix I limit of other Schedule 6 or 7 poisons were being labelled 'WARNING' while those containing less (and presumably less hazardous) were required to be labelled 'POISON' or 'DANGEROUS POISON'.

- The February 2000 NDPSC Meeting therefore amended the remaining schedule entries to include the appropriate exemptions (i.e. the entries for dichloromethane, antimony, barium, cadmium, chromates, lead compounds and selenium).

- The Secretariat has reconfirmed that the various schedule entries for Appendix I listed substances have exemptions for paints / tinters below the Appendix I limits except the following (where, Members agreed, labelling exemptions for paint/tinters did not appear to be appropriate):
  - Antimony for therapeutic use.
  - Barium silicofluoride when coated on paper in an amount not exceeding 8 mg/cm^2.
  - Cadmium compounds for human therapeutic use.
  - Selenium for therapeutic use.

Second Schedule paints

At the February 2008 NDPSC Meeting a Member noted that the substances classified as "Second Schedule" in Appendix I did not appear to be referred to by the regulations set out in Appendix I. The Committee agreed that the review should examine whether the "Second Schedule" was still necessary.

Members were advised that Second Schedule paints were referred to in Part 2 Paragraph 16 (reduced packaging and labelling requirements for paints/tinters). Second Schedule specific labelling requirements are also set out in the Appendix F, Part 3 paint entry.

Reference to industrial use

Regarding application of Appendix I regulations to industrial use Members again noted the discussion above about how Appendix I works.

Regarding the specific references to industrial use in Appendix I, these appeared to have been added following an XXXXX request to the November 1989 Drugs and Poisons Schedule Sub-committee (DPSSC) Meeting. XXXXX asserted that industry had difficulty with the wording "….the interior or exterior of any building…" as this could sweep up industrial situations such as chemical plants and oil refineries where the use of First Schedule paints was considered necessary. The Committee at that time noted that the clauses were intended to cover homes, schools, offices, etc., only, not situations where First Schedule paints would not pose a hazard to public health. XXXXX at that time proposed "for any fence, wall, post, gate or the interior or exterior of any building such as a dwelling, school, office or hospital to which the public has free access but excluding structures such as industrial buildings, mines, oil terminal etc., where the

special protective qualities of a First Schedule paint are essential". This was circulated out of session to Members for comment and finalisation at the February 1990 meeting.

XXXXX comment

XXXXX provided a comment on the lead entries in Appendix I. Members particularly noted the following recommendations:

- The exemption allowing use of lead carbonate in mirror backing should be removed as industry has indicated that this use has been phased out. However, controls are needed to avoid future use of lead carbonate in mirror backing.
- Lead-containing paints should be excluded from Appendix I and, instead, be captured by an entry in Appendix C in a similar manner to lead-containing inks.
- XXXXX suggested two possible options for implementing the above:
- **OPTION 1** (XXXXX preferred)
  - Delete Clause 1, the Third Schedule and the related Clause 3 of Appendix I.
  - Add an entry for lead containing paints in Appendix C. Appendix C entry should either reflect prohibition for:
    - LEAD COMPOUNDS in surface coatings except preparations containing 0.1 per cent or less of lead calculated on the non-volatile content of the surface coating [preferred option]; or
    - LEAD COMPOUNDS in surface coatings containing more than 0.1 per cent lead calculated on the non-volatile content of the surface coating, **except** in surface coatings exclusively used for industrial applications. (Alternative option if the Committee prefers that only domestic uses should be specified in Appendix C).
  - XXXXX also noted that consequential amendments would need to address the references to the Third Schedule in Part 2, paragraph 16 and Appendix F, and the entry for zinc based paints in Schedule 6.
  - Clause 4 of Appendix I should also be amended to include reference to the most current Australian Standard for children's toys (AS/NZS ISO 8124.3:2003) and adding 'or its successor" to avoid inconsistencies in case of update in the future. [Members noted the wording "as specified or amended from time to time" rather than "or its successor" was the usual SUSDP wording convention.]

- **OPTION 2** (the alternative of retaining lead in Appendix I)
  - Delete Clause 1 and the Third Schedule as above. Consequential amendments to Part 2, paragraph 16, Appendix F, Schedule 6 and Clause 4.
  - Replace the current Clause 3 with either:
    - A person must not manufacture, sell, supply or use surface coatings containing more than 0.1 per cent lead calculated on the non-volatile content of the surface coating, for application to any surface accessible to the public or

surfaces where contamination of food or drink is possible. [This may help exclude industrial uses without potential to cause public exposure to lead]; or

- A person must not manufacture, sell, supply or use surface coatings containing more than 0.1 per cent lead calculated on the non-volatile content of the surface coating. [XXXXX asserted that this option considered that the scope of the SUSDP and Appendix I is limited to domestic applications and specific exclusion of industrial application may be redundant].

[Members again noted that the assumption that Appendix I was limited to domestic applications did not reflect the current implementation of Appendix I by jurisdictions.]

Members also noted the following from the XXXXX comment:

Consultation with XXXXX

- XXXXX agreed that:
  - the revision of Appendix I would be addressed incrementally;
  - XXXXX would restrict the review to lead entries as NICNAS had not undertaken PEC assessments of the other chemicals listed in Appendix I; and
  - the cut-offs for the non-lead entries in Appendix I could be part of an NDPSC public consultation process over a number of meetings.

Consultation with industry

- XXXXX had surveyed industry (with XXXXX assistance) to determine the extent of lead carbonate use for mirror backing in 2006 and 2007. Eleven companies responded stating that such paints had not been manufactured, imported, supplied or used for mirror backing during this period. Additionally, a mandatory call-for-information during the NICNAS PEC assessment found that lead carbonate was not imported or manufactured for use in industrial surface coatings from 2003 to 2005. This information suggested that surface coatings containing lead carbonate were no longer used for mirror backings in Australia.
- XXXXX was also invited to propose changes to Appendix I. XXXXX response noted that Appendix I was not the most appropriate way of regulating industrial coatings, as when called up by state governments the industrial aspect was not captured by the state legislation. [Member again noted that this statement did not fully reflect the current implementation of Appendix I by jurisdictions.]
- Industry pointed out that timing of any restrictions/prohibitions considered by the Committee that might affect industrial uses should mirror the PEC recommendation on introduction of lead compounds in industrial surface coatings.

Additional considerations

- From April 2008, following variations to AICS, surface coatings containing more than 0.1 per cent lead carbonate cannot be imported or manufactured for industrial application to mirror backings.

- Clause 3, which applies to lead compounds, did not contain an exemption for "exclusively industrial applications" and it was difficult to clarify the divide between industrial and domestic application, as public exposure to lead containing paint cannot be excluded for most of the applications. XXXXX noted that, while application of lead containing paint to a bridge may be an industrial use, lead exposure to the public was still likely as the public had access to it. Similarly, lead exposure to the public cannot be excluded if lead containing paints are applied to industrial premises that manufacture or process products intended for human consumption [Members noted that this last concern currently appeared to be addressed by subparagraph 4 of Clause 3].
- XXXXX considered that the most appropriate approach for scheduling of lead compounds was to minimise public exposure to lead given that industrial uses could lead to public exposure.
- The Third Schedule of Appendix I currently allows for lead content of up to 0.2 per cent (in the non-volatile content of the paint) for zinc-based paints. This exceeds the cut-off of 0.1 per cent identified during the PEC assessment.
- Appendix I was not adopted or referenced in the State and Territory poisons legislation in a consistent manner.
- There have been a number of substances, such as mercury, that had been removed from Appendix I and replaced with general controls in a schedule entry.
- Clause 4 contained a reference to an outdated Australian Standard for children's toys.

XXXXX response to the XXXXX recommendations

Members were advised that XXXXX had responded to the XXXXX recommendations and was of the view that it was preferable to keep all references to paint within Appendix I (XXXXX Option 2). In regard to the replacement of Clause 3 XXXXX supported proposal (b) rather than (a).

XXXXX asserted that by keeping all the paint references within Appendix I it makes it easier for users of the SUSDP to access the paint section. It should also make it easier for authorities and other stakeholders to reference the paint restrictions through their own legislation, codes of practice, etc. [Members noted that XXXXX did not comment on (and may not be aware) of the divergence in adopting the Appendix I regulations by jurisdictions].

Neither XXXXX nor the XXXXX provided specific comment regarding the control of lead in tinters prior to incorporation into a paint product.

History of the UPS

The UPS was originally a stand-alone document maintained by the NHMRC's Occupational Health Committee (OHC) and then by NHMRC's Public Health Committee

(PHC). The UPS was first incorporated into the SUSDP as Appendix P in 1990. A review was undertaken in 1994 by the Working Group to Review the Paint Standard (WGRPS). The November 1999 NDPSC Meeting agreed to change Appendix P to Appendix I.

Members noted the following summary of the UPS history:

Table 1: Summary of cut-offs for the First, Second and Third Schedule Paints

Substance	**Current Cut-off**	**UPS 1986**	**App P 1990**	**Additional Changes**
The First Schedule				
Antimony or antimony compounds other than antimony titanate pigments	> 5%	> 5%, no antimony titanate exclusion	As current. November 1988 Meeting agreed that antimony titanate pigments should be exempt (low solubility/absorption).	
Barium salts except barium sulfate or barium metaborate	> 5%	As current		
Cadmium or cadmium compounds	> 0.1%	As current		
Chromium as chromates of ammonia, barium, potassium, sodium, strontium or zinc	> 5%	> 5% as chromates of alkali metals and ammonia	As current - March 1988 Advisory Panel recommended replacing alkali metal chromates with barium, strontium, zinc, sodium and potassium (those actually in use). The November 1989 Meeting confirmed the recommendation.	
Selenium or selenium compounds	> 0.1%	As current		
The Second Schedule				
Dichloromethane	> 5% by wt	As current (result of an April 1964 Meeting recommendation to the UPS)		
Ethylene glycol monoalkyl ethers and their acetates	> 10% by vol	No mentioned	As current: 1987/1988 Advisory Panel looked at Schedule 6 substances that may be in paints re whether to add these to the UPS (included ethylene glycol ethers and their acetates, toluene and xylene).	
Toluene	> 50% by vol	Not mentioned	As current (see above)	
Xylene	> 50% by vol	Not mentioned	As current (see above)	
Third Schedule				
Lead or lead compounds	> 0.1%	Class 1 Paint > 1%	Class 1 > 0.5%	April 1989 draft UPS changed 1% to 0.5%. November 1989 Meeting 0.25% (allowed 2 year implementation). May 1992 Meeting noted Standards Australia may lower lead in toys from 0.25% to 0.09%. April 1994 Meeting agreed to need to review 0.25%. November 1994 Meeting [WGRPS] agreed to 0.1% (phase in by December 1997). Feb 2004 Meeting considered APMF plan to ban lead paint – referred to NOHSC. October 2007 NDPSC considered NICNAS review of lead and felt that domestic use in paint was already controlled (through the Schedule 6 lead compounds entry and

				Appendix I) while industrial use would be controlled by ASCC.
Lead or lead compounds as an impurity in zinc based paint	> 0.2%	Not mentioned	Not mentioned	November 1994 Meeting [WGRPS] agreed to 0.2%.

Additionally:

- In 1986 antimony (> 5 per cent), mercury (> 0.1 per cent) and tin organic compounds (> 3 per cent) were also UPS Class 1 paints. These substances did not appear in Appendix P of SUSDP 5 (1990).
- In the 1986 UPS benzene (> 1.5 per cent by vol), dichlorethane∗ (> 5 per cent by wt), dichlorethylene (> 10 per cent by wt), dichlorbenzene∗ (> 5 per cent by wt), methanol (> 1 per cent by wt), nitrobenzene (> 1 per cent by wt), pyridine (>2 per cent by wt), trichlorethylene∗ (> 5 per cent by wt) and free organic isocyanates (> 0.1 per cent by wt) were UPS Class 2 paints. ∗Only these substances were subsequently included in the Second Schedule of SUSDP 5 Appendix P. The November 1994 NDPSC Meeting removed dichlorobenzene, dichloroethane and trichloroethylene from the Second Schedule.
- In the 1986 UPS the Class 3 paints referred to a 1980 Australian Standard regarding toxic substances in paints for toys. In SUSDP 5 there was no Third Schedule in Appendix P.

Table 2: Development summary of SUSDP paragraph 16 and Appendix I regulations

Current controls	**UPS 1986**	**Appendix P SUSDP 5 1990**	**Comments on changes**
Paragraph 16			
Exemption from paragraph 7 labels for: •Schedule 5 paints/tinters •First, Second or Third Schedule paints with labels (warning, child access, Appendix F, strength). •First, Second or Third Schedule tinters with labels (strength & if > 0.1% lead, warning, child access, Appendix F)	•SUSDP 1 (1986) – container requirement exemption for paints (**except** cosmetic or therapeutic use). •UPS (1986) – labelling requirements for paint + for Class 1 (re child access) Class 2 (re child access & ventilation) & tinters with > 10% lead (re child access and lead content)	Appendix P Same intent as UPS 1986 with editorial variation.	•The Schedule 5 exemption & moving the UPS concessional labelling to SUSDP labelling section proposed by the 1987/1988 Advisory Panel & November 1989 Meeting. •February 1990 Meeting noted issue with >10% lead for tinters. November 1990 Meeting removed the tinters exemption. •November 1994 Meeting agreed to tinter conditional exemption, with additional controls if >0.1% lead. [WGRPS] Paint / tinter labelling essentially as current (incl. current App F wording), but not separated from App P. •November 1999 Meeting (AHMAC directed) moved

			label requirements to SUSDP Part 2 & Appendix F.
Appendix I Paragraph 1 – white lead restriction			
Restrict to mirror backing (<15%, < 40 microns, when covered by a non-lead paint).	Restrict to mirror backing manufacture authorised by State authorities.	Restrict to application as a mirror backing.	•August & November 1989 Meetings wished to totally prohibit. February 1990 Meeting noted PHC had re-exempted mirror backing. •August 1990 DPSSC noted PHC reservations – Industry committed to phase out lead in mirror backing paints. •November 1994 Meeting agreed to <15%, < 40 microns, when covered by a non-lead paint. •May 1997 Meeting agreed the < 15% was based on non-volatile content.
Appendix I Paragraph 2 – Banned applications of First Schedule Paint			
1) roof, or surface for collection/storage of potable water. 2) furniture. 3) any fence, wall, post, gate or building interior or exterior **except** exclusive industrial building, mining or any oil terminal. 4) premises in contact with human or animal consumption products.	1) roof <u>but not surface for collection/storage of potable water</u>. 2) furniture. 3) any fence, wall, post, gate or <u>exterior</u> of <u>any</u> building or structure, or <u>interior</u> of any building or structure <u>intended for human use</u>. 4) Compliance with an Australian Standard for wraps, containers or any food contact surface.	1), 2), 3) Essentially as current, minor editorial differences. 4) As current except limited to human consumption (animal use not mentioned).	•August & November 1989 & February 1990 Meetings addressed wording and conditions of 1)2)3). •November 1989 and February 1990 Meetings considered exemption for industrial etc – wording set February 1990 Meeting. •February 1990 Meeting also considered premises re human consumption. •August 1992 Meeting considered animal consumption. •November 1994 WGRPS version included animal consumption.
Appendix I Paragraph 3 – Banned applications of Third Schedule Paint			
1), 2) as above. 3) any fence, wall, post, gate or building interior or exterior, bridge, pylon, pipeline, storage tank or any similar structure 4) extending above to also included equipment or utensils	Lead captured as Class 1 paint, so above restrictions applied.	Lead captured as First Schedule paint, so above restrictions applied.	November 1994 [WGRPS] agreed to move lead from First Schedule to new Third Schedule with consequential inclusion of paragraph 3.
Appendix I Paragraph 4 – Controls on any paint for application to toys			
Only if compliant with specifications in Australian Standard 1647	Intent as current (Class 3 paints references AS 1647)	As current, minor editorial differences.	•August 1989 Meeting addressed lead on toys. •June 2006 Meeting confirmed the SUSDP "toy"

			definition captured child play equipment.
Appendix I Paragraph 4 – Controls on any paint containing a pesticide			
Prohibited **except** fungicide, algicide, bactericide or antifouling agent.	Not mentioned.	Not mentioned.	•1987/1988 Advisory Panel: room to consider preservative use (antifungal) but not insecticidal paint. November 1988 Meeting agreed. •November 1994 prohibited insecticide in paint [WGRPS].

DISCUSSION – RELEVANT MATTERS UNDER 52E

The relevant matters under section 52E (1), to this item, included: (a) – toxicity and safety of the substance; (b) risks and benefits; (c) potential hazards; and (d) extent and patterns of use.

A Member noted that the XXXXX recommendation only made allowance for the continued availability of ≤ 0.1 per cent lead in surface coatings due to public health concerns. The Member sought confirmation that XXXXX was specifically recommending discontinuation of the ≤ 0.2 per cent lead when in zinc based paints. XXXXX confirmed that this was the XXXXX position.

The Committee also noted that there was a new Australian/New Zealand Standard for safety of toys (AS/NZS ISO 8124.3:2003) and agreed that it would be appropriate to amend the existing toys reference under Clause 4 of Appendix I to Part 3 of this new standard, together with "as specified or amended from time to time".

Members noted that a move of > 0.1 per cent lead based paints/tinters to Appendix C should have no great impact as voluntary moves to limit lead in these products by the Australian industry had been quite successful.

The Committee generally supported a ban of > 0.1 per cent lead based paints and tinters because of public health concerns from exposure to lead, but noted that this could be achieved either through Appendix C or Appendix I:

Appendix I

- A Member noted that a prohibition such as "A person must not manufacture, sell, supply or use paint containing more than 0.1 per cent lead calculated on the non-volatile content of the paint" in Appendix I would effect a ban. Other Members noted, however, the variability in jurisdictional adoption of the Appendix I regulations and asserted that this could not guarantee a national ban on such products.

Appendix C

- A Member noted that the February 2008 NDPSC Meetings decision to included lead containing ink and ink additives (> 0.1 per cent) in Appendix C could be expanded to encompass paints and tinters. Additionally it was noted that there was precedent for

removing substances from Appendix I due to toxicity (e.g. mercury and tin organic compounds), although this precedent was old and had not been revisited recently. Some Members asserted, however, that an entry in Appendix I remained a logical place for banning > 0.1 per cent lead paints as this was where the paints industry expected to find such controls listed.

In light of the benefits arising from each of these options, Members agreed that both could be done. The Committee felt that the increased clarity justified the duplicative nature of this approach, particularly as this may increase compliance in reducing public exposure to lead. An alternative, of inclusion in Appendix C with a cross-reference to Appendix C from Appendix I, was not generally supported by the Committee.

Members also noted that by banning > 0.1 per cent lead in paints and tinters there no longer remained a need for the Appendix I Third Schedule or the references to this schedule in Part 2, paragraph 16 and Appendix F. The Committee therefore agreed to remove the superfluous entries, which would have the added benefit of simplifying those sections of the SUSDP.

However, given the complexity of the proposed changes and that this issue had not been included in the pre-meeting Gazette Notice, it was agreed that these decisions should be foreshadowed for consideration at the October 2008 NDPSC Meeting. This would also allow time for public comments to address any inadvertent impacts, particularly given the size and diversity of the paint/tinter sector in Australia.

A Member again raised the issue of the application of the Appendix I regulations apparently applying to industry (depending on jurisdictional implementation) when ASCC should probably be dealing with such use. Other Members asserted that this could be addressed as a separate issue at a future meeting should appropriate information be submitted.

A Member also suggested establishing a working group to review Appendix I. The Committee, however, generally agreed that any issues regarding Appendix I could be address if specific concerns arose and that a broad review of the Appendix was not necessary at this time. This was particularly the case with regards to the limits set in the First and Second Schedules of Appendix I as little or no data had been submitted to the Committee on which such a reconsideration could be based.

RESOLUTION 2008/53 - 5

The Committee decided to foreshadow:

- Replacing the current Appendix I Clause 3 with “A person must not manufacture, sell, supply or use paint containing more than 0.1 per cent lead calculated on the non-volatile content of the paint”.
- Deleting Clause 1 of Appendix I (i.e. remove the exemption which allows use of lead carbonate in mirror backing).

- Deleting the Third Schedule.
- Amending Part 2, paragraph 16 and Appendix F by removing reference to the Third Schedule or controls on lead.
- Amending the Schedule 6 lead compounds entry by deleting the exemption for use in zinc based paints and to amend the other paints exemption to exclude all paints, tinters, inks or ink additives (i.e. > 0.1 per cent will be captured instead by the Appendix C entry).
- Amending the Appendix C entry for lead compounds in inks or ink additives (as per the February 2008 NDPSC Resolution 2008/52 – 8) to also include paints or tinters, maintaining an exception for ≤ 0.1 per cent lead.
- Amending Clause 4 of Appendix I to include reference to Part 3 of the current Australian/New Zealand Standard for safety of toys (AS/NZS ISO 8124.3:2003) and add "as specified or amended from time to time".

FORESHADOWED DECISION (for consideration at the October 2008 Meeting)

Part 2 Labels and Containers – Amendment

Paragraph 16 – Amend entry to read:

Paints

16. The requirements of paragraph 7 do not apply to:

(1) paint (other than a paint for therapeutic or cosmetic use) which:

(a) contains only Schedule 5 poisons; or

(b) is a First Schedule or Second Schedule paint that is labelled with:

(i) the word "WARNING", written in bold-face sanserif capital letters, the height of which is not less than 5 mm, on the first line of the main label with no other words written on that line; and

(ii) the expression "KEEP OUT OF REACH OF CHILDREN", written in bold-face sanserif capital letters, the height of which is not less than 2.5 mm, on a separate line immediately below the word "WARNING"; and

(iii) the appropriate warnings specified for the paint in Appendix F, written immediately below the

expression "KEEP OUT OF REACH OF CHILDREN"; and

(vi) the name and proportion of the First Schedule or Second Schedule poisons it contains, provided that where the substance is a metal or metal salt the proportion is expressed as the metallic element present "calculated on the non-volatile content" or "in the dried film" of the paint.

(2) a tinter which contains:

(a) only Schedule 5 poisons; or

(b) a poison included in the First Schedule or Second Schedule to Appendix I, provided that it is labelled with the name and proportion of that poison and, where the poison is a metal or metal salt, the proportion is expressed as the metallic element present as "calculated on the non-volatile content" or "in the dried film".

Schedule 6 – Amendment

LEAD COMPOUNDS – amend entry to read:

† LEAD COMPOUNDS **except**:

(a) when included in Schedule 4 or 5;

(b) in paints, tinters, inks or ink additives;

(c) in preparations for cosmetic use containing 100 mg/kg or less of lead;

(d) in pencil cores, finger colours, showcard colours, pastels, crayons, poster paints/colours or coloured chalks containing 100 mg/kg or less of lead; or

(e) in ceramic glazes when labelled with the warning statement:

CAUTION - Harmful if swallowed. Do not use on surfaces which contact food or drink.

written in letters not less than 1.5 mm in height.

Appendix C – Amendment

LEAD COMPOUNDS – amend entry to read:

LEAD COMPOUNDS in paints, tinters, inks or ink additives **except** preparations containing 0.1 per cent or less of lead calculated on the non-volatile content of the paint, tinter, ink or ink additive.

Appendix F, Part 3 – Amendment

Paint – amend entry to read:

POISON	**WARNING STATEMENTS**	**SAFETY DIRECTIONS**
Paint		
(a) First Schedule paints. 83		
(b) Second Schedule paints.....84		

Appendix I – Amendment

Amend Appendix I to read:

This Appendix provides regulations for adoption by the States and Territories.

1. A person must not manufacture, sell, supply or use a First Schedule Paint for application to:

   (1) a roof or for any surface to be used for the collection or storage of potable water; or

   (2) furniture; or

   (3) any fence, wall, post, gate or building (interior or exterior) other than a building which is used exclusively for industrial purposes or mining or any oil terminal; or

   (4) any premises used for the manufacture, processing, preparation, packing or serving of products intended for human or animal consumption.

2. A person must not manufacture, sell, supply or use a paint containing more than 0.1 per cent lead calculated on the non-volatile content of the paint.

3. A person must not manufacture, sell, supply or use a paint for application to toys unless the paint complies with the specification for coating materials contained

in Part 3 of Australian/New Zealand Standard AS/NZS ISO 8124.3:2003 for Safety of Toys (Migration of certain elements) as specified or amended from time to time.

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

The First Schedule

The proportion of a substance for the purposes of this Schedule is calculated as a percentage of the element present in the non-volatile content of the paint.

Substance	**Proportion**
ANTIMONY or antimony compounds other than antimony titanate pigments	more than 5 per cent
BARIUM salts **except** barium sulfate or barium metaborate	more than 5 per cent
CADMIUM or cadmium compounds	more than 0.1 per cent
CHROMIUM as chromates of ammonia, barium, potassium, sodium, strontium or zinc	more than 5 per cent
SELENIUM or selenium compounds	more than 0.1 per cent

The Second Schedule

Substance	**Proportion**
DICHLOROMETHANE (methylene chloride)	more than 5 per cent by wt
ETHYLENE GLYCOL MONOALKYL ETHERS and their acetates	more than 10 per cent by vol
TOLUENE	more than 50 per cent by vol
XYLENE	more than 50 per cent by vol

AGRICULTURAL/VETERINARY, INDUSTRIAL AND DOMESTIC CHEMICALS

3. MATTERS ARISING FROM THE MINUTES OF THE PREVIOUS MEETING (CONSIDERATION OF POST-MEETING SUBMISSIONS UNDER 42ZCZ)

3.1 PYRITHIONE ZINC

PURPOSE

The Committee considered post-meeting comment on the February 2008 pyrithione zinc resolution (2008/52–10) regarding consequences for cosmetics.

BACKGROUND

Pyrithione zinc is considered to have bacteriostatic, fungistatic, mildewstatic, and algaestatic properties. It is an active ingredient of anti-dandruff products.

The December 1965 PSSC Meeting first included pyrithione zinc in Schedule 2 after consideration of an anti-dandruff cream. The February 1967 PSSC Meeting subsequently agreed to a cut-off from Schedule 2 to Schedule 5 for ≤ 2 per cent. The August 1985 PSC Meeting deleted the Schedule 5 entry, and amended the Schedule 2 entry so that it applied to human therapeutic use only, with exemptions for semi-solid hair preparations or shampoos (≤ 2 per cent, labelled with "keep out of eyes", "if in eyes, rinse well with water"). The November 1988 DPSSC Meeting subsequently agreed that the 2 per cent cut-off (with labelling) need only apply to shampoos, and that the semi-solid hair preparations exemption should be unconditional.

The August 2000 NDPSC Meeting agreed to a Schedule 6 pyrithione zinc entry following consideration of the toxicology of a marine antifouling paint. The Committee also generally agreed that veterinary hair products which contained pyrithione zinc should be exempt from scheduling (general exemption for semi-solid hair preparations, and exemption for shampoos with ≤ 2 per cent pyrithione zinc). In addition, the Committee foreshadowed making this exemption conditional on labelling ("keep out of eyes", "if in eyes, rinse well with water"). The November 2000 NDPSC Meeting agreed to the labelling requirement.

The August 2001 NDPSC Meeting considered the scheduling of pyrithione zinc when incorporated into polymers or surface coatings. The primary concern was eye irritancy (irritant as low as 0.3 per cent). The Committee agreed to an exemption when immobilised in solid preparations containing ≤ 0.5 per cent (exempted existing products while recognising the eye irritancy above this level).

The February 2007 NDPSC Meeting considered the harmonisation of pyrithione zinc and amended the Schedule 2 entry by referring to "for treatment of the scalp" rather than

specifying "semi-solid" or "shampoo", thereby limiting the existing semi-solids exemption to ≤ 2 per cent pyrithione zinc when compliant with the *Required Advisory Statements for Medicine Labels* (RASML). The Members also amended the Schedule 6 entry for consistency with the changes to the Schedule 2 entry. [The June 2008 NDPSC Meeting noted that no record was found to indicate that the August 2000 intention, of including veterinary hair preparations under the Schedule 6 exemption, was considered when the entry was amended to "treatment of the scalp" with labelling by reference to RASML].

The February 2008 NDPSC Meeting decided to include a Schedule 6 to Schedule 5 cut-off for paints containing ≤ 0.5 per cent pyrithione zinc. The Committee also decided to correct the errata arising from the February 2007 decision which inadvertently omitted animal hair products from the Schedule 6 exemption (by restricting to 'treatment of the scalp' and replacing the label statements by reference to RASML) by amending the exemption for 'preparations for the treatment of the scalp containing ≤ 2 per cent pyrithione zinc' with:

- a specific exemption for preparations for the treatment of the human scalp containing ≤ 2 per cent pyrithione zinc when compliant with RASML;
- a general exemption for semi-solid animal hair preparations; and
- an exemption for animal shampoos containing ≤ 2 per cent pyrithione zinc when labelled with the statement "Keep out of eyes" or "If in eyes rinse well with water".

The Committee also considered whether there should be an exemption from the Schedule 6 entry for non therapeutic human use (such as cosmetics) but agreed that such an exemption was not appropriate.

DISCUSSION - SUBMISSIONS

A post-meeting comment was received from XXXXX which:

- Noted that currently, cosmetics containing ≤ 2 per cent of pyrithione zinc for treatment of the scalp were exempt from scheduling [*when compliant with RASML*], just like their therapeutic counterparts.
- Asserted that the proposed amendment to the Schedule 6 pyrithione zinc entry, by use of the words "human therapeutic use" in exception (b), would inadvertently make this group of products Schedule 6 poisons.

  [Members recalled that the February 2008 NDPSC Meeting specifically considered and rejected an exemption for non therapeutic human use. However, the February 2008 NDPSC Meeting may have considered that "anti-dandruff" use was a human therapeutic use, noting that under the SUSDP's definition of therapeutic use it does not matter whether a product is designated a therapeutic good by the TGA, in which case it would be other possible uses (e.g. as a cosmetics preservative etc.) which would be Schedule 6. Members also noted that XXXXX submission made no

comment on anti-dandruff use in terms of the SUSDP definition, nor use in human products which were not anti-dandruff.]

- Asserted that the February 2008 Record of Reasons explained that the intent of the Schedule 6 amendment was to clarify that animal shampoos containing ≤ 2 per cent pyrithione zinc were also exempt from scheduling; not to make cosmetics containing ≤ 2 per cent of pyrithione zinc for treatment of the scalp Schedule 6 poisons.

  [Members noted that this statement appeared to ignore the February 2008 NDPSC Meeting's consideration of non therapeutic human use.]

- Queried why the NDPSC would consider that an exemption for "non therapeutic use (e.g. such as cosmetics)" was not appropriate.

- Asserted that it was previously agreed, following an extensive review and consultation process, that unscheduled anti-dandruff products should be regulated as cosmetics via NICNAS as set out in the Cosmetic Standard 2007. It was asserted that this decision included all unscheduled anti-dandruff products previously defined as exempt therapeutic goods and therefore not required to be included in the ARTG.

  [Members noted that the TGA's *Excluded Goods Order No.1 of 2005* (EGO) did not mention anti-dandruff products. XXXXX has advised that the EGO had yet to be updated to reflect NICNAS's Cosmetic Standard 2007, empowered by the *Industrial Chemicals (Notification and Assessment) Amendment (Cosmetics) Act 2007*. The Cosmetic Standard defines anti-dandruff hair care products as cosmetics when presented as controlling or preventing dandruff only through cleansing, moisturising, exfoliating or drying the scalp. Additionally, the product must not be captured by Schedules 2, 3, 4 or 8. XXXXX has advised that qualifying anti-dandruff products are being treated as cosmetics by TGA in the interim (until the EGO can be updated).]

- Asserted that this agreement excluded the ingredients from the requirement to be included on the Australian Inventory of Chemical Substances (AICS). The change, moving these unscheduled products under the aegis of NICNAS was therefore a strengthening of the regulatory requirements, as well as requiring total disclosure of ingredients on labelling.

- Was not aware of any safety issues that had arisen that would necessitate rescheduling of products containing low levels of pyrithione zinc, nor 'POISON' on the labelling, when similar strength therapeutic goods and veterinary shampoos are exempt from this requirement. Asserted that there was a range of other substances used in human anti-dandruff products that were currently unscheduled.

- Proposed removal of the word "therapeutic" from the Schedule 6 pyrithione zinc entry.

Members also recalled the following relevant points from the February 2008 NDPSC Meeting:

SCCNFP Review

- Members noted a review by the EU's Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers (SCCNFP) European Cosmetic, Toiletry and Perfumery Association (COLIPA) (http://ec.europa.eu/food/fs/sc/sccp/out225_en.pdf. SCCNFP COLIPA) on the safe used of ≤ 2 per cent for preservative and non-preservative purposes in hair products.
- Eye irritation:
  - *0.25 per* cent in soap solution – slight transient irritation (rabbit) with peak effect during the first 4 hours. Completely disappeared in 2-4 days.
  - 2 per cent in undiluted shampoo – extensive damage to the eyes (rabbit), opalescence of the entire cornea, severe iritis and marked conjunctivitis. Rinsing alleviated the condition (very slight to moderate conjunctivitis). In rinsed eyes damage cleared by the 3rd day, in unrinsed eyes had not cleared by day 42.
  - Dilution to 10 per cent (0.2 per cent pyrithione zinc) reduced the eye irritation and the condition was cleared by day 7 (rinsing was effective in alleviating the condition). Repetition in monkeys, with no rinsing, produced superficial damage to the corneal epithelium and/or slight conjunctival irritation with the 2 per cent shampoo (dilution to 0.2 per cent resulted in no ocular irritation).
  - The SCCNFP concluded *that the irritation potential of shampoo in rabbit eyes was not increased by the incorporation of pyrithione zinc.*
- Percutaneous absorption varies from ~0.03 to 3.4 per cent. Pyrithione zinc was distributed throughout the body, and was not concentrated in any particular tissue.
- Oral LD_{50}: 92 - 266 mg/kg (rat), 160 - 1000 mg/kg (mouse), 600 mg/kg (dog).
- The presence of pyrithione zinc in cosmetic formulations did not impact upon the low skin irritation potential of the formulations tested (i.e. ≤ 2 per cent). Pyrithione zinc had a low potential to induce contact hypersensitivity.
- No evidence of a carcinogenic response topically (up to 100 mg/kg/d) in lifetime studies (mice and rats). Exhibited no mutagenic effect in *in vitro* or *in vivo* studies. No reproductive effects were observed from topical exposure of rats and rabbits at up to 15 and 100 mg/kg/d respectively.
- SCCNFP concluded that pyrithione zinc did not pose a health risk when used:
  - for non-preservative purposes in cosmetic rinse-off and leave-on hair care products at a maximum concentration of 1.0 per cent and 0.1 per cent, respectively; or
  - for preservative purposes in cosmetic rinse-off hair care products at a maximum concentration of 1.0 per cent.

2004 US EPA review

- Moderate acute oral toxicity (LD_{50} 267 mg/kg). No significant acute dermal toxicity (LD_{50} > 2000 mg/kg).

- Was a severe eye irritant but did not appear to demonstrate significant dermal irritation. Did not demonstrate dermal sensitization potential.
- Repeat dose:
  - Dermal – relatively non-toxic (decreased food consumption, decreased body weight gain, decreased food efficiency at the limit dose of 1000 mg/kg/day).
  - Oral – significantly greater toxicity (increased relative organ weights, clinical toxicity, and hind limb weakness at 3.75 mg/kg/day).
- Negative for mutagenic effects. Caused adverse developmental effects. Two dietary acute RfDs: females of child bearing age (0.0016 mg/kg/day); and general population (0.0025 mg/kg/day).
- EPA assessed dermal exposure from use in shampoo (conservative scenario, once-daily). The estimated dermal Margin of Exposure (MOE) was 3,300.
- Very high acute toxicity (low ppb) to fish and invertebrates, as well as to aquatic plant species. Causes adverse chronic impacts on freshwater and marine invertebrate reproduction and growth at very low concentrations, which indicate that pyrithione zinc may be a potential human endocrine disrupter. However, pyrithione zinc degrades fairly quickly in water and was not expected to persist for long periods in water or microbial soils and sediments. The reported octanol/water partition coefficient was < 1000 and was therefore not expected to bioaccumulate in aquatic organisms.
- There was concern that the neurotoxic effects of pyrithione zinc had not been completely characterized by the available toxicology data.

August 2000 NDPSC Meeting

XXXXX

Almost no dermal irritation occurred even after daily exposure to approximately XXXXX administration resulting in corrosion to the mucous membranes of the gastro-intestinal tract.

- Ocular test for a XXXXX pyrithione zinc product – severe to corrosive eye irritation. However, in a low volume eye irritation assay, the effect was moderate to severe eye irritancy. The evaluator concluded that corrosive eye irritancy would be likely to occur down to concentration as low as 0.3 per cent.
- The Committee's Schedule 6 decision was based on the acute toxicological profile of pyrithione zinc, in particular its acute oral toxicity and severe eye irritancy/ corrosivity.

August 2001 NDPSC Meeting

- The primary concern with pyrithione zinc had been eye irritancy with the available evidence suggesting it was irritant at concentrations as low as 0.3 per cent.

XXXXX

DISCUSSION – RELEVANT MATTERS UNDER 52E

The relevant matters under section 52E (1), to this item, included: (a) – toxicity and safety of the substance; (b) risks and benefits; (c) potential hazards; and (d) extent and patterns of use.

The Committee generally agreed that while the SUSDP definition of therapeutic use was probably sufficient to address the concerns regarding the "cosmetic" anti-dandruff products qualifying for the Schedule 6 part (b) pyrithione zinc exemption, there remained the possibility of confusion. The Members therefore supported the requested removal of "therapeutic" from pyrithione zinc's Schedule 6 part (b) exemption conditions.

A Member also queried whether there was a problem with requiring a cosmetic to comply with RASML in order to qualify for the exemption from Schedule 6. Other Members agreed that no such issue existed, and that the reference to RASML remained appropriate.

A Member noted that there appeared to be a minor errata in the February 2008 NDPSC Decision – the "or" between the required label statements in part (d) of the Schedule 6 entry should have been an "and". Members agreed that it was the intent of the Committee that both labels were needed in order for animal shampoos to qualify for the exemption from Schedule 6 set out in part (d).

RESOLUTION 2008/53 - 6

The Committee decided to vary the February 2008 NDPSC Resolution 2008/52-10 (the Schedule 6 (b) amendment) to broaden the exemption for preparations for the treatment of the human scalp containing ≤ 2 per cent pyrithione zinc when compliant with RASML from human therapeutic use to all human use.

Schedule 6 – Amendment (Variation to the February 2008 Resolution 2008/52-10)

PYRITHIONE ZINC – Amend entry to read:

PYRITHIONE ZINC **except**:

(a) when included in Schedule 2 or 5;

(b) for human use in preparations for the treatment of the scalp containing 2 per cent or less of pyrithione zinc when compliant with the requirements of the *Required Advisory Statements for Medicine Labels*;

(c) in semi-solid hair preparations for animal use;

(d) in shampoos for animal use containing 2 per cent or less of pyrithione zinc when labelled with the statement "Keep out of eyes" and "If in eyes rinse well with water"; or

(e) when immobilised in solid preparations containing 0.5 per cent or less of pyrithione zinc.

4. OTHER OUTSTANDING MATTERS FROM PREVIOUS MEETINGS

4.1 1,4-BUTANEDIOL

PURPOSE

The Committee considered the scheduling of 1,4-butanediol including a proposed Appendix C entry.

BACKGROUND

1,4-butanediol is an industrial solvent and intermediate used in the production of various plastics and polymers. It is also used in printing inks, cleaning agents, adhesives, paints and cosmetics. If ingested, 1,4-butanediol is converted into γ-hydroxybutyrate (GHB) in the liver by the enzymes alcohol dehydrogenase and aldehyde dehydrogenase thus making it both a precursor chemical for GBH and open to abuse in and of itself.

The June 2003 NDPSC Meeting considered 1,4-butanediol and agreed that control through scheduling was not appropriate due to the large range of legitimate industry uses and that it had no use in human therapeutics. The Committee believed that regulation through the Plastics and Chemicals Industries Association (PACIA) Code-of-Practice (COP) would provide self-regulatory controls on the use of the substance. PACIA subsequently agreed to this measure and amended the COP accordingly.

In November 2007, the distributors of a toy (Bindeez Beads) recalled the product from the market when a number of children had experienced adverse events after swallowing the beads. Toxicological screening found that the children had ingested 1,4-butanediol, a component of the glue in the beads. Further investigations conducted on the toy found that all samples contained 1,4-butanediol which had been substituted in place of 1,5-pentanediol.

The February 2008 NDPSC Meeting considered this issue and generally agreed that, as 1,4-butanediol in its free form did not appear to have any use in the domestic setting, to foreshadow an Appendix C listing for all domestic use including toys, to allow for any unknown domestic uses to be notified to the Committee. The foreshadowed entry was:

Appendix C - New Entry

1,4-BUTANEDIOL (excluding its derivatives) in non-polymerised form for all domestic use, including toys.

DISCUSSION - SUBMISSIONS

XXXXX had, separately to the ongoing NDPSC consideration, prepared a submission on 1,4-butanediol. XXXXX agreed, however, to instead provide this submission as a pre-meeting comment for the current discussion. Members noted the following recommendations from XXXXX:

- These recommendations are for 1,4-butanediol in the monomer form only and do not apply to the chemical in the polymerised form.
- The Committee may consider it appropriate to include 1,4-butanediol:
  - in Schedule 6 for all domestic products except when included in Schedule 5.
  - in Schedule 5 for all domestic products containing < 10 per cent.
  - for use in toys in Appendix C.

  [Members noted that in making this recommendation XXXXX sought information from XXXXX on the use of 1,4-butanediol (as discussed below).]

Members also noted the following points from the XXXXX submission:

- In 2007 concerns were raised with XXXXX after the hospitalisation of children who ingested 'Bindeez' beads that were found to contain 1,4-butanediol. A permanent ban on the sale of all bead toys containing 1,4-butanediol was subsequently imposed by the NSW government with other States and Territories following suit. XXXXX has investigated the use and safety of 1,4-butanediol and the adequacy of current regulatory controls.

Current controls

- Internationally, several countries have imposed bans on the illicit use of 1,4-butanediol:
  - In May 1999, the US Food and Drug Administration (FDA) issued a warning about products containing 1,4-butanediol and declared it to be a Class I Health Hazard (i.e. potentially life-threatening). Although this classification imposed no legal restrictions on manufacture, distribution or possession, when 1,4-butanediol is distributed for human consumption it now meets the definition of a 'controlled substance analogue' and distributors can be prosecuted for supplying a Schedule 1 substance.
  - In New Zealand 1,4-butanediol has been classified as Class B1 substance(i.e. a drug posing a high risk of harm) under the Misuse of Drugs Act 1975.

- The PACIA COP was developed in partnership with law enforcement bodies to provide a best practice guide for companies in the prevention of diversion of

legitimate industrial chemicals into illicit drug manufacture. However, compliance with the COP is voluntary and the States and Territories have not as yet adopted its provisions uniformly.

- 1,4-Butanediol has not been scheduled and, not withstanding the mandatory labelling requirements for cosmetics under the *Trade Practices Act 1974*, no regulations currently exist for use in domestic or cosmetic products in Australia.

Consumer exposure

- XXXXX sought information from XXXXX on the use of 1,4-butanediol. However, XXXXX was only able to provide information from a similar consideration in 2005, where Australian companies reported to XXXXX that 1,4-butanediol was used industrially as an intermediate in the production of various chemicals, plastics and polymers. It was also used as a plasticiser, a carrier solvent in printing ink, a cleaning agent, an adhesive and in paints and varnishes. Use information for specific domestic product categories was not requested or reported, and use in cleaning agents was not specified as to whether it was industrial or domestic. 1,4-butanediol was also reported to be used in cosmetics, however, specific details such as category and concentration ranges were not stated.
- The international *Cosmetics Ingredient Dictionary and Handbook* (11th ed) did not give product categories for 1,4-butanediol, although the "Skin Deep" database of cosmetics ingredients published by the Environmental Working Group reported US use of 1,4-butanediol in eye cosmetics (eye shadow and eye liner).
- One dermal cosmetic available in Australia, 'Cover Girl Eyeslicks Gel Eyecolour', was a pencil containing 1,4-butanediol at an unspecified concentration. The most probable exposure scenario related to moderate term, smll volume dermal contact. However, based on the animal data (below), repeated use was unlikely to result in a risk of local or systemic toxicity. Although it would be unlikely for an adult to swallow any of the cosmetic, a small child may be attracted by the bright iridescent colour and associate it with a confectionery. Hence there would be some concern for the possibility of oral exposure with children.

  [A Member contested the likelihood of a child mistaking the pencil (because of its colour) with a confectionary. The Members were advised that the pencil product had actually been located on an international database and may not actually be an Australian product.]
- Given its rapid absorption and conversion to GHB following ingestion and pronounced neurotoxicity in animals and humans, there is concern about potential risks of adverse effects from exposures to 1,4-butanediol in domestic and cosmetic products. The risk to consumers arises mostly from accidental ingestion of domestic products containing 1,4-BD. A significant risk to children arises from intentional ingestion of toy products containing 1,4-BD.

Possible Cut-offs

- The acute oral LD_{50} values in rodents (below) were consistent with Schedule 6 criteria. Although there was limited data available on the products available to consumers, there was a basis for identification of a cut-off.
- In the combined oral repeat dose and reproductive toxicity study in rats, a LOAEL of 200 mg/kg/day was identified for severe but transient neurotoxicity. As there was full recovery within the time prior to the following dose, this result was indicative of an acute neurotoxic effect. Similar neurotoxic effects have been seen in humans, with limited evidence of CNS depression at 25 mg/kg bw/day, and more pronounced effects, including death, at higher doses.
- Based on the LOAEL value for a serious health effect in animals of 200 mg/kg bw/day (noting this was a narcotic effect level, not an acute toxicity), any product containing < 10 per cent 1,4-butanediol was asserted to be consistent with Schedule 5 (≥ 10 per cent would be consistent with Schedule 6).

Use in toys

- As evidenced by the recent spate of adverse reactions in children after ingestion of "Bindeez' beads, use in toys presents a serious risk. The Committee may consider including 1,4-butanediol for use in toys in Appendix C because of the potential for severe toxic effects following a single dose.
- Several States and Territories have placed a permanent ban on the supply of any bead toys containing 1,4-butanediol.

Members also noted the following toxicity data from the XXXXX submission:

Summary

Acute oral LD_{50}	Rat: 1525-1830 mg/kg bw. Mouse: 2060 mg/kg bw. Rabbit: 2531 mg/kg bw. Guinea pig: 1200 mg/kg bw.
Acute inhalation LC_{50}	Rat: > 5.1 mg/L (4 hr). Slight altered respiratory function (5.1 mg/L, 4 hr).
Acute dermal LD_{50}	Rat: >5000 mg/kg bw.
Acute human toxicity	Unconsciousness, miosis, areflexia, renal failure and death (210-430 mg/kg per rectum). Restlessness, clonic spasms of extremity muscles, sleep (30 mg/kg bw i.v.).
Skin irritation (rabbit)	No reaction observed on intact or abraded skin (24 hr).
Eye irritation (rabbit)	Slight irritant.
Respiratory irritation (rat)	Slight irritant
Skin sensitisation	Guinea pig: Not sensitising.
Repeated dose oral	Mouse: NOAEL 100 mg/kg bw/day (F)

toxicity	Rats: LOAEL 200 mg/kg bw/day (hyperactivity observed)
Repeated dose inhalation toxicity	Rat: NOAEC (systemic) 1.1 mg/L. Reduction in heart and body weight and serum cholesterol; increase in RBCs and haematocrit; atrophy in thymus lymphoid cells (5.2 mg/mL).
Neurotoxicity	Rat: CNS depression, anaesthesia, loss of righting reflex and voluntary motor activity. Neurotoxic in human case reports.
Mutagenicity	No evidence of genotoxicity
Carcinogenicity	No data.
Reproductive toxicity	Rat: NOAEL 800 mg/kg bw/day
Developmental toxicity	Mouse: NOAEL 600 mg/kg bw/day (not teratogenic).

Toxicokinetics

- After oral or intravenous administration, 1,4-butanediol is rapidly and efficiently metabolised in the liver to form GHB, a neuromodulator that exerts potent depressant effects on the central nervous system. In humans, extensive conversion of 1,4-butanediol to GHB after oral dosing indicated that ingestion of 1,4-butanediol was essentially equivalent to GHB intake. Peak blood levels are achieved after 30 to 60 minutes. No data was available on dermal absorption, although comparison of the oral and dermal LD_{50} results indicated that the dermal availability of 1,4-butanediol was lower than its availability by the oral route.

Animal data

- Acute toxicity: Moderate oral toxic; LD_{50}= 1200 mg/kg bw (guinea pigs), 1525-1830 mg/kg bw (rats) and 2060 mg/kg bw (mice). The dermal LD_{50} was > 5000 mg/kg bw (rats). The 4-hour inhalation LC_{50} was > 5.1 mg/L (rats).
- Irritation: In rabbits was not irritating to the skin and at most considered only a slight irritant to the eyes. Slight respiratory irritation observed in rats following exposure to an aerosol of 1,4-butanediol at concentrations > 4.6 mg/L. Studies showed laboured and noisy respiration at 4.6 and 9.4 mg/L (4 h), and accelerated, shallow respiration following exposure to 5.1 mg/L (4h) with recovery noted within 1 day.
- Sensitisation: A study in guinea pigs showed no skin sensitising potential.
- Repeated dose toxicity: In a 10 day oral (gavage) study in mice, a NOAEL of 100 mg/kg bw/day was established for signs of central nervous system intoxication including hypoactivity, immobility, loss of righting reflex and prone posture. Similarly, in a combined repeat dose and reproductive study in rats over 39 to 45 days, a LOAEL of 200 mg/kg/day was established for neurotoxicity with full recovery noted within 5 hours of dosing. In an inhalation study, reduced body weight, increased erythrocyte counts and haematocrits and slight atrophy of lymphoid cells in the thymus were seen from 5 mg/L (4h) with the body weights and thymic atrophy returning to normal during a 14 day recovery period.
- Neurotoxicity: Adverse effects on the nervous system have been observed in acute studies. Appears to have dual toxicological actions: the major neurotoxic effects are

attributable both to its conversion to GHB and another alcohol-like effect due to the diol itself. Administration of 496 mg/kg bw to rats caused CNS depression and induced a state resembling sleep or anesthesia characterized by loss of righting reflex, struggle response and voluntary motor activity. Very similar neuropharmacologic responses were observed after administration of GHB.

- Genotoxicity and carcinogenicity:
  - Negative in an Ames (bacterial mutation) test, a gene mutation and two chromosomal aberration tests in mammalian cells. The only in vivo study available was judged to be unreliable although a negative result was obtained. Overall, 1,4-butanediol was not considered to interact with DNA.
  - Although 1,4-butanediol has not been evaluated for carcinogenicity, γ-butyrolactone, which is also rapidly converted to GHB, has shown no carcinogenic response in rats and mice over a 2 year period. Based on the absence of evidence for genotoxicity and the negative result of the carcinogenicity bioassay for a related compound, 1,4-butanediol was not considered to be carcinogenic in animals.

- *Toxicity to reproduction*: No effect on fertility was seen in male and female rats administered up to 800 mg/kg bw/day. In a developmental toxicity study in the mouse using 100 to 600 mg/kg bw/day, a slight reduction in live foetal weight was seen from 300 mg/kg bw/day in the presence of maternal toxicity. At 100 mg/kg bw/day no developmental toxicity was seen. Therefore, 1,4-butanediol was not considered a developmental toxicant, as the developmental effects seen were a secondary non-specific consequence of maternal toxicity.

Human Data

- Acute toxicity: The critical toxic effect is neurotoxicity. CNS disturbances including decreased alertness, dizziness and respiratory depression have been reported following oral dosing at 25 mg/kg bw. More significant effects occur at higher doses and by other routes of administration with sleep induction, restlessness and myoclonus reported to occur following intravenous administration of 30 mg/kg bw and miosis, areflexia, coma and death observed in patients after rectal administration of 15 or 30g (~200 or 400 mg/kg bw).

- Case reports were available describing the neurological consequences (including agitation, combativeness, respiratory depression, labile level of consciousness, vomiting, seizures and death) in patients known to have ingested illicit products containing 1,4-butanediol. The inability to accurately determine the dose ingested (and the co-exposure to other chemicals present at unreported concentrations) means that it was not possible to correlate the degree of 1,4-butanediol exposure with the severity of neurotoxicity from these reports.

- Recently in Australia, four children were hospitalised after swallowing ‘Bindeez’ brand toy beads that were found to be coated with 1,4-BD, however quantification of the amount of 1,4-butanediol ingested was not reported.

Members also recalled the following from the February 2008 NDPSC Meeting:

- Currently 1,4-butanediol diglycidyl ether and 1,4-butanediol dimethacrylate are contained in 11 products on the ARTG. The products containing 1,4-butanediol diglycidyl ether are tissue reconstructive material and the ones containing 1,4-butanediol dimethacrylate are dental polymers/ cement, which are both currently exempted through the Appendix A entry for medical and veterinary adhesives.
- The Committee recalled the following from the June 2003 Meeting:
  - An XXXXX report advised that XXXXX police had seized a quantity of 1,4-butanediol. The report highlighted that abuse of precursors of GHB and related analogues was an emerging health issue, and that 1,4-butanediol was suspected of being sold for use as a "drink spiking" agent.
  - A number of jurisdictions reported that the only way such substances were controlled was through the SUSDP.
  - Several industry groups expressed concern over possible adverse impacts that restrictive scheduling may have on legitimate industrial users. These groups generally favoured a self-regulatory approach through Category 1 of the PACIA COP, noting that Category 1 lists chemicals that require an End User Declaration with each purchase and may only be sold to "account customers" or customers that are prepared to open an account. In addition, supply of these chemicals to End Users or Distributors must be delayed for a period of not less than 24 hours. It was noted that this would help to protect against the diversion of chemicals and scientific equipment into the illicit products of drugs.

- The industrial uses of 1,4-butanediol were discussed, noting common use in:
  - Thermoplastic polymers (automotive, electrical and appliance industries);
  - Polyesters of which it is either a component or chain extender.
  - As a chain extender in thermoplastic urethane elastomers and as a major component of case urethane elastomers (used in the automotive industry, footwear, recreation equipment, electrical enclosures and furniture).
  - Polyester plasticisers.

- XXXXX advised that it had made a submission to the Productivity Commission study on chemicals and plastics which included information about potentially adopting the COP into relevant State and Territory legislation uniformly in each jurisdiction. It was noted that the provisions of the COP had been picked up into some State legislation already but that these had not been adopted uniformly which could create difficulties in compliance. It was noted that the ACT, NT, SA, Tasmania and Victoria had not adopted any controls from the PACIA COP.
- Members noted that, although industrial use of the substance was controlled by compliance with the PACIA COP, domestic use was not controlled at all. The Members noted that the possibility of 1,4-butanediol being used in a domestic setting had now become apparent and that it therefore needed to be scheduled in order to

restrict use, especially given the harm that had occurred via children ingesting the substance.

- XXXXX
- Members agreed that the issue of concern was the availability of the free form of 1,4-butanediol in the domestic setting, not the polymerised form as this was not ingestible and had no potential for abuse or adverse effects.
- A Member stated that the issue of 1,4-butanediol in toys may be for the Australian Competition and Consumer Commission. Members discussed that scheduling should not occur for products, rather for the chemistry, toxicity and use patterns of a substance and whether there should be no domestic use of the non-polymerised 1,4-butanediol. A Member noted that this issue had been brought before the Committee was because of use in toys and that the Members must be careful of any unintended impact of the scheduling for all domestic use. The Member stated that the evidence and information relating to domestic use of free form 1,4-butanediol would need to be reviewed before a decision could be made to including all domestic use in Appendix C.
- With regard the Bindeez Beads incident, a Member stated that Appendix C listing would not have made a difference in this case as the manufacturer was unaware that the 1,4-butanediol had been substituted for 1,5-pentanediol. Another Member stated, however, that if the substance were in Appendix C then this would enhance compliance, given that companies would be obliged to ensure that it was not used.
- A Member stated that the Committee had an immediate obligation to prevent the use of 1,4-butanediol in toys and that this was a public health concern due to the fact that a number of children became seriously ill due to the use of the free-form of the chemical in a domestic setting. The Member stated that if the Committee did not schedule 1,4-butanediol for domestic use then there would be nothing to prevent this type of incident happening again.

Members also recalled that the SUSDP definition of toy is “an object or number of objects manufactured, designed, labelled or marketed as a plaything for a child or children up to the age of fourteen years”.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The relevant matters under section 52E (1), to this item, included: (a) toxicity and safety of the substance; (b) risks and benefits; (c) potential hazards; (d) extent and patterns of use; and (g) potential for abuse.

A Member noted that while inclusion in Schedule 6 would reflect the toxicity data, additional consideration was necessary regarding the abuse potential. Various jurisdictions indicated that other controls had been individually implemented to address abuse/ diversion concerns (such as recognition by some jurisdictions of the PACIA COP in legislation), particularly regarding industrial use.

The Members generally agreed that the immediate concern before the Committee was domestic use of non-polymerised 1,4-butanediol, and that a ban through Appendix C was warranted for all domestic use.

A Member also noted that no concern had been tabled from pre-meeting public comment regarding the foreshadowed wording of the Appendix C entry. The Committee noted that "including use in toys" was superfluous as "all domestic use" would also capture toys, and agreed that this could be dropped from the proposed entry.

RESOLUTION 2008/53 - 7

The Committee decided to include free form 1,4-butanediol in Appendix C for all domestic use.

Appendix C – New Entry

1,4-BUTANEDIOL (excluding its derivatives) in non-polymerised form in preparations for domestic use.

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

5.1 SUSDP, PART 4

5.1.1 CARBENDAZIM

PURPOSE

The Committee considered the scheduling of carbendazim.

BACKGROUND

Carbendazim is a heterocyclic, broad-spectrum, systemic fungicide that belongs to the benzimidazole group of fungicides used for the control of fungal diseases in a variety of crops. It is the major *in vivo* metabolite of the fungicide, benomyl. Products containing carbendazim are registered for use in many crops.

The first consideration on carbendazim took place in February 1983, when the DPSC noted regulatory actions on benomyl in Finland. The Committee recommended that the toxicology of carbendazim be evaluated urgently due to developmental toxicity and genotoxicity concerns. As a result, a toxicology evaluation of carbendazim was considered by the Committee for scheduling in February 1983. The Committee noted that carbendazim had low acute oral and dermal toxicity XXXXX. With carbendazim dust, the approximate lethal concentration in a 1-h inhalational study XXXXX. Carbendazim was not an eye irritant XXXXX or a skin sensitiser XXXXX.

In August 1988, the Committee also agreed to request copies of the published reports on benomyl from the Finnish National Board of Health.

At the February 1989 DPSC Meeting, the Committee considered the comments from the XXXXX in response to a Committee's request for proposals for upper limits and decided to exempt ≤1 per cent Carbendazim from Schedule 6. Two subsequent DPSC meetings (February and May 1990) considered first aid instructions for carbendazim and safety directions for one of its products.

The August 1990 DPSC Meeting agreed to the current ≤0.5 per cent cut-off for carbendazim exempt from Schedule 6, the entry of which exists to date.

DISCUSSION - SUBMISSIONS

XXXXX had submitted an application seeking an amendment to the current carbendazim schedule entry. The applicant proposed the following amendment:

> "CARBENDAZIM **except** in paint and construction materials containing 0.5 per cent or less of carbendazim".

The Committee noted that no toxicology data were provided with the submission.

The applicant asserted that the manufacturers of wall board jointing compounds needed to provide protection to these products to prevent fungal growth on plaster compounds between application and drying. The applicant affirmed that fungicides may also be added to other plaster products, such as skim coats and sealing compounds that were used to coat surfaces and in joints such as baths, sinks and showers to stop the ingress and/or escape of moisture. The applicant felt that it was important that they be correctly listed in the SUSDP to make it clear what was included.

XXXXX stated that jointing compounds and sealants were commonly referred to as construction products within the industry.

No pre-meeting submissions were received for this matter.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The following matters under 52E(1) were considered particularly relevant to this agenda item: (a) toxicity and safety (b) risks and benefits (c) potential hazards and (d) extent and pattern of use.

A Member asserted that the issue surrounding this item was whether the risk at ≤0.5 per cent carbendazim was greater from materials identified in the application compared to paint. Another Member noted that given the broad general use of paint, the exposure risk was likely to be lower. The Committee generally agreed, therefore, that the Schedule 6 exemption could be broadened to cover some construction materials.

Members noted, however, that the wording proposed by the applicant to amend the entry, i.e. “construction materials” was difficult to define and would have a broader meaning given the range of materials used in the construction industry. The Committee agreed that the wording “sealants and jointing compounds” was appropriate.

RESOLUTION 2008/53 - 8

The Committee agreed to broaden the current Schedule 6 exemption of ≤0.5 per cent in paints to also include ≤0.5 per cent in jointing compounds and sealants.

Schedule 6 - Amendment

CARBENDAZIM – Amend entry to read:

CARBENDAZIM **except** in paints, jointing compounds and sealants containing 0.5 per cent or less carbendazim.

5.1.2 OCTHILINONE

PURPOSE

The Committee considered the scheduling of octhilinone.

BACKGROUND

Octhilinone belongs to the family of isothiazolinones used in the production of broad-spectrum biocides and preservatives such as antiseptic agents, bactericides, slimicides, and fungicides. The biggest application of octhilinone is in the paint industry especially as a marine antifouling agent..

This chemical was originally given a Schedule 6 classification by the Committee in May 1977 under its alternative name of 2N-octyl-4-isothiazolin-3-one. The Committee recommended that the available data be reviewed by the XXXXX and first aid instructions for the chemical were established. At that time the intended use of this substance was as a cotton seed fungicide.

In August 1989, DPSC considered the first toxicology data submission on octhilinone, but noted that it was brief and hence, the registrant was requested to provide more data.

In August 1990, DPSC considered a review of toxicology data in relation to registration of a timber treatment product. Thereafter, DPSC and NDPSC have considered this chemical regarding its nomenclature or revision of first aid instructions, with the last consideration had taken place in November 2000 concerning the nomenclature.

DISCUSSION - SUBMISSIONS

The XXXXX had submitted an application seeking amendment to the current Schedule 6 entry for octhilinone. The applicant has proposed the following wording to amend the existing entry:

> "OCTHILINONE **except** in paint and XXXXX containing 1 per cent or less of octhilinone" calculated on the non-volatile content of the paint".

The Committee noted that no toxicology data were provided with the application.

Members noted the following acute toxicology data for octhilinone at the August 1989 DPSC meeting. Based on the studies conducted in XXXXX, it had moderate acute oral, dermal and inhalational toxicity, severe skin and eye irritancy and was a skin sensitiser.

Acute oral toxicity:	XXXXX
Acute dermal toxicity:	XXXXX
Acute inhalational toxicity:	XXXXX
Skin/eye irritation:	Severe XXXXX
Skin sensitisation:	Sensitiser XXXXX

Members noted that the toxicology data provided in support of past considerations were very old and that no new data were submitted with the current submission. The Secretariat advised that some recent studies seemingly conducted post 1977 covering acute oral, dermal, inhalational toxicity, skin/eye irritation and skin sensitisation aspects had been recently submitted to the USEPA by XXXXX. The Committee therefore considered deferring consideration in order to seek advice from XXXXX regarding these studies. Members generally agreed, however, that it was appropriate to proceed with consideration of the applicant's request at this time and any broader reconsideration could be undertaken should the data become available indicating that reconsideration would be warranted. Members agreed to bring this matter to the attention of XXXXX.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The following matters under 52E(1) were considered particularly relevant to this agenda item: (a) toxicity and safety (b) risks and benefits (c) potential hazards and (d) extent and pattern of use.

A Member noted that the concerns regarding octhilinone for use in jointing material and sealants was very similar to those discussed for carbendazim (Item: 5.1.1). The Member noted that the real concern was again whether the risk at ≤1 per cent octhilinone was greater from materials identified in the application compared to paint. Another Member noted that given the broad general use of paint, the exposure risk was likely to be low. The Committee generally agreed, therefore, that the Schedule 6 exemption could be broaden to cover some construction materials.

Members again noted that the wording proposed by XXXXX ie, "construction materials" is difficult to define and would have a broader meaning given the range of materials used

in the construction industry. The Committee, therefore, agreed that "sealants and jointing compounds" would be appropriate.

A Member stated that because octhilinone concentration in a paint usually calculated based on the levels present in the non-volatile content, it would be appropriate to also calculate the octhilione content in jointing compounds and sealants on the non-volatile content. The Committee agreed.

RESOLUTION 2008/53 - 9

The Committee decided to broaden the current Schedule 6 exemption of ≤1 per cent in paint by also including ≤1 per cent in jointing compounds and sealants.

Schedule 6 – Amendment

OCTHILINONE – Amend entry to read:

OCTHILINONE **except** in paint, jointing materials and sealants containing 1 per cent or less of octhilinone calculated on the non-volatile content.

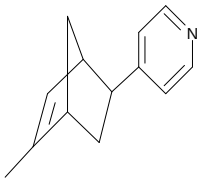
5.1.3 METHYLNORBORNYLPYRIDINE (MNBP)

PURPOSE

The Committee considered the scheduling of methylnorbornylpyridine (MNBP).

BACKGROUND

The reaction of 4-ethenyl-pyridine with 3a,4,7,7a- tetrahydrodimethyl-4,7-methano-1H-indene results in a mix of MNBP isomers (methyl substitution isomers mainly at the 1, 4, 5 and 6 positions on the norbornene ring). Individual isomers are identified by a methyl positional number. MNBP is found as a component of a fragrance oil. The structure of 5-MNBP is:



The October 2007 NDPSC Meeting included MNBP in Schedule 6 with a 0.5 per cent exemption cut-off and an Appendix F warning statement (59 – May cause allergy).

The February 2008 NDPSC Meeting reconsidered the sensitisation data which was the main concern regarding the Schedule 6 exemption cut-off. The Committee generally agreed to foreshadow:

- That the 0.5 per cent exemption cut-off should be overturned, noting concerns regarding the reliability of the human sensitisation test data.
- That this concern did not allow for a cut-off to Schedule 5 to be established.
- That the capture of MNBP in Schedule 6, with an Appendix F warning statement 59 'May cause allergy' was appropriate.

Members noted that the 0.5 per cent exemption cut-off would still be included in the SUSDP 22 Amendment 3 and would remain in place until implementation of any June 2008 decision.

DISCUSSION - SUBMISSIONS

XXXXX

Members recalled that February 2008 Meeting generally considered the following matters under 52E(1) as particularly relevant to the consideration of the 0.5 per cent cut-off from the Schedule 6 MNBP entry: (a) safety and toxicity, particularly the sensitisation potential; and (d) extent and pattern of use, particularly the potential for widespread domestic use.

Members also recalled that the October 2007 NDSPC Meeting, in making its MNBP decision, agreed that XXXXX opinion should be sought as to whether there was sufficient information to consider a Schedule 5 cut-off as a variation at the February 2008 NDPSC Meeting. XXXXX subsequently requested that MNBP be brought to the February 2008 NDPSC Meeting. The February 2008 NDPSC Meeting noted the following from XXXXX comment on MNBP, and on sensitisation generally:

<u>Mechanism of Contact Sensitization</u>

- Allergic contact dermatitis occurs in two phases: initial induction followed by elicitation. The initial phase begins with skin contact with a sensitizing agent. At the site of skin contact there is an immediate release of signalling factors and activation of skin dendritic cells occurs. Dendritic cells process the chemical agent and subsequently mature and migrate to the regional lymph node, where they serve as antigen-presenting cells. Lymphocytes within the node, upon antigen presentation undergo cellular proliferation. Following proliferation, T-lymphocytes are considered "primed", as they have a specific recall for the sensitizing agent. Upon subsequent exposure an antigen-specific response occurs (the elicitation phase). This second phase occurs only if there is elicitation of specific mediators that cause an inflammatory cell influx into the dermal site. This systemic response can occur at locations other than the original site of sensitization. This phase is characterized by erythema and oedema and occurs 24 to 72 hours after the challenge exposure. This response is the end product in traditional guinea pig tests.

<u>Guinea Pig Sensitization Tests – Buehler Test</u>

- For such tests, albino guinea pigs of 250-550g body weight are used, and sensitivity to a common sensitizing chemical such as dinitrochlorobenzene must be demonstrated. The concentration of the substance to be tested varies from undiluted to usage levels. The concentration selected for the tests is that which can produce slight erythema based on the above-mentioned irritancy test. Test and vehicle control groups of 10-20 animals are used, and in the Buehler test the agent is applied in an absorbent patch to the shaved left flank for 6 hours duration, 3 times over 15 days. Fourteen days later the challenge dose at the same concentration is applied for 24 hours to the opposite flank and the incidence and degree of the inflammatory response recorded.
- In the test used for MNBP the induction concentration used was 1 per cent and the challenge concentration was also 1 per cent. The result was an incidence of positive responses in the test group of 6/20 or 30 per cent. The agent thus qualified as a "moderate" sensitizer.

Human Sensitization Assay – Modified Shelanski Test

- For MNBP the human sensitization test was a "repeat insult patch test", one of which in common use is the "Shelanski" test. For this test a panel of human volunteers is used but usually it is not thought to be necessary to do this test if the guinea pig sensitization test is positive. The test involves application of patches impregnated with the agent under semi-occlusive conditions to the skin of the upper arm. The patch is applied for 24 hours 3 times a week on the same site for 5 weeks. 2 to 3 weeks later a patch is placed on a skin site for 48 hours and the response evaluated. The Shelanski test was modified in this study in that the patches were applied for only 3 weeks (9 times), and to the skin of the back, and the challenge was applied one week after the last patch was applied. This constituted a single 24 hour application of the test substance at a new site. The induction and elicitation doses of the test substance were 0.2 mL of a 0.5 per cent solution. Skin reactions were evaluated at 24, 48 and 72 hours.
- The recommended number of subjects used in a panel for such repeat insult patch tests is 150-200. In this MNBP test only 56 subjects were used and the result was found to be negative. It has been shown statistically that if no positive reactions are recorded in 200 randomly selected subjects, as many as 15 per 1000 in a general population may still be found to react. Reducing the sample size to 56 decreased the chance that this test would correctly predict adverse reactions.
- The range of end use products containing MNBP to which the public would be exposed would vary from 0.1 to 10 per cent. Since the potential for sensitization increases in genetically susceptible individuals with the amount of the exposure to the sensitizing agent, then even if "leave-on" exposures of MNBP at 0.5 per cent or less did not result in episodes of dermatitis, then this could not be claimed for regular exposures of up to 10 per cent, as might be expected to occur from time to time.

Recommendation

- The already proposed recommendation for Schedule 6 on account of acute toxicity and potential for sensitization appeared reasonable. The "moderately" positive Buehler test at 1 per cent exposure level for MNBP confirmed the potential for sensitization in humans, but the negatively modified Shelanski test did not give confidence that sensitizations in exposed genetically susceptible humans would not occur occasionally or even frequently.
- In the circumstances, a cut off to Schedule 5 for exposure concentrations at the levels of anticipated leave on use patterns was not proposed.

Members also recalled the recommendations from the assessment under the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) "Pyridine, 4-ethenyl-, reaction products with 3a,4,7,7a-tetrahydrodimethyl-4,7- methano-1H-indene" www.nicnas.gov.au/publications/CAR/new/Ltd/LtdFULLR/ltd1000FR/ltd1308FR.pdf considered at the October 2007 NDPSC Meeting:

- The Committee should consider the notified chemical for scheduling.
- Products containing the notified chemical and available to the public must carry safety directions and warning statements on the label consistent with the following:
  - May cause allergy.
  - Keep out of reach of children.

  [The October 2007 NDPSC Meeting noted that while written as "must" this was actually a labelling recommendation. The 'Keep out of reach of children' statement was already mandated for scheduled substances.]

Members also recalled the following from the NICNAS report:

- MNBP would be imported as a component of a fragrance oil (typically at 4 per cent but may be up to 40 per cent MNBP). The fragrance oil (containing MNBP) would be used in cosmetic and household products.
- Public exposure would be widespread through the use of products containing 0.01-10 per cent MNBP. The main exposure route was expected to be dermal, although ocular exposure to splashes was possible and inhalation exposure could occur when using spray products such as perfumes or spray cleaning products.
- Based on exposure data from a range of products in Europe, public exposure (dermal and inhalation) to MNBP was estimated to be 0.06 to 61 mg/kg bw/day, assuming a bodyweight of 60kg; a 100 per cent dermal absorption factor; a concentration of 0.01 per cent to 10 per cent; and product usage that was similar to Europe. This was likely to be an overestimate.
- It was possible that the cosmetic/personal care product categories include baby care products. Compared with adults, it was expected that children's systemic exposure would be higher due to the physiological features of young children. In addition, since products containing MNBP are stored and used in a domestic environment, there are possibilities of accidental ingestion, especially by young children.

- Toxicological investigations summary:

Endpoint and Result	**Assessment Conclusion**
Rat, acute oral toxicity	harmful (LD_{50} = 1400 mg/kg bw)
Rat, acute dermal toxicity	harmful (LD_{50} = 1300 mg/kg bw)
Rabbit, skin irritation	moderately irritating
Rabbit, eye irritation	slightly irritating
Guinea pig, skin sensitisation – Buehler test	evidence of sensitisation
Human repeated insult patch test	no evidence of skin irritation and sensitisation
Rat, repeat dose oral toxicity – 28 days	NOAEL = 5 mg/kg/day
Genotoxicity – bacterial reverse mutation	non mutagenic
Genotoxicity – *in vivo* (Mammalian Erythrocyte Micronucleus Test)	non genotoxic

- MNBP was moderately irritating to the skin (very slight to well-defined erythema with very slight or slight oedema) and slightly irritating to the eye (scatter or diffuse corneal opacity, iridial inflammation and conjunctival irritation) in rabbits. Although MNBP was harmful by ingestion, the risk of toxic effects from accidental ingestion was considered to be low due to the low typical concentrations of MNBP in products.
- A Buehler guinea pig sensitisation assay indicated that 1 per cent MNBP was a skin sensitiser. However, a human patch test in 56 human subjects using 0.5 per cent MNBP showed negative results.
- There was a risk of skin sensitisation to the general public from use of the products containing high concentration of MNBP, especially for leave-on products, such as body lotions. Appropriate consumer protections would be recommended to minimise the risk. However, the risk should be limited as the typical maximum concentrations of MNBP are low in the majority of products. The risk would also be reduced by use of appropriate warning and safety directions on the label.
- Based on the available data MNBP was classified as hazardous under the National Occupational Health and Safety Commission (NOHSC) Approved Criteria for Classifying Hazardous Substances. The classification and labelling details are:
  - R21/22 Harmful in contact with skin and if swallowed.
  - R43 May cause sensitisation by skin contact.
- There was concern to public health when there was use of certain consumer products that contained high concentrations of MNBP.
- The report recommended that MNBP should only be used:
  - in leave-on type of cosmetics/personal care products containing ≤0.2 per cent, except body lotion (≤0.05 per cent) and deodorant sprays (≤0.03 per cent);
  - in wash-off type of cosmetics/personal care products containing ≤0.6 per cent; and
  - in fragrance type of cosmetics/personal care products containing ≤0.4 per cent.

- The above conditions were recommended to be applied when MNBP was added to the Australian Inventory of Chemical Substances (AICS).

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee noted that no pre-meeting comments had been received in response to the February 2008 foreshadowed decision.

The Committee again confirmed that the human sensitisation data appeared to be unreliable and that a cut-off to exempt was not reasonable, particularly as sensitisation may not be linearly related to concentration. Members noted that no new data had been tabled, and that it therefore reconfirmed that there were no grounds for considering a cut-off to Schedule 5 either.

A Member noted that animal data for substances in cosmetics may become less available for Committee considerations in future as the cosmetics industry reacts to the EU moves to ban cosmetic testing on animals. Another Member noted that the local lymph node assay (LLNA) test remained available.

XXXXX

RESOLUTION 2008/53 - 10

The Committee decided to remove the current 0.5 per cent exemption cut-off from the Schedule 6 MNBP entry.

Schedule 6 – Amendment

METHYLNORBORNYLPYRIDINE – Amend entry to read:

METHYLNORBORNYLPYRIDINE.

5.2 SUSDP, PART 5

Nil.

6. MATTERS REFERRED BY THE AUSTRALIAN PESTICIDES AND VETERINARY MEDICINES AUTHORITY (APVMA)

6.1 PROTHIOCONAZOLE

PURPOSE

The Committee considered the scheduling of prothioconazole including a proposal to up-schedule.

BACKGROUND

Prothioconazole, a triazole conazole fungicide, is a racemate containing a 50:50 ratio of the S and R-enantiomers.

The June 2005 NDPSC Meeting considered an XXXXX evaluation of an application by XXXXX to APVMA for approval of the active prothioconazole and XXXXX. The Committee noted that the toxicological profile of prothioconazole appeared to be a little different from other triazole fungicides (20 triazole fungicides previously scheduled, with 16 classified as Schedule 5 and 4 classified as Schedule 6). The Committee noted that prothioconazole had low oral, dermal and inhalation toxicity, with only slight eye or skin irritation, and was not a skin sensitiser. Based on low oral and inhalation toxicity XXXXX recommended that the Committee consider exempting prothioconazole from the requirements of scheduling. The Members agreed to include prothioconazole in Appendix B.

DISCUSSION - SUBMISSIONS

XXXXX provided data to amend the particulars and conditions of the Australian Pesticides and Veterinary Medicines Authority (APVMA) approved active constituent prothioconazole. XXXXX has undertaken an evaluation of this new data and recommended:

XXXXX

- XXXXX

Public Health Standards

- The existing acceptable daily intake (ADI) for prothioconazole remains appropriate at 0.01 mg/kg bw/day, based on a no observable adverse effect level (NOAEL) of XXXXX in a XXXXX study on prothioconazole-desthio (major metabolite), using a XXXXX safety factor.
- The existing acute reference dose (ARfD) for prothioconazole remains appropriate at 0.03 mg/kg bw/day, based on a NOAEL of XXXXX in a XXXXX study on prothioconazole-desthio (major metabolite), using a XXXXX safety factor.
- On the basis of new evidence that prothioconazole produced using a modified manufacturing process has the potential to cause skin sensitisation, XXXXX recommended that the scheduling of prothioconazole be amended to Schedule 5.

  [Members noted the evaluator's confirmation that the sensitisation concern arose from the by-products of a particular manufacturing process, not from prothioconazole itself. Members considered whether this was a scheduling issue, or whether impurities are a manufacturing quality issue for the regulator. It was noted that if the Committee were to schedule based on an impurity profile this may require reconsideration of scheduling whenever the impurity profile changed (e.g. a change in manufacturing process, or if new suppliers of prothioconazole came into the market).]

Members also noted the following from the evaluation report:

- In the XXXXX application, a manufacturing by-product (and metabolite), prothioconazole-desthio, was identified as a significantly more potent developmental toxin than prothioconazole itself. XXXXX subsequently modified the manufacturing process to eliminate the formation of prothioconazole-desthio.
- However, the new manufacturing process resulted in two new by-products, prothioconazole-triazolidinethione (at XXXXX) and prothioconazole-asymmetric disulfide (at XXXXX), together with increased levels of the by-product prothioconazole-deschloro (XXXXX). [Members noted that the June 2005 NDPSC Minutes relating to the Appendix B decision did not discuss by-products, just the low toxicity of prothioconazole itself.]
- Additional toxicological data had now been provided on these by-products. Except for one study, the acute, genotoxicity and developmental toxicology studies have been conducted in accordance with the contemporary test guidelines. In combination with previously evaluated studies, the toxicological database was considered by the evaluator to be adequate for assessment.
- On the basis of prothioconazole's previously determined toxicological profile, the evaluation of the submitted studies and the maximum concentrations of the 3 by-products, XXXXX determined that prothioconazole produced using the modified manufacturing process (the Technical Grade Active Constituent (TGAC)) had the potential to cause skin sensitisation.
- Both prothioconazole-deschloro and prothioconazole-triazolidinethione caused sensitisation in XXXXX, and the combined concentration of these two by-products was up to XXXXX in the modified manufacturing process. Apart from this, the assessment of the data package found that the acute and reproductive toxicity profile of prothioconazole was not expected to be affected by the presence of the three by-products at the specified maximum concentrations.

Members additionally noted the following toxicity data from the evaluation report:

Prothioconazole (TGAC)

- The TGAC produced using the new manufacturing specification had the potential to cause skin sensitisation. Apart from this, the toxicological profile of the TGAC was unchanged from the 2005 evaluation:
  - Low oral (XXXXX), dermal (XXXXX) and inhalational (XXXXX) toxicity in XXXXX.
  - No skin or eye irritation in XXXXX and not a skin sensitiser in XXXXX.
  - The liver and kidney were target organs in XXXXX. Liver toxicity was characterised by increased liver weight, liver enlargement, raised plasma ALT levels, changes in hepatic enzyme activity (generally increases), and hepatocellular hypertrophy with cytoplasmic (particular in chronic studies), suggesting that the effect appear to be a class effect. The changes were in accord

with extensive metabolism and the presence of high levels of the parent compound in the liver.

– Prothioconazole was not associated with selective effects on the reproductive system or developing offspring in the absence of toxicity in parental animals. The test substance was not genotoxic. There was no evidence of carcinogenic potential.

- No studies were provided regarding the toxicokinetics or metabolism of the new by-products. The major metabolic reactions that were observed in the original TGAC were conjugation with glucuronic acid, desulfuration to produce prothioconazole-desthio, and oxidative hydroxylation of the phenyl moiety. It was not expected that the new by-products would significantly change the identity or relative fraction of the metabolites as determined in the original TGAC evaluation.
- Prothioconazole was not listed on the ASCC Hazardous Substances Information System Database. OCS has classified prothioconazole as a hazardous substance according to National Occupational Health and Safety Commission (NOHSC) Approved Criteria for Classifying Hazardous Substances (R43, ≥ 1 per cent, "May cause sensitisation by skin contact").

Prothioconazole-deschloro

- Prothioconazole-deschloro was of low oral toxicity XXXXX. The compound was found to be a skin sensitiser in XXXXX under the conditions of XXXXX. There was no evidence of genotoxicity in XXXXX, and the substance did not induce chromosome aberrations or forward mutations *in vitro* in XXXXX.
- The applicant supplied a developmental study on prothioconazole-deschloro which found a no observable effect level (NOEL) for maternal toxicity of XXXXX and a no observable effect level (NOEL) for foetal toxicity of XXXXX This is similar to the developmental studies conducted on the original TGAC XXXXX. The endpoints in both studies were similar. Therefore, this by-product was unlikely to significantly impact the developmental toxicity of the TGAC.

Prothioconazole-triazolidinethione

- Prothioconazole-triazolidinethione has low acute toxicity XXXXX, is not a skin irritant but is a moderate eye irritant, based on XXXXX The compound was found to be a skin sensitiser in XXXXX under the conditions of XXXXX. There was no evidence of genotoxicity in XXXXX.

Prothioconazole-asymmetric disulfide

- Prothioconazole-asymmetric disulfide has low acute oral toxicity XXXXX. There was no evidence of genotoxicity in XXXXX.

Members were advised that the issue of impurities in pesticides was discussed in detail at the June 2002 NDPSC Meeting. Members noted:

- Currently the scheduling exemption in Part 1, Paragraph 2 of the SUSDP reads:

(k) any substance present as an impurity in a pesticide, at a concentration at or below the maximum content for that substance, specified for the pesticide in the current version of the *Minimum Compositional Standards (MCS) for Active Constituents* or its successor, as published by the Australian Pesticides and Veterinary Medicines Authority.

- This paragraph arose out of the June 2002 consideration of the scheduled substances when present as impurities (in a pesticide).

June 2002 discussion

- Dimethyl sulphate (Schedule 7 due to carcinogenicity) may be present at low levels as a manufacturing impurity in a diverse range of products. Sulfotep is an organophosphate insecticide included in Schedule 7 which may also be an impurity in various pesticides. Substances in Schedule 7 do not qualify for the general 10 mg/kg exemption. The Committee noted that other Schedule 7 and 6 substances may also be present as impurities in various pesticides.
- Members noted that the Committee did not usually schedule impurities. Examples include where the impurity was specifically excluded e.g. lead from zinc based paints.
- It was noted that recognition of the upper limits in the MCS would still leave impurities scheduled when present at concentrations > than in the MCS (if the impurities were scheduled). The MCS applied only to agricultural TGACs.
- Members agreed that modification of Part 1 Paragraph (1)(2) to exclude substances when listed in the MCS as an impurity offered a generic mechanism for exemption of such impurities. This approach recognised in particular that inclusion in the MCS was based on toxicological assessment that included such impurities in the testing profile.

Members therefore considered foreshadowing separate specific scheduling of prothioconazole-triazolidinethione and prothioconazole-deschloro on the basis of the sensitisation potential. APVMA could then address the prothioconazole-triazolidinethione and prothioconazole-deschloro impurity issue through the listing of prothioconazole in the *APVMA Standards for Active Constituents* (which has replaced the MCS) as part of the registration process for the active.

Members noted that a Schedule 7 parent entry for these two compounds may add enforcement strength to the allowable impurity levels of these substances in products, and also appeared to in line with the scheduling of other impurities of concern in agvet products (e.g. dimethyl sulphate and sulfotep as discussed above). However, as both these impurities appeared to only be of concern because of skin sensitisation potential, the Committee also considered Schedule 6 parent entries for these substances (noting that the examples dimethyl sulphate and sulfotep both had toxicity that was consistent with the Schedule 7 criteria).

Members also considered an editorial amendment to Part 1 Paragraph (1)(2)(k) to update the reference to the MCS to the *APVMA Standards for Active Constituents*.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The relevant matters under section 52E (1), to this item, included: (a) – toxicity and safety of the substance; and (c) potential hazards.

A Member suggested that the option of scheduling the impurities should not be pursued. The Member noted that while the impurities were sensitisers, it had not been determined that the TGAC was a sensitiser. The Member suggested that a Local Lymph Node Assay (LLNA) using the TGAC would have settled the matter.

Another Member noted that the Committee was in a difficult position as sensitisation need not be linearly related to concentration, and that the TGAC had the potential to be a sensitiser. Without data to address this concern the Committee would need to be cautious, XXXXX. The Committee generally agreed that prothioconazole would need to be upscheduled to Schedule 5 unless sensitisation data on the TGAC (such as LLNA) was provided which supported an Appendix B listing. Members agreed that the way to proceed was to foreshadow inclusion of prothioconazole in Schedule 5 (with consequential deletion of the Appendix B entry) for the October 2008 NDPSC Meeting, noting that this intent could be reviewed should sensitisation information become available.

RESOLUTION 2008/53 - 11

The Committee decided to foreshadow rescheduling prothioconazole from Appendix B to Schedule 5.

FORESHADOWED DECISION (for consideration at the October 2008 meeting)

Schedule 5 – New entry

PROTHIOCONAZOLE.

Appendix B – Amendment

PROTHIOCONAZOLE – Delete entry.

6.2 FLUOXETINE

PURPOSE

The Committee considered the scheduling of fluoxetine.

BACKGROUND

Fluoxetine is a selective serotonin reuptake inhibitor (SSRI), which specifically inhibits neuronal re-uptake of serotonin, thus increasing the concentration of serotonin at the synapse and reinforcing serotonergic neuronal transmission. Fluoxetine is registered in Australia as a human therapeutic substance for the treatment of depression, obsessive-compulsive disorder and premenstrual dysphoric disorder.

XXXXX has submitted an application seeking approval of fluoxetine XXXXX. Toxicology studies involving the active constituent were previously evaluated XXXXX. The applicant has provided authorisation to use these evaluation reports for the assessment of the current application.

DISCUSSION - SUBMISSIONS

XXXXX had undertaken an independent evaluation of the applicant's submission on fluoxetine, including consideration of the evaluation report of XXXXX. The XXXXX evaluation report recommended:

XXXXX

- There were no objections on human health grounds to the approval of the new active.
- XXXXX

Public health

- Given that the XXXXX was to be used only as a veterinary medicine in non-food producing animals, establishment of an ADI or ARfD was not necessary.
- Fluoxetine is currently in Schedule 4. The applicant proposed that the existing scheduling was appropriate XXXXX. Based on the toxicology profile of the product and its use as a veterinary therapeutic agent, this classification was considered appropriate. Alternatively, the scheduling of fluoxetine could be amended to separate fluoxetine for human therapeutic use from fluoxetine for veterinary use or the treatment of animals.

Members noted the following aspects from the evaluation report:

- No toxicology studies conducted with the active ingredient were submitted. The applicant provided authorisation to refer to the assessment of the active constituent previously carried out by XXXXX for the registration of the XXXXX. The information provided in XXXXX was relied on XXXXX in considering the current application.
- Fluoxetine was moderately toxic after acute oral administration. Based on the findings of acute studies with the active constituent, XXXXX was expected to have moderate acute oral, dermal and inhalational toxicity. There were no data on skin and eye irritation or skin sensitisation potential of the active constituent or the XXXXX. Given the XXXXX, together with its history of clinical use, these data were not considered necessary.

- The toxicity profile of fluoxetine was similar to that of other serotonergic agents. Fluoxetine reduced food intake (anorectic activity) in both meal-fed and free-feeding animals. It resulted in decreases in body weight in normal-weight and obese animals. Following repeated dosing, the main target organs of toxicity were lungs, liver and adrenal glands where the main pathology lesion was phospholipidosis. The phospholipidosis observed with other amine uptake-inhibitors was considered to be an adaptive response to the drug rather than a toxic effect. Fluoxetine was not genotoxic or carcinogenic in XXXXX.
- Reproductive and developmental toxicity studies with fluoxetine did not show any evidence of teratogenicity XXXXX. The major finding in treated XXXXX was adverse effects on the male reproductive system. Other important findings were growth retardation and skeletal muscle degeneration. These changes have been noted with other members of this class of amine uptake-inhibitor compounds.
- XXXXX

Recommended hazard classification

Active constituent:

- Fluoxetine was not listed on the ASCC Hazardous Substances Information System Database.
- With the available toxicology information, XXXXX classified fluoxetine as a non-hazardous substance according to the NOHSC Approved Criteria for Classifying Hazardous Substances and determined that fluoxetine required no risk labels.
- XXXXX

DISCUSSION – RELEVANT MATTERS UNDER 52E

The following matters under 52E(1) were considered particularly relevant to this consideration: (a) toxicity and safety (b) risks and benefits (c) potential hazards and extent and pattern of use.

The Committee noted that use of this substance in humans was well established and that this product would likely be limited to XXXXX use for treatment of XXXXX.

A Member raised concerns about the palatability and potential toxicological effects of the product, given that a singe XXXXX dose could induce serotonin syndrome in a child. Members noted that serotonin syndrome is a potentially life-threatening adverse drug reaction which is a consequence of excess serotonergic agonism of central nervous system receptors and peripheral serotonergic receptors.

In the ensuing discussion, the Committee acknowledged that while there were a number of potentially toxic substances scheduled as Schedule 4 (prescription animal remedies), there were issues that were specific to this product. Options were discussed, including a

recommendation for strip packaging, obliging vets not to bulk dispense or limiting pack size through registration. The Committee decided that it should leave these matters to the APVMA, but that it would let its concerns be known to the APVMA.

The Committee agreed that it served no purpose to separately stipulate both veterinary and human use in the Schedule 4 entry as the existing entry already captured both of these intended uses.

RESOLUTION 2008/53 - 12

The Committee decided that the existing entry for fluoxetine remained appropriate.

6.3 MAROPITANT

PURPOSE

The Committee considered the scheduling of maropitant.

BACKGROUND

Maropitant is a synthetic, non-peptide, selective neurokinin-1 (NK1) receptor antagonist, specifically developed for use in XXXXX. It selectively binds to Substance P, the key neurotransmitter involved in vomiting, inhibiting the effect of Substance P and resulting in prevention and control of emesis, stimulated via central and peripheral mechanisms. It was intended for the prevention and treatment of emesis in XXXXX.

XXXXX had applied for the approval of this new veterinary therapeutic substance (as maropitant citrate). XXXXX

DISCUSSION - SUBMISSIONS

The XXXXX had undertaken an evaluation of the submission XXXXX on maropitant, including consideration of the evaluation report of XXXXX. The XXXXX report provided the following recommendations:

- XXXXX There were no objections on human health grounds to the approval of maropitant citrate.
- XXXXX

Public health

- Given that the product was to be used only as a veterinary medicine in non-food producing animals, the establishment of an ADI or ARfD was not necessary.
- Based on the toxicity and safety profile and its use as a veterinary therapeutic agent, scheduling was warranted. The NDPSC may wish to include maropitant for veterinary use in Schedule 4.

Members noted the following from the evaluation report:

- Maropitant citrate had low acute oral and dermal toxicity in XXXXX. It was not a skin irritant or a skin sensitiser, but was a severe eye irritant. It was not genotoxic. Inhalational studies were not considered necessary given the low oral toxicity, the proposed scheduling in Schedule 4 and the presentation and packaging of the product. Based on the findings of the acute studies with the active constituent, the product was expected to have low acute oral, dermal and inhalational toxicity.
- The target organs of toxicity in XXXXX were the central nervous, respiratory, endocrinological (adrenal glands), hematopoietic and hepatic systems. The NOEL in these animals was considered to be XXXXX.
- Cardiovascular effects, manifested by QTc prolongation, were observed in XXXXX XXXXX, when given orally for XXXXX months. However, no associated clinical signs were observed.
- Mutagenicity studies demonstrated that it was not genotoxic. No carcinogenicity studies were conducted, which was considered acceptable given it was not mutagenic and its short use pattern.

XXXXX

Exposure discussion

- The XXXXX was intended for use in non-food producing animal species XXXXX XXXXX was intended XXXXX and administered by a professional XXXXX. Exposure to the public was expected only to occur through accidental XXXXX.

Recommended hazard classification

Active constituent:

- Maropitant citrate was not listed on the Australian Safety and Compensation Council Hazardous Substances Information System Database.
- With the available toxicology information, XXXXX classified maropitant citrate as a hazardous substance according to NOHSC Approved Criteria for Classifying Hazardous Substances with the following risk phrases: R36 Irritating to eyes
- No cut-off concentrations apply for maropitant citrate.

Product:

- Given the form of presentation and intended use pattern XXXXX was not considered for classification in accordance with NOHSC Approved Criteria for Classifying Hazardous Substances (NOHSC, 2004).

DISCUSSION – RELEVANT MATTERS UNDER 52E

The following matters under 52E(1) were considered particularly relevant to this consideration: (a) toxicity and safety (b) risks and benefits (c) potential hazards and extent and pattern of use.

The Committee agreed that the toxicology profile of maropitant satisfied the requirements of a Schedule 4 entry.

The Committee noted that while XXXXX were seen, the intended use pattern and dosage alleviated any concerns on this matter. In considering the form of presentation XXXXX and intended use pattern, a Member indicated that the use of the product was likely to be limited to a veterinary surgery. The Members noted that there were no human products in Australia at this time.

Given that the variety of adverse effects of maropitant seen in animal studies occurred only at XXXXX the Committee noted that likelihood of those occurring in the XXXXX was unlikely. The Committee also agreed that it would not be appropriate to restrict a Schedule 4 entry to "veterinary use" as the entry should also capture human use.

RESOLUTION 2008/53 - 13

The Committee decided to create a new entry for maropitant in Schedule 4.

Schedule 4 - New entry

MAROPITANT.

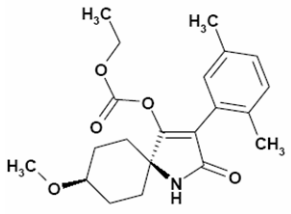
6.4 SPIROTETRAMAT

PURPOSE

The Committee considered the scheduling of spirotetramat.

BACKGROUND

Spirotetramat is the provisionally approved ISO name for the chemical cis-4-(ethoxycarbonyloxy)-8-methoxy-3-(2,5-xylyl)-1-azaspiro[4.5]dec-3-en-2-one, which has the following structure:



Spirotetramat is in a new chemical class (tetramic acids, cyclic ketoenoles) of insecticides that act as Acetyl CoA Carboxylase (ACCase) inhibitors. In eukaryotes and prokaryotes,

ACCase is a key enzyme in fatty acid biosynthesis. The biological activity of cyclic ketoenoles correlates with inhibition of lipogenesis in treated insects, resulting in decreased lipid contents (notably triglycerides and free fatty acids), inhibition of the ability of younger insects to develop through the various growth stages, and ultimately culminating in a diminished capacity of the insect to reproduce as adults. Other lipid biosynthesis inhibitor insecticides include the tetronic acid insecticides spirodiclofen and spiromesifen, which are analogous of spirotetramat.

DISCUSSION - SUBMISSIONS

XXXXX sought XXXXX review for XXXXX spirotetramat XXXXX conducted its own evaluation on the basis of the international assessment. XXXXX evaluation recommended:

- XXXXX

Public Health Standards

- The ADI for spirotetramat was established at 0.05 mg/kg bw/d based on a NOEL of 5 mg/kg bw/d in a one-year XXXXX study and using a 100-fold safety factor.
- The ARfD was established at 1 mg/kg bw/d based a NOEL of 100 mg/kg bw/d in an acute neurotoxic study and using a 100-fold safety factor.
- Based on the toxicity profile, it was recommended that spirotetramat be placed in Schedule 6.

Members also noted the following from the evaluation report:

- The database supplied was considered to be adequate for the purposes of risk assessment.
- XXXXX
- Some issues arose from the difference between the NOELs normally established by XXXXX and the XXXXX approach of using NOAELs. Because of the difficulty in deciding whether observed effects are necessarily adverse, Australian assessments have used NOELs and LOELs instead of NOAELs and LOAELs. However, since the XXXXX report relied significantly on the international assessment, XXXXX has adopted the LOAEL and NOAEL established (with scientific justifications) in the international assessment. In XXXXX view the LOAEL and NOAEL used by XXXXX were technically equivalent to the LOEL and NOEL of toxicological significance used by XXXXX.
- Another issue arose from the differences between the toxicological endpoints used by XXXXX for establishing the NOAELs in XXXXX studies:
    - XXXXX have each expressed different opinions in deciding whether decreased thyroid hormone T3 and T4 levels at XXXXX dose levels in three XXXXX

studies were adverse and hence used different toxicological endpoints for establishing the NOAELs.

- XXXXX believed these thyroid hormone decreases were adverse effects but did not give an underlying rationale. XXXXX reviewers considered the decreases in thyroid hormones to be non-adverse based on the lack of correlative changes in thyroid stimulating hormone (TSH), thyroid weight, or thyroid histopathology at the same dose levels.
- XXXXX proposed that the decreased circulating levels of T4 and T3 were toxicologically significant based on the following considerations:
    - Although changes in thyroid histopathology was not seen at the same dose levels at which decreased T3 and T4 was observed, slight reduced thyroid follicle size did occur in the XXXXX study at XXXXX doses. Since T3 and T4 are produced and stored in thyroid follicles, a reduction in the size of those follicles might underlie the mechanism of decreased T3 and T4 levels. Therefore there was a reasonable connection between the decreased thyroid hormone seen at XXXXX doses and histopathological changes seen at XXXXX doses in the longer term study.
    - There was progressive correlation between decreased thyroid hormones and pathological findings of thymus. Decreased thyroid hormones were always seen at XXXXX doses in all XXXXX studies. Pathological and histopathological effects in thymus were observed at XXXXX doses at XXXXX and XXXXX studies while seen at the XXXXX dose and above in the XXXXX study. Decreased thyroid hormones (T3 and T4) inhibit proliferation and induce death of thymocytes.
    - While the mammalian mode of action (MOA) for spirotetramat was not clear, XXXXX considered that decreased thyroid hormones were potentially involved in the MOA (discussed below).
    - Two structural analogues of spirotetramat (spirodiclofen and spiromesifen) exhibited thyroid toxicity.
- Based on the above analysis, XXXXX considered that decreased circulating levels of T4 and T3, at XXXXX doses in the XXXXX studies were toxicologically significant and agreed with XXXXX on the NOAELs.

Members additionally noted the following toxicity data from the evaluation report:

XXXXX

Acute toxicity

- Moderate to low acute oral, dermal, and inhalation toxicity. Non-irritating to the skin, a severe irritant to the eyes and exhibits skin-sensitization potential XXXXX. The sensitization potential was supported by XXXXX cases of Type IV hypersensitivity (in XXXXX).

Short term toxicity

- The insecticidal mode of action (lipid biosynthesis inhibition) was not reflected in the short-term toxicological studies in XXXXX.
- The thyroid and thymus glands were target organs in a XXXXX study in XXXXX. Declines in circulating thyroid hormones (T3 / T4) at XXXXX were observed. However, correlative changes in thyroid weight, thyroid histopathology, or thyroid stimulating hormone were not observed. The NOAEL was considered to be XXXXX.
- The thymus, thyroid, and brain were target organs following XXXXX exposure of XXXXX. Thymus involution and brain dilation with dose-related severity were observed in XXXXX, while axonal degeneration in the hypothalamus was observed in XXXXX. Brain dilation was observed in XXXXX also, however, it was not observed at XXXXX. Both sexes showed decreases in circulating thyroid hormone T4 at XXXXX and XXXXX also of T3 at XXXXX.
- Reduction in thyroid follicle size, a possible indication of a reduced amount of colloid in the organ, was observed at XXXXX. Correlative changes in thyroid weight or thyroid stimulating hormone were not observed. Clinical signs of neurotoxicity (dehydration, swelling, decreased activity and reactivity, seizures and ataxia) were observed in XXXXX at the XXXXX dose tested, a finding that was consistent with the multi-organ toxicity observed at this dose. No morphological changes in the testes were observed in XXXXX at any dose. The NOAEL was considered to be XXXXX.
- In XXXXX, the testes were the target organ following subchronic oral treatment XXXXX at a XXXXX dose. Abnormal spermatozoa and hypospermia in the epididymis, decreased testicular weight, and testicular degeneration and vacuolation in males were observed after XXXXX of exposure at XXXXX. These effects proved to be reversible in most animals after cessation of treatment. Thyroid and thymus were unaffected in XXXXX at any dose. The NOAEL was considered to be XXXXX.
- Unlike the XXXXX, no adverse effects of any kind were observed in XXXXX tested orally up to the limit dose. *In vitro* results from a comparative metabolism study using hepatocytes from XXXXX revealed species differences in the metabolism of spirotetramat. Specifically, XXXXX hepatocytes were better able than XXXXX or XXXXX liver cells to metabolize BYI 08330-enol via glucuronidation. Potentially lower levels of the enol metabolite in XXXXX *in vivo* may account for the lack of testicular toxicity observed in this species. The NOAEL was considered to be XXXXX.
- Subchronic exposure of XXXXX by the dermal route yielded no evidence of systemic toxicity when tested up to XXXXX.

Long-Term toxicity and carcinogenicity

- Chronic toxicity/carcinogenicity was tested in XXXXX following application for XXXXX years, respectively. Target organs in XXXXX were the kidney (both sexes) at XXXXX doses and the liver (females) at the XXXXX dose only. These results are consistent with the excretory and/or detoxification roles of the kidney and liver. Consistent with the subchronic study the lung demonstrated treatment-related presence of alveolar macrophages in XXXXX dose males and XXXXX dose females. Testicular histopathology in XXXXX was not observed following XXXXX of oral exposure; however, after XXXXX spermatid degeneration in the testes and germ cell exfoliated debris in the epididymis were observed in XXXXX.
- No adverse findings were observed in XXXXX up to the limit dose following XXXXX treatment with spirotetramat.

Genotoxicity

- Overall, assays for XXXXX (both *in vivo* and *in vitro*) were negative for spirotetramat. A weak positive finding was noted in a XXXXX, but at cytotoxic concentrations only. Negative findings in XXXXX studies and one XXXXX XXXXX using XXXXX do not suggest a genotoxic concern for spirotetramat.

Reproductive Toxicity

- In addition to testicular histopathology observed following subchronic and chronic exposure of XXXXX, evidence of male reproductive toxicity was provided in a XXXXX. Abnormal sperm cells were reported in F1-generation male XXXXX treated with XXXXX, and decreased reproductive performance was also observed in XXXXX. Similar results were obtained in a XXXXX study. The highest dose level of XXXXX was associated with no fertility in parental generation animals. There were no implantation sites noted in the females due to treatment-related effects on sperm cells of males at this dose level.
- In February 2008 XXXXX submitted a position paper XXXXX asserting that the effects on testicular spermatogenesis were attributed to the BYI 08330-enol (the main metabolite in XXXXX). In XXXXX, conjugation of BYI 08330-enol with glucuronic acid accounted for approximately XXXXX per cent. In XXXXX liver cells, conjugation to BYI 08330-enol-glucuronic acid was XXXXX per cent. The article asserted that glucuronidation of the BYI 08330-enol in XXXXX led to much lower systemic levels of free BYI 08330-enol when compared to XXXXX. The conjugation enabled XXXXX to utilize separate active transport systems in the kidneys, thus avoiding a saturation of the elimination process and rendering XXXXX less sensitive to BYI 08330-mediated testicular toxicity than XXXXX. The article asserted that, based on the metabolic similarity between XXXXX, it was likely that XXXXX were also less sensitive to BYI 08330-mediated testicular toxicity than XXXXX.
- This statement XXXXX could not be agreed to. In XXXXX the ability to conjugate BYI 08330-enol with glucuronic acid is XXXXX lower than for the XXXXX (dependent on the concentration). Therefore a similarity in the metabolic pathway

can not be followed and it can not be assumed that XXXXX are less sensitive to spirotetramat than XXXXX.

- Due to abnormal sperm cells, decreased sperm motility and progression and decreased reproductive performance, spirotetramat should be classified to category 3 of reproductive substances and labelled with risk phrase 62 (Possible risk of impaired fertility) according to Annex VI of the EC Council Directive 67/548/EEC.

Developmental toxicity

- In a XXXXX developmental toxicity study, toxicity to the offspring was observed in the presence of maternal toxicity. Increased incidences of skeletal malformations and skeletal deviations were indicated at a maternally toxic dose XXXXX, with a NOEL of XXXXX. Decreased food consumption and body weight/gain were also observed in parental animals at XXXXX. Although the developmental toxicity was observed in the presence of maternal toxicity, due to increased incidences of skeletal malformations and skeletal deviations and according to Annex VI of the EC Council Directive 67/548/EEC, the XXXXX report concluded that spirotetramat should be classified to "category 3 of reproductive substances" and labelled with the risk phrase "R 63 – Possible risk of harm to the unborn child".
- XXXXX also considered that spirotetramat merited a Category 3 classification due to concern for humans owning to possible developmental toxic effects due to the following:
  - Although a clear developmental toxic effect was not seen in the absence of a maternal toxic effect, a supplementary developmental study in XXXXX revealed that the maternal toxicity NOAEL was XXXXX while the developmental toxicity NOAEL was XXXXX.
  - The thyroid toxic effects in XXXXX provided addition information for supporting spirotetramat for a Category 3 classification with possible developmental toxic effects to XXXXX.

Neurotoxicity

- Spirotetramat has been assessed for potential neurotoxicity in XXXXX acute neurotoxicity studies in XXXXX and was shown to have no neurotoxic potential. The NOAEL for systemic effects was established at XXXXX. Neurotoxic effects were not observed up to a limit dose of XXXXX.

Mechanistic studies

- In a mechanistic study designed to explore the time of onset of testicular toxicity of spirotetramat in XXXXX, decreased epididymal sperm counts were recorded XXXXX. Repeated dosing, therefore, was necessary to produce male reproductive toxicity in XXXXX.
- In a second mechanistic study, XXXXX were treated with the enol metabolite for XXXXX at a dose of XXXXX. Spermatotoxicity, abnormal sperm, and Sertoli cell vacuolation were observed in the testes-epididymides of treated animals. Therefore,

male reproductive toxicity in XXXXX was likely due to the enol metabolite of spirotetramat.

Proposed mammalian Mode of Action (MOA)

- The MOA for insecticide activity implied that spirotetramat might interrupt lipid metabolism in mammals. Two analogues, spirodiclofen and spiromesifen (also lipid biosynthesis inhibitors in insects) have been shown to interrupt lipid metabolism in mammals. Spirotetramat could interfere with metabolism of lipid-based hormones (e.g. sex hormones) which may lead to toxic effects. Nevertheless, this hypothesis was not supported by the observation that XXXXX did not exhibit changes in plasma lipid parameters in XXXXX studies.
- A structure comparison with a variety of anti-thyroid chemicals revealed that (to a degree) spirotetramat was structurally similar to isoflavone. Isoflavones have been found to interfere with the biosynthesis of thyroid hormone and exhibit *in vivo* estrogenicity. Spirotetramat (or its metabolites) could behave similarly to isofavones and target the thyroid through inactivation of human thyroid peroxidase (TPO) and target reproductive systems as estrogen mimics. TPO is a key enzyme mainly expressed in the thyroid that liberates iodine for addition onto tyrosine residues on thyroglobulin for the production of T3 and T4.
- <u>Thyroid and thymus toxicity MOA</u>
  - Decreased circulating levels of T3 and T4, thymus atrophy, and reduced thyroid follicle sizes were consistently observed in the XXXXX studies. Based on this information XXXXX proposed a thyroid/thymus MOA with the following key events:
    - Spirotetramat metabolised to a toxicologically significant compound e.g. the enol metabolite.
    - This metabolite inhibited the activity of TPO in the thyroid.
    - Decreased production of T3 / T4 leads to decreased circulating T3 / T4 levels.
    - Decreased circulating T3 / T4 levels inhibited proliferation and induced the death of thymocytes - subsequent thymus atrophy and reduced thymus weight.
    - Pathological changes in thyroid gland (e.g., reduced thyroid follicle size).
    - Developmental toxicity.
  - Spirotetramat may therefore produce deleterious effects on brain development by interfering with thyroid hormone action in the developing brain. As a result, developmental toxicity may also be a relevant endpoint for this MOA although no XXXXX developmental toxicity data was available. Interestingly, spirotetramat neither induced thyroid toxicity nor toxicity in the developing brain in XXXXX although it did cause increased incidences of skeletal malformations and skeletal deviations.
  - It was noted that data gaps existed for the first two key events of the MOA - metabolism of spirotetramat in XXXXX and inhibition of TPO in the thyroid.
- <u>Reproductive MOA</u>

- In XXXXX reproductive studies showed that spirotetramat treatment leads to increased numbers of abnormal sperms, reduced epididymal sperm counts, decline in both motility and progression of epididymal sperm cells, decreased absolute and relative weight of the cauda epididymis, spermatid degeneration in testes, and reduced reproductive performance. Mechanistic studies further reveal that the male reproductive toxicity is possibly induced by the enol metabolite of spirotetramat. Based on those observations XXXXX proposed a reproductive MOA with the following key events:
  - Spirotetramat metabolised to toxicologically significant compound, e.g., its enol metabolite.
  - Spirotetramat-enol might act as an anti-androgen or estrogen–like agent and disrupt sex hormone homeostasis.
  - Abnormal sperm findings (e.g., reduced motility, increased abnormal sperm cells).
  - Pathological / histopathological findings in testis and epididymis.
  - Reduced male reproductive performance.
- The data supports a sequence of key events leading to infertility. However there was a data-gap concerning disruption of sex hormone homeostasis.

- Relevance to humans
  - The effects appeared to be species-specific given that the thyroid/thymus toxicity was only observed in XXXXX, reproductive toxicity was seen only in XXXXX and almost no toxicities were seen in XXXXX. Differences in the metabolism of spirotetramat was likely to be the underlying mechanism for these species-specific toxicities.
  - In vitro results from a XXXXX study revealed that XXXXX hepatocytes were better able than XXXXX or XXXXX liver cells to metabolize BYI 08330-enol. Potentially lower levels of the enol-metabolite in XXXXX in vivo may account for the lack of testicular toxicity. For XXXXX the ability to conjugate BYI 08330-enol with glucuronic acid is XXXXX lower than for XXXXX (dependent on the concentration) and it cannot be assumed that XXXXX are less sensitive to spirotetramat than XXXXX. Similar kinetic profiles between XXXXX and XXXXX support that the male reproductive toxicity seen in XXXXX was relevant to XXXXX.
  - While XXXXX are very sensitive to compounds affecting thyroid hormone balance and therefore the XXXXX relevance of XXXXX thyroid toxicity could be low, in this case the thyroid toxicity was observed in XXXXX, not in XXXXX. There was no XXXXX metabolism data so it was not known whether metabolism pathways differed between XXXXX and XXXXX. So far there was no information suggesting that XXXXX was an ultra-sensitive species to compounds affecting thyroid hormones. Taking into account the data gaps XXXXX considered that the thyroid/thymus MOA was relevance to XXXXX but the degree of relevance was uncertain.

- Based on the above analyses, XXXXX concluded that human relevancy of the above two MOAs cannot be reasonably excluded on the basis of fundamental qualities or quantitative differences in either kinetics or dynamic factors between animals and humans. For male reproductive MOA, the relevance to human is high while for thyroid/thymus MOA, there was a relevance to human but the degree was uncertain.

Hazard Classification

- XXXXX classified spirotetramat as a hazardous substance according to NOHSC Approved Criteria for Classifying Hazardous Substances, with the following risk phrases:
  - Conc. ≥ 20 per cent R36 "Irritating to eyes".
  - Conc. ≥ 1 per cent R43 "May cause sensitisation by skin contact".
  - Conc. ≥ 5 per cent R62 "Possible risk of impaired fertility".
  - Conc. ≥ 5 per cent R63 "Possible risk of harm *to the unborn child"*.

XXXXX

Acute toxicity

- XXXXX (24 per cent spirotetramat) had low acute toxicity XXXXX by the oral XXXXX, dermal XXXXX and inhalation XXXXX routes. XXXXX was non-irritating to the skin but it was a slight irritant to eyes in XXXXX. XXXXX was a skin-sensitiser in XXXXX however its XXXXX.

XXXXX provided a comment regarding the XXXXX evaluation report. Members noted:

- XXXXX unfortunately did not receive the XXXXX evaluation report XXXXX until 22 May (the deadline for comments).
- XXXXX would consider the report and, if necessary, seek to make a late pre-meeting comment. [Members noted that no late pre-meeting comment was received.]

DISCUSSION – RELEVANT MATTERS UNDER 52E

The relevant matters under section 52E (1), to this item, included: (a) toxicity and safety of the substance; (b) risks and benefits; and (c) potential hazards.

Members generally agreed that the effects on lipid synthesis and change in thyroid function, together with the skin sensitisation and eye irritancy, certainly warranted control through Schedule 6.

A Member noted that XXXXX had also classified spirotetramat as a severe eye irritant, skin sensitiser and reproductive toxicant. However, XXXXX had not classified XXXXX (24 per cent spirotetramat) to be an eye irritant (unlike the slight eye irritant classification from the XXXXX evaluation report). The Committee was advised, however, that this

was due to the slight differences in classification criteria for eye irritancy between the New Zealand system and those used by the NDPSC.

Members noted advice from XXXXX that XXXXX did not object to Schedule 6 with no cut-off. XXXXX.

Members also acknowledged that the pre-meeting Gazette Notice had inadvertently misspelt spirotetramat as spiratetramat.

RESOLUTION 2008/53 - 14

The Committee decided to create a new Schedule 6 entry for spirotetramat.

Schedule 6 – New entry

SPIROTETRAMAT.

6.5 DELTAMETHRIN

PURPOSE

The Committee considered the scheduling of deltamethrin.

BACKGROUND

Deltamethrin is a synthetic dibromo-cyanopyrethroid insecticide, containing only the d-cis-isomer. Deltamethrin products are registered for use in Australia, a number of OECD countries and a number of African countries. However, Denmark has banned the outdoor use of deltamethrin products, due to concerns for the safety of the environment.

The February 1979 PSC Meeting first scheduled deltamethrin (in Schedule 6). This was changed to Schedule 7 at the May 1979 PSC Meeting due to occupational health concerns. This classification was reviewed several times in the following years and ultimately confirmed by the November 1988 DPSSC Meeting based on the available acute and chronic toxicity data.

The November 1988 Meeting also considered the scheduling of an aqueous suspension formulation of 1 per cent deltamethrin and agreed to a Schedule 5 entry for 1 per cent deltamethrin when formulated with no organic solvent other than a glycol.

The February 1993 DPSSC Meeting considered the scheduling of a 2.5 per cent deltamethrin formulation and agreed that this should be captured in Schedule 6. Over the subsequent years a wide range of products containing deltamethrin were considered by the Committee for inclusion in Schedule 5 or Schedule 6.

The February 2002 NDPSC Meeting considered the scheduling of a 25 per cent deltamethrin insecticide. The Committee agreed that, although the acute toxicity profile of the product was appropriate for Schedule 5, Members remained concerned of the potential for neurotoxicity and the likely flow-on effects for other deltamethrin products. Accordingly, the Committee agreed that the product should be labelled as a Schedule 6 poison.

The October 2004 NDPSC Meeting agreed to a requested change to the scheduling of deltamethrin, based on a 25 per cent deltamethrin as water dispersible granules product, from Schedule 6 to Schedule 5. Members had expressed concern regarding the child-resistance potential of the proposed packaging but generally agreed that this was an issue for the regulator.

DISCUSSION - SUBMISSIONS

XXXXX has applied to APVMA to XXXXX, containing deltamethrin at 25 g/L. While not a home garden product it may be used in residential or public environments by professional operators. XXXXX therefore sought rescheduling for 2.5 per cent deltamethrin from Schedule 6 to Schedule 5. XXXXX had undertaken an evaluation and recommended:

XXXXX

- XXXXX

Public Health Standards

- The ADI for deltamethrin was established in 1980 at 0.01 mg/kg bw/day, based on a NOEL of 1 mg/kg bw/day in a chronic XXXXX study and using a 100-fold safety factor. No ARfD was established for deltamethrin.
- Based on the content and toxicology profile of the product, the current classification (Schedule 6) was considered appropriate.

Members also noted the following from the evaluation report:

- The submission data package comprised of six acute toxicology studies on products similar to XXXXX. The acute toxicology studies were conducted in accordance with contemporary test guidelines. The acute toxicology data submitted was considered adequate for the assessment.
- The applicant did not provide specific argument as to why the product should not be considered under the current scheduling criteria for deltamethrin products. XXXXX contained 2.5 per cent deltamethrin, XXXXX. It conformed to the current criteria for a Schedule 6 deltamethrin product.

Members additionally noted the following toxicity data from the evaluation report:

Deltamethrin

- No acute toxicity studies on deltamethrin were submitted. The applicant instead referred to previously assessed deltamethrin data. The toxicity database for deltamethrin was considered adequate for this assessment.

Acute toxicity

- XXXXX
- Deltamethrin was not an irritant on XXXXX skin and only a mild eye irritant in XXXXX. It did not cause sensitisation on XXXXX skin. Clinical observations of XXXXX indicated that deltamethrin was irritating to skin and mucous membranes. Initial lesions were tenacious and painful pruritus (prickling sensation), followed by a blotchy burning sensation with blotchy erythema. Effects lasted for several days. XXXXX.
- Toxic symptoms include muscular contractions, piloerection, respiratory defects, convulsions and paresis of hind quarters. Toxicity in both XXXXX varied, depending on the carrier vehicle.

Subchronic studies

- Sub-chronic XXXXX studies resulted in decreases in male bodyweight XXXXX with no pathological changes. XXXXX studies at doses up to XXXXX, resulted in decreases in weight gain and the occurrence of liquid faeces in all treatment groups. CNS effects were seen at the high dose level only. Depression of the patellar reflex was observed at XXXXX. Histopathological examination was unremarkable.

Chronic studies

- Chronic studies were performed in XXXXX.
  - In XXXXX, there was no effect on behaviour, bodyweight, or on biochemical, haematological or urinanalytical parameters. There was no increase in tumour incidence. Histopathology was unremarkable. The NOEL was XXXXX.
  - In XXXXX there was no change in behaviour, and a small decrease in bodyweight gain at the high dose level. There was no significant change in biochemical or haematological parameters. Pathological examination revealed a slightly increased incidence of axonal degeneration in nerves at XXXXX. There was an apparent increase in interstitial adenomas in the testes of high dose males. The NOEL was XXXXX.
  - In XXXXX there were no clinical signs of toxicity nor any decrease of bodyweight gain. Biochemical and haematological parameters were normal. Histopathology was unremarkable. The NOEL was XXXXX.

Reproduction / Teratogenicity / Genotoxicity

- In a 3 generation XXXXX reproduction study XXXXX there were no clinical signs of toxicity in the parents although there was a decrease in bodyweight at the high dose level. There was no change in fertility, gestation length, lactation, viability or litter

size. XXXXX bodyweight was somewhat lower at the high dose level. Histopathology of F3 XXXXX was unremarkable.

- Teratology studies have been performed in the XXXXX:
  - In two XXXXX studies (doses up to XXXXX) maternal toxicity was observed, particularly at the high dose level. There was no effect on implantation sites, foetal weight, or number of ossification sites. There was a significant increase in the number of supernumerary ribs. There was no increase in skeletal or visceral abnormalities.
  - In XXXXX there was a dose related decrease in maternal bodyweight gain. There was no effect on implantation sites, foetal weight, or number of ossification centres. There was no increase in skeletal or visceral abnormalities but delayed ossification was seen at XXXXX.
  - In XXXXX there was a slight reduction in maternal bodyweight gain at the high dose level and also a decrease in foetal bodyweight at this dose level. There was no treatment related increase in skeletal or visceral abnormalities.

- A number of genotoxicity tests have been performed. Negative results were obtained in XXXXX. There was no increase in chromosome aberrations or SCEs in XXXXX. There was no increase in micronuclei or in chromosome aberrations in XXXXX. The XXXXX was negative.

Neurotoxicity

- In a neurotoxicity study in XXXXX, deltamethrin at single doses up to XXXXX induced no clinical, macroscopic or histological signs of delayed neurotoxicity.

Hazard Classification

- Deltamethrin was listed on the ASCC Hazardous Substances Information System (HSIS) Database with the following risk phrases:

- R23/25 (≥ 25 per cent) Toxic by inhalation and if swallowed.

- R20/22 (3 per cent < Conc. < 25 per cent) Harmful by inhalation and if swallowed.

Product

- The applicant advised that, in the interests of animal welfare and due to the availability of toxicity data for a very similar formulation, no studies were performed with XXXXX. The comparator product was a suspension concentrate formulation containing similar deltamethrin concentrations (5 per cent vs. 2.5 per cent in XXXXX).

Acute toxicity (estimated)

- XXXXX

- A toxicological package on a comparable product (5 per cent deltamethrin) was used to estimate that the product would have low acute oral toxicity XXXXX, low acute

dermal toxicity XXXXX and low inhalation toxicity XXXXX in XXXXX. The comparable product was a non-irritant to the skin and a slight irritant to the eyes. The comparable product was not a skin sensitiser.

- XXXXX

Exposure

- XXXXX is for use on insect pests in domestic, commercial, industrial and public buildings, and associated external areas.
- The product was not intended for use by the public in the home garden, however, it may be used by professional operators in domestic and public buildings. Public exposure would therefore be limited to post-use situations, such as coming into contact with treated areas. Under these situations, limited dermal and oral exposure was possible, particularly by small children. There was also some bystander exposure risk during application, however, the public would be advised to stay clear of the treatment area during application. The product is not to be used on foods crops. There was only a very small possibility for residues to occur in food as a result of the use of the product in food storage areas. Low exposure, coupled with low dermal toxicity and XXXXX, suggested that the product was unlikely to pose any significant health risk to the public.
- The product will be applied by professional Pest Control Operators, probably frequently throughout the year. Workers may be exposed to the product when opening containers, application and cleaning up spills and entering treated areas. The likely routes of exposure for the professional user were dermal, inhalation and ocular.
- A sub-chronic NOEL was considered appropriate. The sub-chronic oral NOEL was established as XXXXX, and was appropriate for a product that is used by Pest Control Operators. The NOEL was based on decreased bodyweight gain at XXXXX, there were no pathological changes. The oral absorption of deltamethrin was determined to be XXXXX.
- Deltamethrin poisonings accounted for a small percentage (0.04 per cent) of agricultural cases reported to the Anti-poisoning Centre in Marseille. Of 573 cases of acute pyrethroid poisoning in Chinese literature, 325 cases were due to 2.5 per cent emulsifiable concentrate, and only two people were reported to have died after convulsions, all others recovered.

XXXXX

XXXXX submitted a pre-meeting comment. Members particularly noted the following:

- It was asserted that the new toxicological data demonstrated that the product was of low acute toxicity and reiterated the request for the product to be Schedule 5.
- Noted that the data gave acute oral and dermal LD_{50}'s [for the product] well above the criteria for Schedule 5.

- The acute inhalation toxicity of the product was given as XXXXX, which was the maximum achievable concentration in the study. Using Finney's harmonic-mean formula, XXXXX estimated an LC_{50} of XXXXX. Although this was slightly below the minimum of XXXXX for Schedule 5, the product was still considered to be of low inhalation toxicity. In addition, the product was applied XXXXX, and inhalation exposure of XXXXX was highly unlikely.
- Eye and skin irritancy studies (on a formulation similar to the product) did not show any skin or eye irritation potential. The product classification as slightly irritating to the skin and eyes was based on the recommendation of XXXXX. Asserted that even considering this revised classification, the product would be within the scope of Schedule 5.
- Noted that the classification of the product as a sensitiser was based on the presence of XXXXX.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The relevant matters under section 52E (1), to this item, included: (a) toxicity and safety of the substance; (c) potential hazards; and (e) dosage and formulation.

A Member noted that while the applicant had requested a ≤ 2.5 per cent cut-off from Schedule 6 to Schedule 5 (for aqueous preparations when no organic solvent other than a glycol was present), the data provided was for a 5 per cent concentration, so this should be the cut-off under consideration. The Committee generally agreed that a 5 per cent cut-off was supported by the data presented.

A Member therefore queried whether the other Schedule 6 to Schedule 5 cut-offs for deltamethrin should also be reconsidered. It was noted, however, that the data presented at this Meeting had been specific to an aqueous preparation with no organic solvent other than glycol present. The Committee agreed that it would be inappropriate to reconsidered these other cut-offs until specific data had been submitted that would support such a change, especially given that the parent entry of deltamethrin was Schedule 7.

The Members also confirmed that while the product had a constituent that was a skin sensitiser this was not relevant to the scheduling consideration of deltamethrin.

RESOLUTION 2008/53 - 15

The Committee decided to expand the Schedule 5 deltamethrin listing for aqueous preparations (when no organic solvent other than a glycol is present) from 1 per cent to 5 per cent.

Schedule 5 – Amendment

DELTAMETHRIN:

(a) in aqueous preparations containing 5 per cent or less of deltamethrin when no organic solvent other than a glycol is present;

(b) in wettable granular preparations containing 25 per cent or less of deltamethrin when packed in child-resistant packaging each containing 3 grams or less of the formulation;

(c) in water-dispersible tablets each containing 500 mg or less of deltamethrin in child-resistant packaging; or

(d) in other preparations containing 0.5 per cent or less of deltamethrin.

6.6 ABAMECTIN

PURPOSE

The Committee considered the scheduling of abamectin including a proposal to increase the current ≤ 2 per cent cut-off from Schedule 7 to Schedule 6.

BACKGROUND

Abamectin is a macrocyclic lactone. It stimulates the release of GABA from nerve endings and enhances the binding of GABA to receptor sites on the post-synaptic membrane of inhibitory motor neurones of nematodes. In insects and arthropods, it enhances the binding of GABA on the post-junction membrane of muscle cells. This enhanced GABA binding results in an increased flow of chloride ions into the cell, with consequent hyperpolarisation and elimination of signal transduction resulting in an inhibition of neurotransmission.

The November 1984 PSC Meeting considered the scheduling of a 1 per cent avermectin B1 injection for parasite control in animals and agreed to a Schedule 7 listing due to toxicity. However, the Committee also noted the intent to only market a sealed container product for use with automated injection equipment and agreed to a Schedule 6 cut-off for such preparations when ≤ 10 mL. This decision was confirmed by the November 1985 PSC Meeting upon receipt of new studies. The August 1986 DPSSC Meeting amended the Schedule 6 entry to ≤ 1 per cent in a sealed container for use with automated injection equipment.

The November 1986 DPSSC Meeting appears to have agreed to the Appendix J entry for avermectin B1 (no discussion was recorded in the Minutes of that Meeting). The May 1992 DPSSC Meeting agreed to a request to change the “avermectin B1” entries in the SUSDP to “abamectin”, noting that this was the name that been approved by the Standards Association of Australia (now known as Standards Australia).

The August 1994 NDPSC Meeting considered a request to broaden the Schedule 6 entry for abamectin from injectable forms to pesticidal use at ≤ 18 g/L. The Committee noted that abamectin was at the low end of the range for moderate oral toxicity, had severe eye irritation with some concerning developmental toxicity. The Committee agreed to amend Schedule 6 to capture ≤ 2 per cent for pesticidal use and ≤ 1 per cent for the treatment of animals.

The August 1995 NDPSC Meeting agreed to include ≤ 1 per cent for animal internal use in Schedule 5. The resulting Schedule 5, 6 and 7 entries were as per the current SUSDP entries.

DISCUSSION - SUBMISSIONS

XXXXX has applied to APVMA to XXXXX abamectin at 80 g/kg XXXXX. The applicant has requested that abamectin in slow-release cattle ear tags weighing ≤ 10 g and containing ≤ 0.8 g abamectin, be rescheduled to Schedule 6. XXXXX undertook an evaluation and recommended:

XXXXX

- XXXXX

Public Health Standards

- The ADI for abamectin was established in 1998 at 0.0005 mg/kg bw/day based on a NOEL of 0.5 mg/kg bw/day in a XXXXX developmental study (foetal abnormalities at the next highest dose of 1 mg/kg bw/day, using a 1000-fold safety factor).
- The ARfD for abamectin is 0.005 mg/kg bw, based on a NOEL of 0.5 mg/kg bw/day, established in a XXXXX developmental study using a 100-fold safety factor.
- The Committee considered whether to amend the Schedule 6 entry for abamectin to read as follows (new part (b)):

ABAMECTIN:

(a) in preparations for pesticidal use containing 2 per cent or less of abamectin **except** when included in Schedule 5; or

(b) in slow-release plastic matrix ear tags for livestock each containing 1 g or less of abamectin.

Members also noted the following from the evaluation report:

- The data package provided comprised of four acute toxicology studies on the product, plus a study on the rate of release of the active ingredients from the product. These

studies were conducted in accordance with contemporary test guidelines, and were considered to be adequate for the assessment.

- The OHS risk assessment indicated that a risk of dermal toxicity existed with long-term use of the product. Appropriate Personal Protective Equipment (PPE) was recommended to mitigate this risk.

Members additionally noted the following toxicity data from the evaluation report:

Abamectin

Absorption / distribution / metabolism

- Exposure of XXXXX skin *in vitro* showed dermal penetration of < 1 per cent. No data was available on absorption from the gut. Following oral administration, abamectin was widely distributed, with total residue levels highest in fat, kidney, liver and muscle. The principal metabolites in XXXXX are 24 hydroxymethyl avermectin B1a and 3" desmethyl avermectin B1a. In XXXXX, by XXXXX days post treatment, XXXXX of the administered dose had been excreted in faeces, with a further XXXXX appearing in urine.

Acute toxicity

- High acute oral toxicity XXXXX and moderate acute dermal toxicity XXXXX. Was a slight eye irritant but not a dermal irritant in XXXXX. No data on skin sensitisation potential.

Repeat dose toxicity

- During oral XXXXX for XXXXX half those fed XXXXX died after XXXXX day and half of those dosed with XXXXX died after XXXXX days. Evidence of toxicity included ataxia, tremors, salivation, mydriasis, liver changes and reduced body weight in all but the lowest dose group. The NOEL was XXXXX.
- During diet administration to XXXXX for XXXXX, all 3 high-dose XXXXX died at XXXXX weeks, and mydriasis was seen at the upper 2 doses. The NOEL was XXXXX. During diet administration to XXXXX for XXXXX, the high dose was raised to XXXXX in week XXXXX, causing CNS toxicity. Tremors persisted a week later, despite the high dose being returned to XXXXX. The NOEL was XXXXX.

Reproduction

- In a two-generation reproduction study, XXXXX were dosed XXXXX. At XXXXX there was increased XXXXX mortality and decreased body weight at weaning in the F1a and F1b XXXXX, together with retinal abnormalities in the F1b and F2b XXXXX Increased XXXXX mortality and decreased viability to weaning also occurred in the F2a and F2b XXXXX. The NOEL was XXXXX.

- A developmental toxicity study in XXXXX used oral doses XXXXX on days XXXXX of pregnancy. There was maternal weight loss at XXXXX and various teratogenic effects at XXXXX (clubbed forefeet, cleft palate, vertebral and sternebral malformations, delayed ossification). The NOEL was XXXXX.

Mutagenicity / carcenogenicity / teratogenicity

- Not mutagenic in a XXXXX. Gave negative results for XXXXX.
- The ADI of 0.0005 mg/kg bw/day was set on the basis of teratogenic effects in a developmental study with a safety factor of 1000. The safety factor of 1000 was selected because the foetal abnormalities produced may represent an acute toxic effect and the establishment of an ADI was intended to represent a safe intake for a lifetime.

NOEL for occupation risk assessment

- Teratogenicity is the most appropriate toxicological end-point for OHS assessment. The NOEL selected for OHS risk assessment was XXXXX, based on teratogenic effects in the developmental toxicity study in XXXXX, with a margin of exposure (MOE) of 1000 because of the severity of the toxic endpoint (teratogenicity) and the possibility that it was an acute effect. This study was considered more appropriate than the 18-week dietary study in XXXXX, which had a NOEL of XXXXX, with an MOE of 100.

Recommended Hazard Classification Statements

- Listed on the ASCC Hazardous Substances Information System with the risk phrases:
  - ≥ 25 per cent — R24/25 — Toxic in contact with skin and if swallowed.
  - 3 per cent < Conc. < 25 per cent — R21/22 — Harmful in contact with skin *and if swallowed.*

Product XXXXX

Toxicity

Moderate acute oral toxicity and low acute dermal toxicity. Was not a skin irritant, nor a skin sensitiser. No acute inhalational toxicity study was conducted as this route of exposure would not occur from a plastic ear tag. The results of a release rate study indicate that abamectin was released at XXXXX.

XXXXX

Exposure

- The most likely route of exposure for professional users of the product was dermal. Oral exposure was unlikely to occur, unless the tags were sucked or chewed. As the active ingredients were enclosed within the plastic tag, inhalational exposure was unlikely to occur, nor was bystander exposure. The product was not intended for home/garden use.

- The likely pattern of exposure was brief, intermittent and infrequent. The tags were applied at a rate of XXXXX per animal, removed after a period of XXXXX weeks. A worker could handle several hundred tags in a single day, but further exposure would be unlikely until the tags were removed.
- A release rate study indicated that 7 days after application, abamectin was released at XXXXX from each tag. The actives were released from the tags in smaller amounts on each subsequent day.
- No worker exposure studies were included with the submission. In the absence of exposure data the tolerable daily dose was calculated using an appropriate NOEL and dermal absorption factor representing a worst-case scenario, in which a worker spends the entire working day in direct dermal contact with the ear tags, equivalent to handling one tag continually for an entire working day.
- A 70 kg worker could be exposed to XXXXX abamectin per day, XXXXX. Taking into consideration the dermal absorption factors for XXXXX, the systemic exposure would be XXXXX. These values were more than 300 and 21 000 times lower than the NOELs chosen for the OHS risk assessment XXXXX. It could be assumed that gloves provided a 90 per cent reduction in exposure to hands. A worker wearing gloves would be exposed to XXXXX abamectin.

  [Members noted that the release rate after XXXXX days was used in the above estimate because the first data point available was on day XXXXX. The evaluator asserted, and the Members generally agreed, that, while it was possible that actual exposure could be somewhat higher than estimated, this was the best estimate with the available data, and that the large margin of safety sufficiently addressed the potential for underestimation.]
- The tags would be re-handled when they are removed. The exposure was likely to be minimal, due to the small amount of active released per day after the tags have been in place for XXXXX weeks XXXXX.
- XXXXX.
- There was an oral toxicity risk associated if this product were placed in the mouth which will require First Aid Instructions and Safety Directions to be established, including advice to use rubber gloves, and that the product is harmful if sucked.

XXXXX.

Members also noted a pre-meeting comment from XXXXX advising that it was an interested party and stakeholder with regard to abamectin.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The relevant matters under section 52E (1), to this item, included: (a) toxicity and safety of the substance; (b) risks and benefits; (c) potential hazards; (e) dosage and formulation; and (f) the need for access.

A Member advised that there was a real need for access to abamectin as XXXXX was a significant problem (particularly in northern Australia) and there were also resistance issues in combating XXXXX that would be overcome through the use of abamectin. The Member asserted that the slow-release ear tag presentation was an effective approach to delivering abamectin in a highly targeted way with little exposure or residues risk.

A Member agreed that the key risk mitigation factor was that the abamectin was impregnated in a slow-release plastic matrix. The Member asserted that this presentation would probably limit risk even in the unlikely scenario of the tag being chewed and swallowed. A Member was concerned, however, that there may be initial material on the surface of the tags that could lead to a greater exposure than that estimated by the release study. The Committee agreed that this concern, particularly given abamectin's high toxicity, reinforced the need for this presentation to be Schedule 6 despite the risk mitigation of the slow-release plastic matrix. Members noted with approval the evaluator's recommendation to APVMA regarding use of gloves.

A Member noted no objection to allowing this specific presentation (≤ 1 g abamectin in slow release ear tags) into Schedule 6, for livestock only. The Committee considered whether to broaden this to all slow-release plastic matrix presentations for livestock use but agreed that the data had been specific to the ear tag presentation alone and that there were too many unknown risks with a broader entry. Members further agreed that the Schedule 6 entry should specify "livestock" as it was not the Committee's intention to allow such a presentation for use with domestic/ companion animals, noting that the APVMA had a clear definition of "livestock".

RESOLUTION 2008/53 - 16

The Committee decided to down schedule slow-release plastic matrix ear tags for livestock use containing 1 g or less of abamectin.

Schedule 6 – Amendment

ABAMECTIN – Amend entry to read:

ABAMECTIN:

(a) in preparations for pesticidal use containing 2 per cent or less of abamectin **except** when included in Schedule 5; or

(b) in slow-release plastic matrix ear tags for livestock use containing 1 g or less of abamectin.

6.7 COUMAPHOS

PURPOSE

The Committee considered the scheduling of coumaphos including a proposal for a Schedule 7 to Schedule 6 cut-off of ≤ 20 per cent when in a slow-release plastic matrix for livestock.

BACKGROUND

Coumaphos is an organophosphorus insecticide that has been used in veterinary practice for the control of ticks, lice and fleas in cattle, sheep, pigs, horses and dogs.

The February 1975 PSC Meeting agreed to include coumaphos in Schedule 7. The July 1976 PSC Meeting agreed to a cut-off to Schedule 6 for ≤ 5 per cent.

The June 1991 DPSSC Meeting generally agreed that coumaphos was too toxic for domestic use and advised the applicant that the Committee was reconsidering the Schedule 6 entry for coumaphos. A decision was deferred to await further toxicology data.

The April 1994 NDPSC Meeting considered data submitted in response to the concern that ≤ 5 per cent may be too toxic for the home veterinary market. This data indicated that the acute oral LD_{50} of a 5 per cent formulation was between XXXXX and that of a 1 per cent formulation was XXXXX and between XXXXX. The Committee considered that these wide ranges were unsatisfactory. Mortality data in the 5 per cent acute oral study suggested the LD_{50} was probably less than the NDPSC guideline of 1500 mg/kg for domestic pesticides. [Members noted that this statement from the April 1994 NDPSC Minutes was unclear. Schedule 6 products are normally allowed for domestic use, while the NDPSC guideline for a Schedule 6 to Schedule 7 based on acute oral toxicity is 50 mg/kg. However, Members were advised that the APVMA's current AgMORAG states, under acute oral toxicity, that "*Any domestic pesticide formulation that may be ingested should not be expected to be acutely toxic to a child at doses up to 1500 mg/kg bw*".] The April 1994 NDPSC Meeting recommended that, since the formulations may not meet the NDPSC guidelines [see clarification above] for home veterinary products and data was lacking for other toxicological properties, they not be registered for home veterinary use and remain in Schedule 6.

DISCUSSION - SUBMISSIONS

XXXXX has requested a reconsideration of scheduling for XXXXX 200 g/kg coumaphos XXXXX. The applicant requested, based on a formulation where the active ingredient was contained in a plastic matrix and upon a low level of dermal toxicity, that the Schedule 6 coumaphos entry be amended to read:

COUMAPHOS - in plastic matrix preparations containing 20 per cent or less of coumaphos, in other preparations containing 5 per cent or less of coumaphos.

[The Committee noted that the evaluator's report replaced the applicants requested ≤ 20 per cent cut-off with a 20 g per tag cut-off. The evaluator advised the Committee that this was an error in the report and should have been 6 g.]

Members noted that the XXXXX undertook an evaluation and recommended:

Public Health Standards

- The coumaphos ADI (established in 1971) is 0.0005 mg/kg bw/d, based on a NOEL of 0.05 mg/kg bw/d from inhibition of serum cholinesterase at the next highest dose in a 1 year dog dietary study. XXXXX became aware of new toxicological data which was likely to impact on the ADI (see discussion below).
- No ARfD had been established for coumaphos.
- Based on the nature of the product and the use pattern the Committee may wish to consider amending the Schedule 6 entry for coumaphos to include slow-release plastic matrix ear tags for livestock each containing ≤ 20 g coumaphos with the follow suggested wording:

COUMAPHOS:

(a) in external plastic matrix preparations for livestock containing 20 grams or less of coumaphos.

(b) in other preparation containing 5 per cent or less of coumaphos.

[Members again noted evaluator's advise that 20 g in part (a) should be 6 g.]

Members additionally noted the following from the evaluation report:

- The XXXXX application XXXXX did not include data to identify the exposure risk posed by the product during application or removal, and assumed that the entire active was available for exposure. Additional data was provided which has enabled XXXXX to assess the worker exposure with greater accuracy (discussed below).
- The initial assessment of the product included a XXXXX acute dermal toxicity study. No data was provided for other acute toxicological endpoints, so an assessment of the likely toxicity of the product was made on the basis of the available toxicity data for the ingredients.
- Coumaphos was recently re-approved under section 14A of the Agricultural and Veterinary Chemicals Code Act (i.e. APVMA approved the active and was satisfied that the active constituent was well known, in common use and had a history of safety in the context of use). However, XXXXX became aware of new toxicological data on coumaphos that was evaluated by the US EPA in 2000 (US EPA, 2000). This data included acute, subchronic, chronic and multigenerational studies in XXXXX and XXXXX. It was likely that this data would impact on the existing ADI and permit the establishment of an acute reference dose.

[Members observed that, while the US EPA data was noted in the discussion on ADI and ARfD, there was no further reference to the acute, subchronic, chronic and multigenerational studies. Members were advised that the evaluator had confirmed that these studies were not provided to XXXXX in time for inclusion in the evaluation report. However, a number of studies were received subsequent to finalisation of the evaluation report – see discussion below.]

Members also noted the following toxicity data from the evaluation report:

Coumaphos

US ADI and ARfD

- In 2000 the US EPA established a reference dose (equivalent to the ADI) of XXXXX that was based on the application of a 100-fold safety factor to the NOAEL of XXXXX for cholinesterase inhibition at the LOAEL of XXXXX in a XXXXX chronic toxicity study in XXXXX. The ARfD set by the US EPA was XXXXX, based on the application of a 300-fold safety factor to the LOAEL of XXXXX, which was based on cholinesterase inhibition in an acute oral neurotoxicity study in XXXXX.

Acute toxicity

- The acute toxicity of coumaphos has previously been evaluated (i.e. data unchanged from the April 1994 NDPSC Meeting – See discussion above regarding the inability of XXXXX to obtain the 2000 US EPA data prior to finalisation of the evaluation report.).

LD_{50} oral, XXXXX	XXXXX (High oral toxicity)
LD_{50} dermal, XXXXX	XXXXX (High dermal toxicity)
LC_{50} inhalation, XXXXX	XXXXX Moderate inhalational toxicity)
Skin irritation, XXXXX	Moderate
Eye irritation, XXXXX	Moderate
Skin sensitisation, XXXXX	None

Neurotoxicity

- Coumaphos is an organophosphorus insecticide which has the potential to elicit delayed neurotoxicity. This hazard was of concern for OHS risk assessment purposes because there was data to show that it may be mediated following dermal exposure.
- Following a single dermal exposure (low dose XXXXX with no acute signs of cholinergic toxicity) in XXXXX, signs of delayed neurotoxicity were observed. Signs of neurotoxicity ranged from gross ataxia to complete paralysis. Following this dermal treatment, unequivocal histopathological changes (degenerating axons, appearance of macrophages) occurred in the spinal cords of about XXXXX. In XXXXX that survived oral dosing some clinical signs of neurotoxicity were observed, however no histopathological changes were observed in the spinal cords or peripheral nerves. A NOEL for delayed neurotoxicity was not established.

[Members noted that this was old data first considered at the April 1994 NDSPC Meeting. The evaluator confirmed that the data submitted by the applicant did not include any more recent data on neurotoxicity.]

Hazard classification

- Coumaphos is listed on the NOHSC Hazardous Substances Information System (HSIS) Database with the following risk phrases:
- R21 (≥ 25 per cent) Harmful in contact with skin
- R22 (0.1 per cent < Conc. < 1 per cent) Harmful if swallowed
- R25 (1 per cent < Conc. < 7 per cent) Danger of serious damage to health by prolonged exposure if swallowed.
- R28 (≥ 7 per cent) Very toxic if swallowed

Product XXXXX

Acute toxicity

- The initial assessment of this product included a XXXXX acute dermal toxicity study of the product (20 per cent coumaphos, XXXXX) which gave an LD_{50} of XXXXX. No data was provided for other acute toxicological endpoints. An assessment of the likely product toxicity was made on the basis of the available toxicity data for the ingredients. The product toxicology, as determined from the studies provided or as extrapolated from the individual constituents, is summarised below:

Toxicity end point	Toxicity
Oral	High*
Dermal	Low XXXXX
Inhalation	Moderate*
Skin irritation	Moderate*
Eye irritation	Moderate*
Skin sensitisation	Not a skin sensitiser*

*based on the toxicological profile of all ingredients in the product

- Given the nature of the product (PVC-resin-based ear tags designed to provide a slow release of the pesticide) the acute toxicity of the product was likely to be less.

XXXXX

Exposure

- XXXXX ear tags were unlikely to present a risk through inhalation or continued contact because the active ingredient was enclosed within a plastic material with a slow release rate. The product would be handled only very briefly and there was no potential for misuse.
- Farmers and their employees will be the main users of the product.
- The product was not intended for home/garden use. Exposure to the general public was not expected as the tags would be attached to farm animals. Public exposure

during application, bystander exposure, and/or post-application would be very limited.

- The applicant provided data from a depletion study which indicated that the highest rate of daily active lost per tag for coumaphos was XXXXX. From this data, the maximum exposure per worker was XXXXX, assuming the worker was handling tags all day (i.e. exposed to the equivalent of one day's release). This assumed that ~ XXXXX would be present on the surface of the tag during a day.
- The tolerable daily dermal exposure for a 70kg worker would be XXXXX of coumaphos. Using a 10 per cent dermal absorption factor as indicated for coumaphos, a worker could be contaminated with XXXXX applied per day. Therefore the margin of exposure was unacceptable and the use of gloves was recommended.
- Workers may also be dermally exposed to the product when the tags are removed, however at this stage the tag will be exhausted and exposure to the actives will be low (expected highest exposure ~ XXXXX).
- The applicant argued that the worker exposure risk would not be further mitigated by a Schedule 7 classification for this product, and that the scheduling system was not particularly related to considerations of worker exposure during application of a product in an industrial setting. In other words, workers applying a product industrially have the same level of exposure regardless of poison scheduling. Also asserted that worker protection was assured by means of appropriate safety directions rather than by packaging, labelling and access restrictions imposed by scheduling.

NOEL for occupational risk assessment

- As the product was not used by Pest Control Operators or shearers, it was best practice to consider only studies with a duration of ≤ 3 months when determining the NOEL for OHS risk assessment. However, based on the available data no NOEL could be definitively established for sub-chronic exposure to coumaphos
- Therefore an oral NOEL for use in OHS risk assessment was set at XXXXX. A web-based literature search determined that additional studies were available on coumaphos and it was considered important that these studies be submitted to XXXXX so that the potential for delayed neuropathy could be assessed. [Members noted that the evaluator had confirmed that the data submitted by the applicant did not include these studies.]
- In order to perform a risk assessment for coumaphos it was necessary to derive an internal-dose NOEL by applying a correction factor, to account for absorption in the gut, to the oral NOEL. In XXXXX of radioactivity was excreted in urine after dosing with XXXXX of radiolabelled coumaphos. Therefore it was appropriate to assume that XXXXX of the oral dose would be absorbed by the gut in humans. Applying a correction factor of XXXXX to the oral NOEL provided an internal-dose NOEL of XXXXX.

XXXXX

As mentioned above, a number of studies were recently received by XXXXX after completion of the evaluation report on coumaphos:

- Chronic feeding toxicity study in XXXXX.
- A two-generation dietary reproduction study in XXXXX.
- An acute oral neurotoxicity screening study in XXXXX.
- Repeated dose (XXXXX exposure) dermal toxicity study in XXXXX.
- Subchronic neurotoxicity screening in XXXXX in the diet).
- Micronucleus cytogenetic assay in XXXXX.
- Repeat dose (XXXXX -day) dermal toxicity study in XXXXX.
- Micronucleus cytogenetic assay in XXXXX.

XXXXX has confirmed that these studies were the "new toxicological data" mentioned in the evaluation report with regard to the ADI. XXXXX has confirmed that a preliminary examination of this data indicated that it would not impact on the XXXXX recommendations for coumaphos scheduling. XXXXX therefore wished the June 2008 NDPSC Meeting to proceed with a consideration of the coumaphos scheduling issue on the basis of the data in the evaluation report.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The relevant matters under section 52E (1), to this item, included: (a) toxicity and safety of the substance; (b) risks and benefits; (c) potential hazards; (e) dosage and formulation; and (f) the need for access.

Members noted that this consideration (which followed item 6.6 – abamectin) had many similar issues and concerns as raised for the abamectin slow-release ear tags. Members particularly noted:

- That there was a need for access to substances such as coumaphos (as there was for abamectin) as XXXXX was a significant problem (particularly in northern Australia) and there were resistance issues in combating XXXXX that could be overcome through the use of high toxicity substances such as coumaphos. A Member reiterated that a slow-release ear tag presentation was an effective approach to delivering substances such as coumaphos in a highly targeted way to livestock with little exposure or residues risk.
- Members again noted that the key risk mitigation factor was that the coumaphos was impregnated in a slow-release plastic matrix. A Member remained concerned, however, that there may be initial material on the surface of the tags that could lead to a greater exposure than that estimated by the depletion study and noted that an initial wipe test on ear tags straight from the packaging would have been useful information to have. The Committee agreed that this concern, particularly given coumaphos's high toxicity, reinforced the need for this presentation to be Schedule 6 despite the risk mitigation of the slow-release plastic matrix. Members noted that the evaluator

report recommendations to APVMA again included use of gloves and agreed, even more than for the abamectin issue, that gloves were necessary.

- The Committee considered whether to broaden the propose Schedule 6 entry to all slow-release plastic matrix presentations but agreed that the data had been specific to the ear tag presentation alone and that there were too many unknown risks with a broader entry.

Members additionally noted advice from the evaluator there was some potential for out-gassing of coumaphos from the slow-release plastic matrix that, while not a problem for livestock in a farm setting, could be a problem if used for domestic/ companion animals. A Member also noted that organophosphates are particularly dangerous to children. The Committee agreed that the Schedule 6 entry should specify "livestock" as it was not the Committee's intention to allow such a presentation for use in a domestic setting, noting that the APVMA had a clear definition of "livestock".

Members also discussed whether a Schedule 6 entry should be restricted to ≤ 20 per cent or to the weight of coumaphos per ear tag (~6 g). Members noted that the depletion data provided was from to a product containing ~6 g coumaphos, and if this were not specified in scheduling (i.e. if 20 per cent were used instead) then there was nothing to stop a much larger ear tag (with ≤ 20 per cent, but potentially > 6 g coumaphos) from qualifying for the Schedule 6 entry. Members generally felt that this possibility should be excluded and agreed that the entry should refer to ≤ 6 g.

RESOLUTION 2008/53 - 17

The Committee decided to amend the Schedule 6 entry for coumaphos to include slow-release plastic matrix ear tags for livestock use containing ≤ 6 g coumaphos.

Schedule 6 – Amendment

COUMAPHOS – Amend entry to read:

COUMAPHOS:

(a) in slow-release plastic matrix ear tags for livestock use containing 6 g or less of coumaphos; or

(b) in other preparations containing 5 per cent or less of coumaphos.

6.8 CYANOGEN (ETHANEDINITRILE)

PURPOSE

The Committee considered the scheduling of cyanogen (ethanedinitrile).

BACKGROUND

Ethanedinitrile, commonly referred to as cyanogen, has the structure:

In animals, humans and the environment cyanogen hydrolyses to cyanide, which is responsible for the toxicity effects observed. Cyanogen and cyanide are readily absorbed by inhalation, distributed to all organs and tissues, detoxicated to thiocyanate and other compounds and eliminated mainly through the urine.

Cyanide compounds are used in a number of industries including electroplating, gold and silver mining, plastics procession and tanning. Exposure has been reported to cause a range of symptoms including fatigue, dizziness, paresthesia, loss of appetite, dyspnea, precordial pain, palpitations and chest pain.

Cyanogen is not currently scheduled. While cyanogen may by considered a source of cyanide, the Schedule 7 general cyanides entry only refers to metallic cyanides. Additionally there are specific schedule entries for hydrocyanic acid (an aqueous solution of hydrogen cyanide). However, the Schedule 7 hydrocyanic acid excludes salts and derivatives, so only therapeutic uses of cyanogen would possibly be captured by the Schedule 4 hydrocyanic acid entry.

DISCUSSION - SUBMISSIONS

XXXXX have applied to APVMA for approval of a new active constituent, ethanedinitrile (cyanogen), XXXXX undertook an evaluation and recommended:

- Based on the toxicology and metabolism profile of cyanogen, XXXXX recommended that cyanogen be included in Schedule 7, which is consistent with the existing scheduling for cyanides and hydrocyanic acid. XXXXX also recommended inclusion in Appendix J with condition 1 “not to be available except to authorised or licensed persons”.

Members also noted the following from the evaluation report:

- The report, while titled ethanedinitrile, referred throughout to cyanogen.
- Two genotoxicity studies on cyanogen were submitted. These studies, together with toxicology information on cyanide from published papers, from international reports (WHO) and other national reports (US ATSDR and Netherlands) were used by XXXXX to assess the potential human health risks. XXXXX.
- The use of cyanogen as a fumigant was developed and patented by CSIRO Entomology. The product has not been registered in other countries.

Members additionally noted the following toxicity data from the evaluation report:

Summary XXXXX

Absorption, distribution, metabolism and excretion in mammals

Rate and extent of absorption	Rapid and extensive by inhalation
Dermal absorption	Rapid (cyanide)
Distribution	Rapid and uniform to all organs and tissues
Potential for accumulation	No evidence for accumulation.
Rate and extent of excretion	Mainly excreted through urine.
Metabolism	Hydrolyse into cyanide and cyanate, and further to thiocyanate and other compounds.
Toxicologically significant compounds (animals, plants and environment)	Hydrogen cyanide and other cyanides.
Toxicologically relevant compounds for residue definition	Hydrogen cyanide and other cyanides.

Acute toxicity

Rat oral LD_{50}	8 mg/kg bw (cyanide)
Worst oral LD_{50} in other species	< 4 mg/kg bw (cyanide, mice) 1.52 mg/kg bw (cyanide, humans)
Rat dermal LD_{50}	No data
Worst dermal LD_{50} in other species	6.7 mg/kg bw (cyanide, rabbits) 100 mg/kg bw (cyanide, humans)
Rat inhalation LC_{50}	750 mg/m^3 (cyanogen) for 60 min 151 mg/m^3 (137 ppm, cyanide) for 60 min.
Worst inhalation LC_{50} in other species	210 mg/m^3 (cyanogen) for 2-3 hours lethal to cats 176 mg/m^3 (159 ppm cyanide) 30 min for mice 578 mg/m^3 (524 ppm cyanide) 10 min for humans
Skin irritation	Non-irritant (cyanogen) Irritant (cyanide)
Eye irritation	Irritant (cyanogen and cyanide)
Skin sensitization	No data

Short-term toxicity

Target/critical effect	Changes in male reproductive organs and functions; Pulmonary, liver and kidney effects.
Lowest relevant oral NOEL	0.5 mg/kg bw/day (cyanide)

Lowest relevant inhalation NOEC	24 mg/m^3 (cyanogen)
Genotoxicity	Genotoxic (cyanogen & cyanide)

Long-term toxicity and carcinogenicity

Target/critical effect	CNS, reproduction / developmental systems.
Lowest relevant NOEL	No adequate data.
Carcinogenicity	A conclusion cannot be made due to small group size and limited exposure time in two long-term studies.

Reproductive toxicity

Reproduction target/critical effect	Reduction in sperm motility and in the weight of cauda epididymidis.
Lowest relevant reproductive NOEL	0.5 mg/kg bw/day (30 mg NaCN/L drinking water)

Developmental toxicity

Developmental target/critical effect	Vertebral and rib anomalies and encephalocoeles and skeletal malformations in hamster.
Lowest relevant developmental NOEL	7.4 mg/kg bw (cyanide), single dose

Neurotoxicity

Acute and delayed neurotoxicity	Cyanogen: poor coordinated movements, tremors and behaviour changes. Cyanide: weak and ataxic movements, convulsions, Parkinsons like signs, dystonic and apraxia, apathetic, agitation, involuntary movements, akinetic mutism, loss of muscle strength, damage to centra axonal auditory and somatosensory signal propagation, etc.

- There was limited toxicology information for cyanogen available. It was the CN- portion of the cyanogen which was of toxicological concern. Cyanogen reacts slowly with water to produce hydrogen cyanide and cyanate ion (OCN-).
- In biological systems, the cyanide ion will complex with iron in cytochrome oxidase thereby interfering with cellular respiration. Cytochrome C oxidase was the most significant target of cyanide exposure since its inhibition prevents tissues from using oxygen. The result is a reduction in oxygen sufficient to cause tissue damage throughout the body, with the most vulnerable tissues being those with high oxygen demands. Alternatively, the cyanide ion may accept a sulphur donor to form a thiocyanate for detoxification. These metabolites will then breakdown (oxidization and further hydrolysis) to form ammonia. The cyanate ion can form salts such as ammonium cyanate and ultimately urea.

Acute toxicity

- The high acute inhalation toxicity of cyanogen is a function of exposure time and concentration. Its acute toxicity is similar to another fumigant gas phosphine, but higher than most other fumigants including methyl bromide.
- The 60-min LC_{50} for cyanogen was 750 mg/m^3 in rats. Exposures to 210 mg/m^3 for 2-3 hours, and to 840 mg/m^3 for less than 2 hours were lethal to cats and rabbits, respectively.
- Based on case reports for humans with cyanides, an inhalation LC_{50} was 524 ppm for a 10 minute exposure, an oral LD_{50} was 1.52 mg/kg, and a dermal LD_{50} was 100 mg/kg, assuming that CN- is readily released from the compound.

Neurotoxicity

- The most significant effects of cyanide exposure occur in the nervous system, especially in the brain. Acute inhalation of high cyanide concentrations cyanide provoked a brief CNS stimulation followed by depression, convulsions, coma, and death in humans and animals. The effects are probably due to rapid biochemical changes in the brain, such as changes in iron flux, neurotransmitter release, and possibly peroxide formation. Death in acute cases is associated with effects on neurological centre controlling respiration. Convulsions and coma were also reported in humans and animals following acute dermal exposure to cyanide.
- Adverse effects on the CNS are of the most consequence to the organism because of the high metabolic demand for oxygen in neurons and its control of respiratory function. Initial stimulation of carotid and aortic bodies and effects on the CNS adversely affect the function of the respiratory system, which contributes to the global histiotoxic hypoxia leading to death. Thus, the adverse effect of cyanide on respiration operates on both the cellular and physiological levels. High inhalation, oral or dermal exposure levels result in convulsions, unconsciousness, and death due to inactivation of the centre controlling respiration. Lower exposure may result in headache or dizziness.

Genotoxicity and Carcinogenicity

- Both cyanogen and cyanide showed mutagenesis in XXXXX, and DNA damage effects in XXXXX. However, available long-term toxicology studies in animals do not provide adequate information with regard to the possible carcinogenicity of cyanides. No human data was located regarding cancer effects in humans.

Reproductive and developmental toxicity

- Cyanide induced changes in reproduction organs and functions in male rats, and caused developmental changes (vertebral and rib anomalies and encephalocoeles and skeletal malformations) in hamster by a single oral dose. In tropical countries, maternal ingestion of cassava (which naturally contains some cyanide) during pregnancy has been associated with congenital hypothyroidism in some offspring.

ADI and ARFD

- The applicant advised that no residues of cyanogen were present in fumigated soil and grain. In the absence of food residue concerns, no ADI or ARfD was necessary for the proposed use.

Exposure

- Professional fumigation workers were likely to use the product frequently and inhalational exposures to cyanogen / cyanide was the major concern.
- In human volunteers, no irritation was observed during a 6-minute exposure to 18 mg/m^3 cyanogen while eye and nasal irritation were experienced at 35 mg/m^3. However, the single exposures were not adequate for occupational risk assessment.
- In a survey on workers exposed to NaCN at 6.4 ppm CN- for 5 to 15 years, confusion, hallucination, headache, dizziness, weakness, dyspnea, irritation of throat, precordial pain, vomiting, increased hemoglobin and lymphocytes, thyroid enlargement and lacrimation were reported. An inhalational LOEL of 7.17 mg/m^3 was established for humans based on this study. On an equal molar basis, this LOEL for cyanide equates to a LOEL of 14 mg/m^3 for cyanogen.

Product use pattern XXXXX

- XXXXX
- The applicant has indicated the following will apply in relation to the use of the product:
  - Only trained and licensed fumigators will use the product and will be responsible for ensuring: only approved personnel are permitted within the vicinity of the fumigation; personnel within the risk area wear protective clothing, including appropriate respirators if required; the structure being fumigated has been appropriately sealed; the air is monitored for cyanogen; and there are no sources of flame or ignition in the vicinity of the fumigation.
  - A risk area will be established around each fumigation site (including any pits or tunnels beneath the fumigation area) until monitoring has shown concentrations of cyanogen to be less than 10 ppm. Only authorised personnel wearing appropriate protective clothing and respirators are permitted within the risk area during the fumigation period and until the fumigator in charge has confirmed the level of cyanogen is below 10 ppm.
  - If the area can not be physically secured, a watchman will be stationed to keep people out of the risk area. The watchman will stay out of the risk area unless appropriately protected.
  - In all cases, fumigation sites will be appropriately signed.
  - After the required exposure time has elapsed, the treated area / storage facility should be thoroughly ventilated before re-entry.
  - It is indicated in the product label (Restraints): "Do not use this product unless trained in the proper use of required respirator and detection devices, emergency procedures and safe use and handling of the fumigant. Fumigators *must hold the relevant State/Territory license for fumigation."*

Hazard classification

- Cyanogen is listed on the ASCC Hazardous Substances Information System (HSIS) Database with the following risk and safety phrases:
  - R20 0.5 per cent ≥ Conc. > 5 per cent Harmful by inhalation.
  - R23 Conc. ≥ 5 per cent Toxic by inhalation.
  - S1/2 Keep locked up / Keep out of the reach of children.
  - S23 Do not breathe the gas.
  - S45 In case of accident or if you feel unwell seek medical advice immediately.
- However, based on the toxicology information available, XXXXX has revised this classification, as follows:
  - R26/27/28 Very toxic by inhalation, in contact with skin and if swallowed
  - R36/37 Irritating to eyes and respiratory system
  - R46 May cause heritable genetic damage
  - R60 May impair fertility
  - R61 May cause harm to the unborn child

- The following (revised) cut-off concentrations apply to cyanogen:
  - Conc. ≥ 5 per cent R26/27/28, R36/37, R46, R60, R61
  - 0.5 per cent ≥ Conc. > 5 per cent R46, R60, R61

DISCUSSION – RELEVANT MATTERS UNDER 52E

The relevant matters under section 52E (1), to this item, included: (a) toxicity and safety of the substance; and (c) potential hazards.

A Member noted that, due to the toxicity of cyanogen, the only reasonable schedule was Schedule 7. The Members generally agreed, with the addition of an Appendix J listing with condition 1 "not to be available except to authorised or licensed persons", as there was a clear need to restrict access to trained and licensed persons.

A Member noted that this chemical should fall into the same category as phophine and queried whether there was an assessment of the public health risk to people living near a site and how would exclusion zones for a risk area be established. The Committee generally agreed that these issues would be addressed through the registration process.

Members also considered whether to schedule as "ethanedinitrile" or as "cyanogen". A Member suggested that cyanogen better communicated what the substance is. The Committee agreed that, for the sake of clarity, cyanogen be used for the entries in Schedule 7 and Appendix J with a cross reference from ethanedinitrile to cyanogen in the SUSDP index.

RESOLUTION 2008/53 - 18

The Committee decided to create new Schedule 7 and Appendix J (condition 1 - Not to be available except to authorised or licensed persons) entries for cyanogen. The Committee also decided to cross-reference ethanedinitrile to cyanogen in the SUSDP index.

Schedule 7 – New entry

CYANOGEN.

Appendix J, Part 2 – New entry

POISON	**CONDITION**
Cyanogen	1

SUSDP Index – New entry to the Index in the SUSDP 24 consolidation.

ETHANEDINITRILE
See CYANOGEN

7. MATTERS REFERRED BY OFFICE OF CHEMICAL SAFETY (OCS) OR THE NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

7.1 ATROPINE

PURPOSE

The Committee noted the findings of the Working Group on anticholinesterase pesticide poisoning, including the use of atropine as an antidote.

BACKGROUND

Atropine is a tertiary amine antimuscarinic alkaloid with both central and peripheral actions. Atropine initially stimulates, and then depresses the CNS. It has antispasmodic actions on smooth muscle and reduces secretions, especially salivary and bronchial secretions. It also decreases perspiration with little effect on biliary or pancreatic secretion. Atropine depresses the vagus nerve resulting in an increase in the heart rate. When given orally, atropine reduces smooth muscle tone and diminishes gastric and intestinal motility, but has little effect on gastric secretion in usual therapeutic doses. Atropine has a range of uses including the treatment of poisoning with organophosphorus (OP) and carbamate pesticides.

Currently, the OP and carbamate pesticide products registered for use in Australia must display a precautionary statement on labels directing the user to obtain an emergency antidote supply of atropine tablets in case of poisoning (Statement 373 – Obtain an emergency supply of atropine tablets 0.6 mg). Compliance with this is mandatory under

the Workplace Health and Safety Act. Atropine sulfate tablets with the recommended strength of 0.6 mg were previously manufactured by Fawns & McAllan Pty Ltd.

XXXXX, in October 2007, received confirmation from XXXXX that the manufacturing of atropine sulfate tablets was discontinued as of February 2006 and there were no other manufacturers in Australia registered to manufacture this product. Future manufacturing of this product was not likely due to the restricted and small market of consumers. Because this product was also required under a First Aid Instruction (statement "m" - "give atropine if instructed") in case of poisoning, its lack of availability in prescribed tablet form suggested that the current and future product users would be in breach of workplace health and safety legislation. The First Aid Instruction statement, however, did not specify the form of the product or dose levels to be administered. The First Aid Instruction would provide sufficient flexibility to allow for alternative dose forms of atropine if they became available.

This issue was reported to the Committee at its October 2007 Meeting and it was agreed that a working party be formed to investigate options for alternative product presentations and treatment methods (ampoules and preloaded auto injectors), although no auto injectors were registered in Australia at that time.

DISCUSSION - SUBMISSIONS

To address regulatory and industry concerns about the lack of availability of an antidote supply of atropine sulfate tablets, XXXXX had undertaken a study of the requirement for a readily available, emergency supply of an antidote for OP and carbamate poisoning in an agricultural workplace setting. The study was undertaken by a working group established by XXXXX. The working group included a clinical toxicologist, an occupational health clinician, an emergency medicine specialist, and XXXXX.

The working group considered a contemporary position required for providing an antidote for self administration by non-medical professionals in the event of carbamate or OP poisoning, with a primary focus on the agricultural work place setting. The working group considered all uses of OPs and carbamates, including veterinary products. XXXXX review report established the following:

- The data from the NSW and Victorian Poisons Information Centres suggested that the incidence of OP and carbamate exposure had decreased in recent years [Members were advised that was by about 30-80 per cent from 2003 to 2007]. The clinical advice was that occurrences of severe poisonings were rare and the majority, if not all, had occurred as a result of deliberate self-poisoning.
- The decreased reporting rates and the severity of accidental poisonings were thought to be consequences of some regulatory initiatives (e.g. stricter implementation of the legislative requirements for Schedule 7 chemicals, which had lead to the improved training of chemical operators, promotion of alternative and less toxic chemicals by regulatory agencies and integrated management practices).

- The literature on treatments for OP poisoning was equivocal in regard to the ability of alternative antidotes (oximes, benzodiazepines and combination treatment) to atropine to reduce morbidity and mortality in humans. The injectable form of atropine was considered to be most effective.
- The clinical advisory group guiding the current review agreed that atropine would only be a valuable first-aid measure in cases of severe poisoning. In cases of mild and moderate poisoning, an OP would induce symptoms over the course of days which, in all likelihood, would give adequate time for workers to seek a detailed diagnosis and treatment from a health professional. The conclusion was drawn that immediate first-aid treatment was not essential in such cases, provided that medical advice was sought.
- Effective and safe treatment of poisoning required atropine dosing to be titrated based the clinical signs and symptoms, and early administration was needed in the case of severe poisoning. Preferably, the treatment should be done by a health professional or following advice from a health professional (e.g. Poisons Information Centre). Any first-aid atropine treatment must be accompanied by immediate medical follow-up and definitive management by medical professionals.
- Given that the clinical signs of severe OP and carbamate poisoning may include frothing at the mouth and unconsciousness, the administration of atropine sulphate in tablet form was likely to be impractical in such situations.
- Administration of atropine sulfate tablets when it was feasible or any injectable form of atropine, with advice from a health professional, could be life saving in some situations (remote, rural areas where increased incidence of accidental exposures have been reported), as the condition of an affected individual could deteriorate rapidly. Training and other programs seemed to have markedly reduced incidents of accidental poisoning. However, evidence suggested that isolated incidents of poor compliance with OHS measures with OP use by some workers in remote, rural areas. Nonetheless, increased capacity for farmers in these areas to obtain an effective treatment from trained health professionals had resulted in decreased need for a readily available antidote.

The conclusions of the XXXXX report included the following:

- Atropine was still the best treatment for OP poisoning, when administered under the supervision of a health professional.
- Available evidence indicated that decreasing incidence of OP exposure reporting and the severity of poisoning cases in an environment where atropine sulphate tablets are no longer available.
- Atropine, in tablet form, would be difficult to administer to an unconscious patient. Atropine treatment may not be crucial for mild to moderate cases but diagnosis and treatment by a health professional was still be necessary. Therefore, the retention of the requirement for readily available atropine sulfate tablets as a first-aid treatment was difficult to justify.

- While evidence pointed to some non-compliance in sub-groups of remote farmers, increased access to training and rural health networks would have contributed to compliance and reduced the need for a first-aid atropine antidote.

XXXXX report recommended that warning statements and safety directions on OP and carbamate product labels instructing users to obtain atropine were no longer warranted. Therefore, FAISD and SUSDP entries pertaining to the requirement of atropine for the treatment of carbamate and OP poisonings should be amended.

A pre-meeting comment from XXXXX indicated that, as the scheduling changes for atropine had not been proposed at that stage, they may wish to provide comment if any changes impacted the current cut-off levels.

DISCUSSION – RELEVANT MATTERS UNDER 52E

A Member noted that requirements for atropine related First Aid Instructions were reviewed in 2000 and at that time the clinicians recommended to retain relevant statements in the SUSDP supporting atropine use. The Member asserted that the conditions have changed since then due to reduction of OP and carbamate use, increased training programs, and switch over to less toxic alternatives. During this time, the withdrawal of atropine tablets from the market has also occurred, yet there was no evidence of increased incidence in reported poisoning. The Committee was in general agreement that, due to the above reasons, it was no longer necessary to require OP and carbamate users to have a supply of atropine tablets at hand.

A Member highlighted that the data on incidence of reported poisonings in no way suggested that OPs and carbamates were less toxic substances than had been previously established.

A Member asserted that there was no need to remove the current Schedule 2 part (b) entry as proposed, given that there were some occupations where access to atropine product was still required. This would also mean that remote area nurses would have access to such products. Another Member, however, expressed concerns on whether the availability through Schedule 2 would be the safest way to make such products available and suggested that availability Schedule 4 would be more appropriate. A Member also advised that there were mechanisms under jurisdictional legislation to allow remote area nurses to have access to Schedule 4 products. The Committee therefore agreed that proper use of atropine required a doctors advice and, as pesticide users could obtain prescriptions for Schedule 4 atropine products prior to pesticide use, there was no reason to retain part (b) of current Schedule 2 entry.

Whilst noting that there was no need to remove the existing Standard Statement SP1 in part 1 of Appendix E supporting use of atropine as it was still the most effective and appropriate first aid measure available for OP and carbamate poisoning, the Members recognised that the registration requirements for atropine availability would be addressed via APVMA processes.

A Member suggested that part (b) of the atropine Schedule 2 entry should be amended to read as "organophosphate and carbamate poisoning" instead of "organophosphorous poisoning". The Committee noted, however, the intent to delete part (b) entirely.

A Member stated that follow up actions would also be important to advise the medical professionals regarding these developments. The Committee agreed that the report of the working group should be made publicly available on the OCS website (http://www.ocs.gov.au).

RESOLUTION 2008/53 - 19

The Committee noted and supported the report of the XXXXX working group and its recommendations, and decided to foreshadow amending the Schedule 2 entry for atropine by deleting part (b).

FORESHADOWED DECISION (for consideration at the October 2008 Meeting)

Schedule 2 – Amendment

ATROPINE (excluding atropine methonitrate) for oral use:

(a) in undivided preparations containing 0.03 per cent or less of total solanaceous alkaloids when labelled with a dose of 0.3 mg or less of totalsolanaceous alkaloids and a recommended daily dose of 1.2 mg or less of total solanaceous alkaloids; or

(b) in divided preparations containing 0.3 mg or less of total solanaceous alkaloids per dosage unit when labelled with a recommended daily dose of 1.2 mg or less of total solanaceous alkaloids.

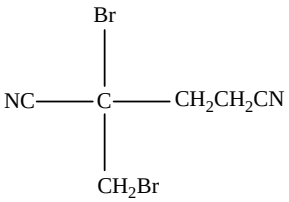
7.2 METHYLDIBROMO-GLUTARONITRILE (MDBGN)

PURPOSE

The Committee considered the scheduling of methyldibromo glutaronitrile (MDBGN) including a possible ban for cosmetic use.

BACKGROUND

Methyldibromo glutaronitrile is the common name (and AAN) for the chemical 1,2-dibromo-2,4-dicyanobutane (listed on AICS as pentanedinitrile, 2-bromo-2-(bromomethyl)-). The structure of MDBGN is:



MDBGN is used as a preservative and biocide in a wide range of products, including paints, emulsions, dispersed pigments, adhesives, joint cements, metalworking fluids, cosmetics, paper, inks, waxes and household detergents. In the mid 1980s, MDBGN began to be used as a preservative in cosmetics and the first case reports of contact sensitivity due to MDBGN preserved cosmetics were reported in the late 1980s and early 1990s.

DISCUSSION - SUBMISSIONS

XXXXX had undertaken a hazard assessment for MDBGN which recommended that, due to oral toxicity, skin and eye irritation and skin sensitising potential, the Committee may wish:

- To include MDBGN in Appendix C for cosmetic use and products intended to be in contact with the skin.
- For uses other than cosmetics and products intended to be in contact with the skin, the Committee may consider it appropriate to include MDBGN in Schedule 6 with specified warning statements and safety directions, or to consider a Schedule 6 entry unless such specified statements and safety directions are used.

The XXXXX hazard assessment used information from previously published reports of the Cosmetic Ingredient Review (CIR) Expert Panel (1996), the USEPA R.E.D Facts (1996) and the National Toxicology Program (NTP) Technical Report (2008). Three opinions by the EU's Scientific Committee on Cosmetic Products and Non-food Products Intended for Consumers (SCCNFP) (2002) and the Scientific Committee on Consumer Products (SCCP) (2005 and 2006) and literature searches conducted until March 2007 (which provided relevant supplementary studies).

XXXXX therefore sought a scheduling consideration of MDBGN, based on the hazard assessment. Members particularly noted the following:

- Following a NICNAS call for information from Industry on the Australian use of MDBGN in 2007, MDBGN was reported in products such as adhesives and coatings, and personal care products, including sunscreens, shampoos, shower gels and wet wipe hand towels. A recently Australian case report noted sensitisation from the use of MDBGN in adhesives used in female sanitary pads.
- Until recently, in the EU, MDBGN was permitted in rinse off cosmetic products at a maximum concentration of 0.1 per cent and was prohibited from use in cosmetic sunscreen products at a concentration of > 0.025 per cent. However, based on the 2006 SCCP opinion that MDBGN was a skin sensitiser and that no safe use-levels in

cosmetic leave-on and rinse-off products could be established, MDBGN was removed from Annex VI of the EU Cosmetics Directive (List of Preservatives which Cosmetic Products May Contain) and was no longer allowed to be present in any cosmetic products in the EU.

- Regulations in the USA permit the use of MDBGN in cosmetics at up to 0.025 per cent in leave on products and 0.06 per cent for rinse off products.
- MDBGN has not been classified according to the Approved Criteria for Classifying Hazardous Substances.

Absorption and metabolism

- In animals, MDBGN was readily absorbed following oral, dermal and intravenous administration. 72 hours after oral administration, most of the dose was excreted in the urine, exhaled, or present within the animal's tissues and only 10 per cent was recovered from the faeces. When applied to the skin at doses between 5 and 25 mg/kg bw, ~12-22 per cent was absorbed through the skin within 3 to 4 days.
- Once inside the body, MDBGN was rapidly metabolised to 2-methyleneglutaronitrile (2-MGN) before eventually being eliminated from the body, mostly via urine (in the form of N-acetyl-S-(2,4-dicyanobutane-L-cysteine). 2-MGN was reported to be the reactive species responsible for binding to macromolecules following exposure to MDBGN.
- In *in vitro* absorption studies using excised skin from rats and humans, human skin showed greater absorption of MDBGN than rat skin when MDBGN was applied in aqueous solution, but less than rat skin for MDBGN in a sunscreen formulation.

Acute toxicity

- MDBGN is moderately toxic by oral route (LD_{50} 770 mg/kg for males and 515 mg/kg for females), and was of low acute toxicity by dermal ($LD_{50} > 5$ g/kg) and inhalation ($LC_{50} > 13$ mg/L) exposures.

Irritancy

- MDBGN (98 per cent) is a severe eye irritant.
- Equivocal results were obtained from skin irritation tests in animal studies. However, repeat dose dermal toxicity tests reported moderate to severe erythema, and slight to moderate oedema. Non-neoplastic skin lesions were also reported.

Sensitisation

- The skin sensitising potential of MDBGN has been extensively investigated in numerous animal and human studies. Results obtained from animal studies vary according to the type of animal study undertaken. Based upon positive results obtained from LLNA studies available animal data on a weight of evidence suggest that MDBGN is a skin sensitiser.

- In humans, the prevalence of MDBGN sensitivity has been monitored in numerous countries and over an extended period by the routine patch testing of contact dermatitis patients. The rate varies significantly between countries, but this is to be expected as the use of MDBGN as a preservative is more widespread in some countries than others. Across all available patch test surveys (concentration range of 0.03-0.5 per cent MDBGN), the prevalence rate of positive reaction ranged from 0-11.7 per cent with a median prevalence rate of 2.0 per cent. The prevalence rate increased up to 19.6 per cent when 0.3 per cent MDBGN was tested in patients sensitised to their own cosmetics.
- A number of studies have been carried out on individuals pre-sensitised to MDBGN, and apart from a single contradictory study, these individuals developed dermatitis upon re-exposure to lotions or ointments containing MDBGN. The prevalence rate of positive reaction ranged from 7.7-92 per cent when patients were patch tested with MDBGN at concentrations of 0.0001-1 per cent.
- There have been multiple case reports of MDBGN contact sensitivity, rarely in the 1980s but with a greater frequency from 1990 onwards. Most case reports were attributed to cosmetics or toiletries. In contrast, human repeat insult patch tests carried out in the early 1980s on naïve individuals indicated that MDBGN was not a sensitising agent.
- Overall, despite negative results from repeat insult patch tests, available human data from diagnostic patch test surveys, individual case reports and elicitation studies in MDBGN sensitised individuals indicate that MDBGN is a human skin sensitiser. In 2006, the SCCP concluded that MDBGN is a skin sensitiser and that no safe use-levels in cosmetic leave-on and rinse-off products could be established.

Repeat dose toxicity

- In long-term repeat oral studies, the observed effects of MDBGN were thyroid follicular cell hypertrophy, thyroid hyperplasia, increased pigmentation of the liver and spleen and increased extramedullary haematopoiesis when administered at high doses (4000 ppm) in dogs. Follow-up studies found no significant changes in levels of thyroid hormones.
- Repeated dermal application of MDBGN was associated with moderate to severe erythema, and slight to moderate oedema. Non-neoplastic lesions at the application site consisting of epidermal hyperplasia, hyperkeratosis, parakeratosis, necrosis, and ulcers; dermal chronic active inflammation and sebaceous gland hyperplasia were also reported.

Genotoxicity and carcinogenicity

- MDBGN was positive in an *in vitro* chromosome aberration test. However, this positive finding was not confirmed by other mutagenicity assays conducted *in vitro* and *in vivo*. Overall, the evidence indicated that MDBGN was not mutagenic. The 2-year dermal studies conducted in rats and mice showed no evidence of carcinogenic effect of MDBGN.

Reproduction

- Available information suggests that MDBGN is neither a reproductive nor a developmental toxin. In an oral study in rats, a significantly higher resorption rate (10 per cent) with a 175 mg/kg bw/day dose was reported. However, the incidence of resorptions was not considered to be associated with potential developmental toxicity of MDBGN but rather related to maternal toxicity. Therefore, the NOAEL was determined to be 175 mg/kg bw/day (the highest dose tested).

Exposure

- MDBGN is used in Australia as a preservative and biocide in a range of products. Limited information is available on the final use concentration in certain products. MDBGN was reported to be present in shower gels and shampoos at concentrations between 0.003 and 0.004 per cent, and in sunscreens at 0.04 per cent. A recently Australian case report noted use of MDBGN in adhesives used in female sanitary pads leading to an individual with dermal sensitisation.
- Consumer exposure to MDBGN is likely to be widespread because of its use in cosmetics and a variety of other consumer products. The main route of consumer exposure is through dermal contact. Dermal exposure to MDBGN may occur during application of cosmetic products to different parts of the body. Oral exposure to MDBGN may also occur, but only through accidental ingestion of small amounts of cosmetic products. Similarly, ocular exposure is not expected; however, accidental eye contact may occur when using any of the cosmetic products.
- In Australia, allergy clinics have reported cases of allergy (prevalence of 0.7 per cent) associated with the use of MDBGN as a preservative, mostly in hand cleaners.

Members also noted the following points from XXXXX discussion of the data above:

- MDBGN is used in products designed for skin care (cosmetics, hand wipes etc.) and is also used in products not designed for skin care, but which require skin contact (sanitary pads etc.). MDBGN is also used in products not designed for, nor requiring, skin contact.
- The SCCP in 2006 was unable to determine a safe level for MDBGN in any cosmetics due to sensitisation potential. Although some data on levels of MDBGN in other types of products in Australian are available, it is not possible to determine the overall likely potential for exposure to MDBGN from use of these products. Therefore, it is not possible to determine a cut-off value for safe use either in cosmetics or other non-cosmetic, non-skin contact products.
- Given the low levels of MDBGN (≤ 0.04 per cent) currently used in products, skin sensitisation is the primary health effect of concern.
- The XXXXX recommendation to include MDBGN in Appendix C for cosmetic use and products intended to be in contact with the skin was based on the expected

widespread public exposure from use of cosmetics containing MDBGN, the acute oral toxicity, the skin sensitisation potential, the eye and skin irritation potential, and the lack of an established safe use-level in leave-on and rinse-off products, and the current prohibition of MDBGN for use in cosmetics within the EU.

Recommended Warning Statements

– 28 Repeated exposure may cause sensitisation.

Recommended Safety Directions

– 1 Avoid contact with eyes.
– 4 Avoid contact with skin.
– 7 Wash hands thoroughly after use.

Members also noted advice that a search of the ARTG located 45 products containing MDBGN (44 sunscreens and 1 antibacterial liquid handwash). However, all products were tagged as export only medicines.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The relevant matters under section 52E (1), to this item, included: (a) toxicity and safety of the substance; (b) risks and benefits; (c) potential hazards; and (d) extent and patterns of use.

A Member supported XXXXX recommendation of an Appendix C entry for products intended to be in contact with the skin because of the sensitisation risk but suggested that the entry could simply refer to "human use". The Committee agreed, however, that it would be clearer to use "in preparations intended to be in contact with the skin, including cosmetic use". The Committee also generally agreed that Schedule 6 with warning statements and safety directions would be appropriate for other use patterns given the reduced risk of repeated dermal exposure and sensitisation.

RESOLUTION 2008/53 - 20

The Committee decided:

- to include MDBGN in Appendix C for cosmetic use and for products intended to be in contact with the skin.
- to include a parent MDBGN entry in Schedule 6 to capture any uses not caught by the Appendix C entry.
- to include MDBGN in Appendix F Part 3 (Warning Statement 28 –"Repeated exposure may cause sensitisation" and Safety Directions 1,4 and 7 – "Avoid contact with eyes", "Avoid contact with skin" and "Wash hands thoroughly after use").

Schedule 6 – New entry

† METHYLDIBROMO GLUTARONITRILE **except** in preparations intended to be in contact with the skin, including cosmetic use.

Appendix C – New entry

METHYLDIBROMO GLUTARONITRILE in preparations intended to be in contact with the skin, including cosmetic use.

Appendix F, Part 3 – New entry

POISON	**WARNING STATEMENTS**	**SAFETY DIRECTIONS**
Methyldibromo glutaronitrile	28	1,4,7

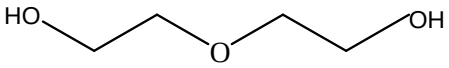
7.3 DIETHYLENE GLYCOL (DEG)

PURPOSE

The Committee considered the scheduling of diethylene glycol (DEG) including possible restrictions for use in oral cosmetic products such as toothpaste.

BACKGROUND

Diethylene glycol (DEG) is the common name for the chemical 2,2'-oxybisethanol (listed on AICS as ethanol, 2,2'-oxybis-). The structure of DEG is:



DEG is an industrial chemical with uses worldwide as a chemical intermediate in the production of polyester resins, polyurethanes, explosives and other glycols. It is used in cement grinding, as an anti-freeze agent, as a constituent of brake fluids, as a humectant for tobacco, glues and corks and as a plasticiser for paper, packaging materials and coatings. It is also used as a solvent for paints, lacquers and cosmetics for dermal application.

The May 1974 PSSC Meeting, in considering a number of chemicals used in insecticides, agreed that diethylene glycol should be exempted from the requirement of scheduling. DEG remains unscheduled.

The June 2007 NDPSC Meeting was advised that XXXXX had recently been involved with the removal of toothpaste containing DEG. This followed the recall of product from stores in XXXXX and a number of media articles. The October 2007 NDPSC Meeting noted that the National Industrial Chemicals Notification and Assessment Scheme

(NICNAS) had undertaken a call for information on DEG in oral cosmetic products (e.g. toothpaste and mouthwash) to determine the extent of use.

DISCUSSION - SUBMISSIONS

Members recalled that chemicals in toothpastes are regulated as either cosmetics by NICNAS or therapeutic goods by TGA, depending on their characteristics and performance claims. The TGA regulates toothpastes when they are classed as medicines. A toothpaste is classed as a medicine if the benefits claimed to result from its use go beyond those normal claims made for toothpastes (improvements to oral hygiene or the use of fluoride for the prevention of tooth decay) or if it contains an ingredient captured by scheduling. No dental whitener or dental bleach was considered a therapeutic good by TGA (regardless of whether it contained an ingredient captured by scheduling).

NICNAS recently undertook a hazard assessment for DEG in oral cosmetic products which included the recommendation that the Committee include DEG in Appendix C for intentional oral cosmetic use because of the potential for toxic effects following a single high oral dose or repeated lower oral doses.

The NICNAS hazard assessment used information from the OECD SIDS Initial Assessment Report on the Ethylene Glycols Category (OECD, 2004) and the Dutch Expert Committee on Occupational Standards report - Health-Based Recommended Occupational Exposure Limit for Diethylene Glycol (Health Council of the Netherlands, 2007). The OECD report was a category assessment that included data not only on DEG but also on several other ethylene glycols. Literature searches conducted up to December 2007 provided relevant supplementary studies.

XXXXX therefore sought a scheduling consideration of DEG in oral cosmetic products, based on the NICNAS hazard assessment. Members particularly noted the following:

- In 2007, DEG was found in certain brands of imported toothpaste. In conjunction with advice from XXXXX, the ACCC issued recall notices for some toothpaste brands, while others were withdrawn from sale. Subsequently, the ACCC issued a Consumer Protection Notice banning the supply of toothpaste containing > 0.25 per cent of DEG, effective 3 August 2007 for a period of 18 months.
- Several countries have imposed restrictions and bans on the use of DEG in toothpaste. Chinese authorities announced in July 2007 that it had banned the use of DEG in toothpaste. In Europe, the Italian and Spanish authorities ordered the precautionary seizure of toothpastes including counterfeited well-known Western branded products and toothpaste samples.
- There are currently no medicines, including toothpastes, or foods containing DEG as an allowable ingredient approved for general sale in Australia. [Members noted advice that a search of the ARTG located a hospital grade disinfectant registered as a device for use in Australia which contained ~10 per cent DEG.]

- In cosmetic products (including toothpastes), the presence of DEG is required to be disclosed through labelling (disclosure of the concentration, however, was not mandated) (cosmetics requirements under the *Trade Practices Act 1974*).

Absorption and metabolism

- In animals, absorption of oral DEG is rapid and distribution occurs to all organs and tissues. Dermally administered DEG is slowly and incompletely absorbed. DEG and metabolites are readily cleared from the blood and excreted in the urine. Depending on the dose administered, approximately 45-70 per cent of an oral dose is excreted unchanged in the urine within 48 hours, and 11-37 per cent as 2-HEAA after oxidative metabolism. Saturation of metabolism occurs at high doses.

Acute toxicity

- In laboratory animals, DEG has low acute toxicity. The oral LD_{50} values for mice and rats are in the range of 13-30 g/kg bw, and the dermal LD_{50} for rabbits is 12-13 g/kg bw. However, humans appear to be 10 times more susceptible to oral toxic effects of DEG compared to experimental animals (see discussion under exposure below).
- Toxicokinetic studies in rats report narcosis, metabolic acidosis, increased urine volumes, anuria and hydropic degeneration of renal tubules following oral administration of DEG at various doses.

Irritation and sensitisation

- DEG produces no or only minimal eye and skin irritation. DEG causes respiratory depression in mice, but the characteristics were reported not to be typical of a pure airways irritant. No other information on respiratory irritation was available.
- DEG does not cause skin sensitisation in animals. A single case of skin sensitisation to DEG was identified in a man who had been smoking cigarettes containing DEG.

Repeat dose toxicity

- In animals, repeated exposures to DEG was associated with effects mainly in the kidney (increased urine volumes, hydropic degeneration and tubular necrosis) and to a lesser extent the liver (vacuolar degeneration). From 98-day and 225-day studies in Wistar rats, a LOAEL for increases in urine volume was established at 230 mg/kg bw/d with the NOAEL at 100 mg/kg bw/d. A LOAEL based on renal hydropic degeneration was established at 1.6 g/kg bw/day with the NOAEL at 300 mg/kg bw/d.

Genotoxicity and carcinogenicity

- The available data indicated that DEG was negative in *in vitro* genotoxicity tests. Some positive results were obtained in *in vivo* genotoxicity studies, however, only at high toxic doses. Taken together, DEG was considered non-genotoxic.
- Urinary bladder calculus and tumour response were recorded in some long-term oral rat studies. These were considered to result from chronic irritation of the bladder wall by DEG-induced stones. No information was found in the literature concerning the

occurrence of bladder stones in humans after DEG ingestion. Human data was insufficient to evaluate the carcinogenic potential of DEG. The International Agency for Research on Cancer (IARC) had not evaluated DEG as a carcinogen.

Reproduction

- Several animal reproduction toxicity studies indicated that DEG induced adverse effects on fertility and development, but only at doses higher than those associated with repeat dose effects and in the presence of biologically relevant maternal toxicity. From these studies, the LOAEL for fertility / developmental effects was established at 6.1 g/kg bw/d based on reductions in litters/pair, live pups/litter and live pup weight. The NOAEL was 3.1 g/kg bw/d. Maternal toxicity (decrease in body weight) was noted at 6.1 g/kg bw/d.

Human oral exposure to DEG

- A number of mass poisonings in humans involving substitution of DEG for more expensive, non-toxic glycols in medicinal preparations have been documented over the last 70 years. Typical features of toxicity include neurological impairment, metabolic acidosis and acute renal failure. Early mortality and morbidity are high, with most deaths occurring within the first 2 weeks post exposure.
- Large overlaps in ranges of lethal and non-lethal doses have been observed for adults and children. A median lethal oral dose of 1.49 g/kg bw DEG (range 0.25-4.9 g/kg bw) was estimated from large-scale intoxication of Haitian children with a paracetamol syrup contaminated with DEG. On this basis, humans appeared to be about ten times more sensitive to the toxic effects of DEG than the animal species used in toxicity studies.
- Previously, DEG has been improperly used as counterfeit glycerin in overseas consumer products based on its pleasant smell, sweet taste and lower cost. In 2007, DEG was detected in Australia as a component of some imported toothpastes.
- NICNAS sought information on the Australian use of DEG in oral cosmetic products (e.g. toothpaste and mouthwash) from industry in August 2007. No manufacture or importation of oral cosmetic products containing DEG was reported by Australian companies. No information on Australian uses of DEG in other types of cosmetics is available, although information overseas indicates use in specific brands of foundations, facial powders and concealers.

Members may also wish to note the following points from the XXXXX discussion of the data above:

- Although DEG was not an allowable ingredient in foods or medicines, it is a known impurity in PEG, an allowable ingredient for these applications. PEG is also used in cosmetics. Therefore, there was potential for very low levels of DEG to be present in cosmetics, including oral cosmetics.
- Given its rapid absorption following ingestion and documented oral toxicity in animals and humans, there was concern about potential risks of adverse effects from

exposures to DEG in oral cosmetic products such as toothpaste and mouthwash. Toothpastes and mouthwashes are not intended to be swallowed, but unintentional swallowing or ingestion of products containing DEG has a meaningful risk to certain populations, such as children or individuals with kidney or liver disease.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The relevant matters under section 52E (1), to this item, included: (a) toxicity and safety of the substance; (b) risks and benefits; (c) potential hazards; and (d) extent and patterns of use.

Members noted that NICNAS had made no recommendation regarding scheduling of DEG to address the risk of inadvertent ingestion for use patterns other than intentional oral cosmetic use. A Member suggested that the estimated acute oral toxicity (~LD_{50} of 1490 mg/kg bw – the Haitian paracetamol syrup contaminated with DEG incident) could provide a basis for consideration of a general DEG schedule entry (i.e. Schedule 6). The Committee did not support this approach.

Instead, the Committee agreed that the scheduling consideration should be restricted, at this time, to use in toothpastes and mouthwashes since there was clear evidence of misuse of DEG in these products and this concern had been the focus of the NICNAS assessment. Members generally felt that it was appropriate to ban DEG in toothpastes and mouthwashes through Appendix C as there was a clear risk to health, especially for children, from DEG in these products. The Committee agreed, however, that the wording suggested by NICNAS "intentional oral cosmetic use" could create problems with interpretation. A Member suggest the Appendix C entry could ban "oral use" but the Committee instead supported the specific wording "toothpastes and mouthwashes".

Members also noted that the "for intentional oral cosmetic use" in the NICNAS recommendation appeared to be trying to make allowance for unavoidable trace levels of DEG in polyethylene glycol (PEG), an allowable ingredient for food and medicines which may also be used in toothpastes or mouthwashes. Members therefore agreed that an Appendix C exemption at ≤ 0.25 per cent, in line with the ACCC's Consumer Protection Notice (discussed above), would be appropriate.

RESOLUTION 2008/53 - 21

The Committee decided to include diethylene glycol for use in toothpastes and mouthwashes in Appendix C, with an exemption cut-off of 0.25 per cent.

Appendix C – New entry

DIETHYLENE GLYCOL for use in toothpastes or mouthwashes **except** in preparations containing 0.25 per cent or less of diethylene glycol.

8. OTHER MATTERS FOR CONSIDERATION

Item deleted

9. INFORMATION ITEMS (AG/VET, INDUSTRIAL AND DOMESTIC CHEMICALS)

Nil.

PHARMACEUTICALS

10. MATTERS ARISING FROM THE MINUTES OF THE PREVIOUS MEETING (CONSIDERATION OF POST-MEETING SUBMISSIONS UNDER 42ZCY(1)(C))

10.1 SEDATING ANTHIHISTAMINES

PURPOSE

The Committee considered post Meeting comment on the decision to include sedating antihistamines in Schedule 4 when for use in children <2 years.

BACKGROUND

The June 2007 NDPSC Meeting considered the scheduling of all sedating antihistamines when for use in children, including children < 2. At this Meeting the Committee agreed that the sedating antihistamines promethazine and trimeprazine posed a particular risk to children < 2 and as such should only be available as prescription medicines to this age group, regardless of the presence of a sympathomimetic decongestant. The Committee also agreed that there was currently insufficient evidence to consider that this risk applies to the remaining non-phenothiazine sedating antihistamines.

At its' December 2007 Meeting, the MCC considered the scheduling status of sedating antihistamines. MCC noted the considerations of the USFDA on the use of cough and cold medicines in children and further noted that the Medsafe had prepared a report for the Medicines Adverse Reactions Committee (MARC) who had considered the issue the previous day. The Medsafe report had concluded that there was little efficacy data for these substances in children and that it had been largely extrapolated from adult data. The MCC agreed that if there was no benefit to be obtained from a medicine, then any risk was relevant. MCC agreed that doctors rarely prescribed these substances for young children and would not know the appropriate doses of the substances for this age group. It was also commented that pharmacists did not have access to such information. The MCC agreed that use of sedating antihistamines should be contraindicated in children <2 years (which is essentially a labelling issue).

The Secretariat received clarification that all sedating antihistamines are Prescription Medicines for use in children <2 in NZ and this has been in effect for 12-18 months.

At the February 2008 NDPSC Meeting, the Committee considered an application from XXXXX requesting that the remaining non-phenothiazine sedating antihistamines also be included in Schedule 4 when for use in children <2. After reviewing all the evidence provided, the Committee agreed that Schedule 4 was the appropriate schedule for these substances for children <2 given their seeming lack of efficacy while still having the potential to cause serious adverse drug reactions.

DISCUSSION - SUBMISSIONS

The Committee recalled the following from the February 2008 Meeting:

- It was suggested that the main issue might be that many parents were giving pre-school-age children OTC drugs with no proven benefits. It was noted that although the substances of concern had a long history of use, the label indications did not cater for children <2 years of age and they can produce serious side-effects.
- With regard to concerns relating to increased morbidity and mortality in children <2 years of age, the Committee agreed that there appeared to be very little evidence for this in Australia. Moreover, it was suggested that the US reports only illustrated the well-known epidemiology of non-intentional poisoning of any substance, reflecting the availability of these drugs to young children, thus re-scheduling was unlikely to further reduce the already very low risk of poisoning in children <2 years of age.
- However, the Committee agreed that there was evidence for lack of efficacy of the substances, many of which were in combination products. It was noted that there was no actual data for children in this age group and the data available was obtained via extrapolation to this age-group of results from studies done in older children or adults.
- The Committee also agreed that side effects with these substances as a class were common. The Committee felt that, given the lack of evidence of efficacy, more weight had to be put on the possibility of potential side effects or idiosyncratic effects occurring without the patient deriving any benefit from the substance.
- It was agreed that when these actual and possible side-effects were balanced against the lack of efficacy, the re-scheduling to Schedule 4 could be justified, as the substances did fit the Schedule 4 guidelines. Members felt that it was not desirable to expose children <2 years of age to the risk of side effects when the medication would provide them little benefit and therefore, these substances should only be used in this age group under medical supervision.

XXXXX provided a post-Meeting comment in which it stated that the change to the scheduling of non-sedating antihistamines for use in children <2 was not appropriate. The following points were made:

- XXXXX stated it was concerned that there appeared to be a lack of action following the Committee's decision to make these substances Schedule 4. It was stated that it was expected the Committee would have sought further information and advice on the matter from relevant sources including the applicant and ADEC.
- It was stated that, given the lack of evidence of efficacy in children <2, it was counterintuitive to expect that doctors could make evidence-based decisions about the prescribing of these substances. It was further stated that despite counselling from a pharmacist about other treatment options, a parent may still insist they need to see a doctor to obtain the substances as they were familiar with its use. XXXXX asserted that this may put undue pressure on the doctor to prescribe the substance as well as

potentially being a waste of time and resource for both parties. XXXXX also questioned whether it was reasonable to include the management of such self-limiting conditions to a GPs workload.

- Significant concerns were raised regarding the possibility of parents purchasing a product for use in an older child, but administering it to a child <2. It was stated that this may lead to the parent trying to guess an appropriate dose for the younger child without any guidance which may, in turn, lead to adverse consequences.
- XXXXX noted that there was significant confusion in the community surrounding the release of information regarding the NDPSC's decision on sedating antihistamines and the release of the TGA advisory on the labelling of all cough and cold medications for children <2. It was requested that, in the future, such information be clarified better prior to release.
- XXXXX referred to its submission to the February 2008 Meeting in which it stated that it strongly felt a consumer education program would be of benefit as this could provide a clear message to the public about the safety and appropriate use of these substances in children. It was stated that such a campaign would compliment the mandatory changes to packaging and labelling that would occur if the Committee's decision was ratified. The Committee noted that XXXXX may have been confused here about the TGA labelling action and the NDPSC rescheduling of sedating antihistamines.

XXXXX provided a post-Meeting comment in which it addressed two assertions from the February 2008 Record of Reasons (RoR) and stated that sedating antihistamines in children <2 should remain Schedule 3 substances. The following points were made:

- With regard to the assertion that non-phenothiazine sedating antihistamines lack efficacy, XXXXX outlined a number of comments the Committee made, particularly "The Committee agreed… that there was a lack of evidence for efficacy of the products, many of which were combination products containing sedating antihistamines…" XXXXX asserted that this statement implied that there was evidence that these products lacked benefit. XXXXX stated that it could find no supporting information for this claim. It was also asserted that the background information in the Record of Reasons discredited this by claiming that there was a lack of good data, most likely due to the long term availability of the products and the difficulties in conducting research in children <2.
- Further support for XXXXX assertion was provided in the form of a quote from the Consumer Health Care Products Association to the USFDA which stated "… several smaller placebo controlled studies in children had not shown significant differences in favour of cough and cold medicines, possibly because of the difficulty in evaluating the symptoms of a cold in this young age group." XXXXX stated that it would welcome research into this issue, but felt that on its own is not a reason for rescheduling. It was further stated that before any regulatory action was taken robust evidence should be required which supported the action.

- It was stated that a number of comments had been received from pharmacists expressing concern that products which have been used safely would no longer be available to the community.
- Additionally, XXXXX focussed on the assertion made by the Committee that the side effect profile of sedating antihistamines merited further investigation. It was agreed that under the NDPSC Guidelines, Schedule 4 is an appropriate place for substances which have a side effect profile requiring further investigation. However, it was asserted that the side effect profile of non-phenothiazine sedating antihistamines did not require further examination. The Record of Reasons was pointed to as stating that there was little evidence of morbidity and mortality with these substances in children <2 and that these events generally occurred at doses significantly higher than recommended. It was stated that this was also the experience of pharmacists and healthcare providers. XXXXX contended that the ADR profile for these substances was well known and there was no new pattern of adverse events emerging that requires investigation. Thus, XXXXX felt that it was difficult to conclude that the ADR profile of these substances warranted further investigation.
- The adverse event data from the United States (US) was discussed and it was stated that the side effects experienced in the US were mainly due the fact that these substances are unregulated. XXXXX. It was stated that this demonstrated the importance of the role of a pharmacist in counselling consumers on the correct use of such substances.
- Information was also provided on the impact of moving these substances to Schedule 4. It was stated that scheduling substances differently based on age was a relatively infrequent action in Australia and had the potential to cause great confusion for healthcare providers and consumers. Concerns were raised that consumers may provide false information regarding their child's age in order to obtain the medicine and that this may lead to overdoses and adverse events due to inappropriate dosing information being given.
- It was contended that placing non-phenothiazine sedating antihistamines in Schedule 4 sent a confusing message in light of the recent TGA advisory regarding the use of all cough and cold medicines in children <2. XXXXX felt that members of the public who receive doctor's prescriptions for these substances and thus believed they were appropriate for their child, may place undue pressure on pharmacists who were now uncomfortable with dispensing the medicines to supply them.
- It was clearly stated that the decision by the NDPSC was a vote of no confidence in pharmacists' ability to exercise professional judgement. It was strongly felt that pharmacist were qualified to recognise contraindications and which medicines were inappropriate for patients and were responsible in undertaking this duty. It was also stated that, due to the long history of supply of these substances by pharmacists, they may be in a better position to advise on and supply them than a doctor who is relatively inexperienced in their use.

- XXXXX also commented on the statement from the RoR regarding the under reporting of ADRs. It was asserted that pharmacists were well positioned to discuss ADRs with consumers and to refer them for medical assessment if required. Pharmacists were also well placed to report any such reactions. XXXXX noted that ADRAC reporting was dependant on the patient consulting a healthcare professional rather than regulation of supply of substances.
- XXXXX also stated its concern about the confusion surrounding the simultaneous release of the NDPSC and TGA decisions on sedating antihistamines and cough and cold preparations respectively. XXXXX believed that a more open dialogue between government, professional bodies and industry may have averted this.

The Committee noted that there were no other submissions received on this issue, however it was noted that in the media articles (Canberra Times and Sydney Morning Herald) reporting on the Committee's decision, the Royal Australian College of Physicians and Dr Colin Robertson, Director of Respiratory Medicine at the Royal Children's Hospital in Melbourne, stated their agreement with the Committee's decision to include these substances in Schedule 4.

DISCUSSION – RELEVANT MATTERS UNDER 52E

A Member stated, in reference to the comment made by XXXXX, that in making its decision at the February 2008 meeting the Committee had followed due process. That is to say the Committee had looked at the overall balance of risks and benefits of the use of these substances in children <2 and felt that the lack of evidence of benefit was outweighed by the potential for risk to the patients.

A Member stated that the post meeting comments presented no new evidence and that the points raised had been considered in full by the Committee at previous Meetings.

The Committee discussed the evidence available pertaining to the efficacy in children <2 years of age. The Committee agreed that there was a definite lack of evidence of efficacy available in this age group and that there was also a lack of clinical trials (including dose-finding studies) conducted on this age group. A Member stated that the doses recommended for children had been extrapolated from adult data and thus, the argument put forward that pharmacists would be best able to advise on appropriate dosing was not derived from evidence of efficacy.

A Member stated that, given this lack of data and risk/ benefit profile, the level of oversight for use of the substances was such that a medical practitioners intervention was required. Concern was raised that this may lead to undue pressure on doctors to prescribe the substances. It was pointed out that upscheduling these substances to Prescription Only does not oblige medical practitioners to prescribe them.

The Committee discussed why the cut-off was made at 2 years of age. Members recalled that data presented to the February 2008 Meeting indicated that the distribution of ADR

data showed that the majority of ADRs for these substances occurred in children <2 years of age.

A Member pointed to the fact that medical practitioners were unfamiliar with products containing sedating antihistamines. The Member suggested that there was a risk that parents might administer OTC products to their <2 year old children and guess the dose. Another Member thought it was unlikely that parents would do so, given the label would specifically instruct them not to. Further, even if some parents were to do so, this was not a useful argument against upscheduling.

Members agreed that it was a valid criticism that the simultaneous release of information about the NDPSC decision and the TGA action on labelling of cough and cold preparations was confusing to both industry and consumers. Members further agreed that this information should have been clarified to lessen confusion experienced by industry and consumers.

The Committee agreed that there had been no new evidence on safety or efficacy of these substances submitted to it that would cause it to amend the decision it made at its February 2008 Meeting.

RESOLUTION 2008/53 - 23

The Committee confirmed the February 2008 NDPSC decision (2008/52-20).

10.2 FLUORIDES

PURPOSE

The Committee considered post-meeting comment on the February 2008 NDPSC Resolution (2008/52-2, scheduling of fluorides).

BACKGROUND

The June 2007 NDPSC Meeting established a Fluorides Working Party (FWP) to review the fluoride scheduling framework. The October 2007 NDPSC Meeting noted FWP progress, including a number of proposals that the Committee agreed should be considered at the February 2008 NDPSC Meeting (including a proposal for a general exemption for "supply of fluoride for human use to a dental professional").

The February 2008 NDPSC Meeting decided:

<u>General</u>

- To confirm that Schedule 4 was the fluoride parent entry for all human use.
- To confirm the ≤ 15 mg/kg fluoride ion general exemption. A proposed general exemption for fluoride supply for human use to a dental professional was not supported.

Ingestion

- To reduce the Schedule 4 to Schedule 2 cut-off for preparations for ingestion (i.e. fluoride supplements) to ≤ 0.5 mg fluoride ion per dosage unit.

Liquid

- To capture liquid preparations for topical use in Schedule 4 unless:
  - ≤ 220 mg/kg, in packs containing ≤ 120 mg total fluoride, fitted with a child-resistant closure (CRC) and labelled:
    - according to the *Required Advisory Statements for Medicine Labels* (RASML) when for therapeutic use; or
    - with warning statements to the effect of "Do not swallow" and "Do not use in children 6 years of age or less" when for non therapeutic use,

    which will be exempt from scheduling.
  - ≤ 1000 mg/kg, fitted with a CRC and labelled as above, which will be Schedule 2 unless exempted above.
  - ≤ 5500 mg/kg, fitted with a CRC, which will be Schedule 3 unless exempted above or captured by Schedule 2.

Non-liquid

- To capture non-liquid preparations for topical use in Schedule 4 unless:
  - ≤ 1000 mg/kg, which will be exempt from scheduling;
  - > 1000 mg/kg and ≤ 1500 mg/kg, which will also be exempt when labelled:
    - according to the RASML when for therapeutic use; or
    - with warning statements to the effect of "Do not swallow" and "Do not use in children 6 years of age or less" when not in a therapeutic product.
  - ≤ 5500 mg/kg, which will be Schedule 3 unless exempted above.

- The Committee also decided to simplify the various schedule entries (including use of the expression "when included in or expressly excluded from").

DISCUSSION - SUBMISSIONS

Post-meeting comment was received from XXXXX and XXXXX:

XXXXX

- Generally supported the February 2008 decision but was concerned that the proposed dental professional exemption was not agreed to. As a consequence a range of high fluoride topical products (> 5500mg/kg), currently Schedule 3 and used exclusively by dentists for in-surgery treatments, will move to Schedule 4.
- Recalled XXXXX pre-February 2008 position that support for a change to the cut-off for topical fluoride from ≤ 2.5 per cent in Schedule 2 to a proposed Schedule 3 / 4 cut-off of 5500 mg/kg (≤ 1000 ppm liquids in Schedule 2 or exempt and ≤ 1500 ppm solids exempt – with conditions) was on the assumption that the dental professionals

exemption would be supported (i.e. would enable high fluoride professional in-surgery products with > 5500mg/kg to be exempt from the parent Schedule 4 entry).

- The February 2008 Record of Reasons suggested that the Committee did not support the exemption due to concerns over the lack of uniformity of the definition of dental professional, which may encourage inappropriate access, and that exemptions could be addressed by the jurisdictions.
- XXXXX asserted the only non-surgery use of these > 5500mg/kg products would be when used in remote community dental health programs.
- Advised that XXXXX has XXXXX affected therapeutic products XXXXX These products have been supplied in Australia as non-prescription since XXXXX. Over that time these products have only been supplied to the dentist via the dental distribution channel, and there was no indication that these have been inappropriately accessed.
- Advised that XXXXX was not a prescription medicines XXXXX and the regulatory costs of moving these products from non-prescription to prescription were significant. XXXXX asserted that XXXXX would need to seriously re-evaluate supply of these products. XXXXX also had new in-surgery products that XXXXX is considering introducing, that would be unlikely to be supplied in light of up scheduling to Schedule 4.
- XXXXX sought the Committee's reconsideration of some form of exemption for fluoride products > 5500mg/kg when used for in-surgery patient treatments by a dentist. Confining the scheduling exemption to high fluoride products used in-surgery under the direction of a dentist should address the concerns expressed by the Committee and not add significant additional costs to supply these to the profession.
- A suggested exemption from scheduling could be:

  "Non-liquid and liquid preparations containing 5500 mg/kg or more of fluoride ion, when supplied to dentists for in-surgery patient use".

XXXXX

- XXXXX advised that XXXXX shared the concern of a colleague (working with XXXXX) that certain companies may withdraw from supplying high fluoride XXXXX (varnish) and like products. If this were to occur the public sector would need to find a “preferred” provider (or in fact become a “purchaser” itself for these useful products).
- Was uncertain of the consequences for seeking an “exemption” as they were “in-surgery” only products. Investigations were underway into how varnish products may be used effectively in “out-reach” preventive programs (e.g. in schools or pre-schools) which were always by authorised oral health providers, but not necessarily within a “dental surgery”.

XXXXX

- According to the February 2008 Record of Reasons all pre-meeting comments which commented on the professional exemption were supportive. In addition, all those that specifically commented on the up-scheduling of > 5500 mg/kg to Schedule 4 stated that support was provided conditional on a dental professional exemption.
- The products most affected by the changes will be those which are used by dental professionals (e.g. fluoride treatments and high fluoride pastes).
- The February 2008 Record of Reasons did not include any discussion of an increased risk associated with the use of high fluoride products by dental professionals to support the up-scheduling to Schedule 4.
- By not providing a dental professional exemption these products will be regulated as prescription products rather than OTC (as Schedule 2 or 3). As a result of this increased burden of regulatory compliance there was:
  - Potential of loss of these products due to the withdrawal because of the increased burden (i.e. documentation and fees required to supply a prescription medicine).
  - Potential for increases in prices to cover the increased regulatory burden.
  - Potential to minimise (or eliminate) new products as the data requirements, cost of submission preparation and the TGA fees for a submission would increase.
- Given the adverse impact that the proposed changes will have on the dental industry, dental professionals and ultimately patients/ consumers, XXXXX asked that either:
  - *the Committee implement Resolution 2008/52-2 with an additional exemption for* supply to dental professionals; or
  - the Committee modify Resolution 2008/52-2 to reinstate the current Schedule 2 and Schedule 3 cut-off limits in products for supply to dental professionals:
    Liquids
    - Schedule 2: Preparations for topical use containing 1000 – 25,000 mg/kg for supply to dental professionals, except when included in Schedule 3.
    - Schedule 3: Preparations that are dental hygiene, whitening or bleaching products containing > 5500 mg/kg fluoride ion for supply to dental professionals.

    Non-liquids
    - Schedule 3: In preparations containing > 5500 mg/kg for supply to dental professionals.
- XXXXX asserted that the above modifications would allow dental professionals to continue to have access to fluoride products with > 5500 mg/kg.

XXXXX

- Supported the amendments but was concerned that dental professional use was not exempted. A small group of high fluoride topical products are currently supplied to dental professionals as Schedule 2 which would be up-scheduled to Schedule 4.
- Given the limited and controlled supply chain, XXXXX did not believe that the risk posed by these products warranted up-scheduling to Schedule 4 and the consequential compliance costs and licences that would be required.

- Indications from some companies show that up-scheduling would potentially reduce dental professionals' access as companies reconsider supply due to cost and administration of new compliance measures.
- Noted the February 2008 NDPSC Meeting's concern that the definition of dental professional was not uniform and this might encourage inappropriate access. Taking on board this concern, but recognising the need for continued supply to the dental profession, XXXXX suggested the following exemption from scheduling to address the concerns raised: "Non-liquid and Liquid preparations containing fluoride, when supplied to dentists for in-surgery patient use".

The FWP had also examined the above comments and the proposed resolutions. The Committee particularly noted the following comments:

XXXXX

- Noted industry's reluctance to have their products moved from OTC to prescription status, with associated costs and possible consequential withdrawal of useful products.
- Noted the issue of defining "dental professional" to accommodate use of high-fluoride topical products by appropriately qualified/trained/supervised workers in dental surgeries.
- Noted the need for these products to be used in remote community dental health programs, school/preschool health programs, nursing homes etc by persons with no dental qualifications e.g., Environmental Health Workers, RNs and GPs.
- Asserted that even if products supplied to dentists (a term that, unlike "dental professional" did not need definition) was exempt, either through individual schedule entries or with a new entry in Appendix A, the use of these products outside dental surgeries would not be catered for. [Member's recalled the Committee's previous position that specific exemptions through schedule entries were preferable to an Appendix A entry – see below.]
- However, it may be that the jurisdictions could allow these activities to take place under a dentist's supervision, whether through something like a standing order (or, in Queensland, "Drug Therapy Protocols") or the dentist's direct personal supervision throughout the treatment. If the exemptions were limited to supply to dentists and not further narrowed by a condition that specified use in surgery, this would mean that dentists would be able to obtain the products, use them in their surgeries and supply them, taking responsibility for their use by others, in accordance with whatever requirements are imposed by State/Territory legislation. While not ideal, in that other trained dental workers such as dental hygienists would be subject to a dentist's supervision, this approach may solve the problems.

XXXXX

- Supported the proposed resolutions. However, the Member could not see a way forward in resolving XXXXX concerns.

- It would be reasonable to make the high strength products available to "dental professionals" as this was supported by the dental bodies as a good public health measure, particularly in remote areas. However, for XXXXX to make regulation changes to allow this would require a definition of the appropriate groups (especially since only some "dental professionals" may be registered).
- Had concerns at high strength products being available only labelled "for in-surgery use" or similar with no restrictions on supply (e.g. some beauty operations already conduct teeth whitening procedures and may be interested in taking up varnishing).
- Understood the reluctance of companies to meet more stringent registration requirements with substantial fees.
- Noted that an exemption for "dentists" would not allow for use by "dental professionals" and nurses who might appropriately apply treatments, particularly in remote areas. Would welcome further discussion on this issue.

Members also recalled the following points from the February 2008 NDPSC Minutes regarding an exemption for dental professionals:

FWP

- A meeting of the Fluorides Working Party (FWP) prior to the February 2008 NDPSC Meeting noted that, in addition to discussing the various proposals arising from the October 2007 NDSPC Meeting (which included a proposed general exemption for dental professionals), the pre-meeting comments suggested some additional proposals including:
  - Broadening the proposed general dental professionals exemption to apply to all health workers, particularly to address concerns over access to topical varnishes for use in rural and remote dental programs. The preferred professionally applied fluoride for prevention in high risk infants, children, adolescents and adults were the high fluoride rapidly setting varnishes (e.g. XXXXX varnish, 22,600 ppm, 10 mL). The FWP generally agreed that an exemption for all health workers was inappropriate, but agreed that a specific exemption for use of varnishes for rural and remote dental programs was a proposal worth considering. Alternatively, a FWP Member suggested that there were existing State and Territory mechanisms for remote/rural access to scheduled therapeutic substances that could address any such access issues.

Pre-meeting comments

- XXXXX supported including a dental professional exemption.
- XXXXX queried what an exemption for dental devices for supply to dental professionals included. The most difficult issue was that of fluoride varnishes. International literature (and Australian experience, especially remote Indigenous communities) indicated that non-dental health professionals and health workers with little training could effectively apply fluoride varnish and that this had reasonable efficacy in children down to 18 months of age. No adverse health effects had been

reported. Registered nurses may wish to apply varnish in residential care facilities. The use of such products by 'professionals' who are not dental professionals may therefore need to be accommodated.

- XXXXX asserted that the proposed exemption for professional use would jeopardise a potential preventive strategy for disadvantaged children if the definition was limited to dental clinicians (dentists, dental therapists and dental hygienists). Current work in remote communities aimed to train GP's, Aboriginal health workers etc. to apply varnish to children at high risk of caries. This built on US work where non-dental health professionals successfully applied varnish to disadvantaged children.
- XXXXX and XXXXX all supported the proposed specific exemption for supply to dental professionals. XXXXX also asserted that these products were already registered therapeutic products and as such were controlled by the TGA's labelling requirements i.e. there was no need for additional scheduling requirements.

The October 2007 NDPSC discussion

- The evaluator recommended creation of an Appendix A exemption for dental devices for supply to dental professionals.
- A Member queried what difference it would make to a dentist whether a product was scheduled or not, given that scheduled substances were already in use by dentists. Another Member indicated that there would be labelling and supply issues, and that there would be the question of use by dental professionals who were not dentists (i.e. recognised dental auxiliaries such as dental hygienists). There was also a question as to why an exemption should be limited to dental devices, and who would determine what was, or was not, a dental device.
- The FWP and Committee agreed that the option for consideration in February 2008 should be consideration of a specific exemption from the fluoride schedule entries when for use by a dental professional, rather than a broad Appendix A listing.
- The evaluator noted that the acute oral toxic dose is ~5 mg/kg bw – an oral toxic dose of 350 mg for a 70 kg adult and 100 mg for a 20 kg infant. The Schedule 2 entry at that time included preparations containing up to 2.5 per cent fluoride (25000 mg/kg). In the form of a mouth wash such a preparation, if swallowed, would deliver a toxic dose in 14 mL for an adult and 4 mL for a small child. The evaluator asserted that 2.5 per cent fluoride was clearly too high, a child's single swallow should not deliver a toxic dose from a Schedule 2 product.
- The FWP noted the evaluator's recommendation to reduce the 2.5 per cent topical use cut-off to 1000 ppm. The Committee agreed that this was an option for consideration. A Member noted that the 2.5 per cent topical use cut-off may have existed due to use by dental professionals of high strength fluoride liquids.
- The evaluator recommended that products containing fluoride > 5500 mg/kg should only be available for dental professionals for use in dental surgeries. These products include fluoride gels, foams and varnishes. They contain from 9000 to 22,600 mg/kg.

The February 2008 NDPSC discussion

- A Member provided departmental advice that the use of "dental professional" would be problematic and noted that jurisdictions already had alternatives to address access issues such as varnishes being used in remote areas.
- Another Member noted that the jurisdictional controls on high strength products could be undermined by the proposed exemption for "dental professionals", particularly as the definition of "dental professional" was not uniform and this might encourage inappropriate access e.g. through the internet. The Committee agreed to no scheduling exemption for "dental professionals" (including no specific exemption for varnishes) at this time, as any need for such exemptions could be addressed by the Jurisdictions through their alternative mechanisms.

A Member has also referred an article from the January 2008 issue of Scientific American (*Second Thoughts about Fluoride*, Fagin, p58-65) for the information of Members. The Committee particularly noted the following:

- Some recent studies suggest that over consumption of fluoride could raise the risks of disorders affecting teeth, bones, the brain and the thyroid gland.
- A 2006 US National Research Council (NRC) report concluded that the US EPA's current limit for fluoride in drinking water (4 mg/L) should be lowered because of health risks to both children and adults.
- While most fluoridated water contained much less fluoride than the EPA limit, the article asserted that the situation was worrisome because of uncertainty over how much additional fluoride was ingested from food, beverages and dental products.
- The NRC report noted that, while certain effects (bone cancer and damage to the brain and thyroid gland) were still unproved, they deserved further study.
- The article asserted that, despite all the uncertainties, some fluoride researchers had come to the view that some children, especially very young ones, were probably getting more fluoride than they should. Most of these scientists still supported water fluoridation as a proved method of controlling tooth decay, especially in populations where oral hygiene was poor. However, in communities with good dental care the case for fluoridation was not as strong as it use to be.
- There was no universally accepted optimal level for daily intake of fluoride but the range most often cited by researchers was 0.05 to 0.07 mg/kg bw/d.
- Asserted that epidemiological studies and tests on lab animals suggested that high fluoride exposure increased the risk of bone fracture, especially in vulnerable populations such as the elderly and diabetics.
- Asserted that the biggest current debate was over osteosarcoma. Because fluoride stimulates the production of osteoblasts, several researchers had suggested that it might induce malignant tumours. However, most epidemiological studies in human populations have been ambiguous at best.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The relevant matters under section 52E (1), to this item, included: (a) toxicity and safety; (b) risks and benefits; (c) potential hazards; (d) extent and patterns of use; and (f) need for access.

The Committee noted that, apart from the issue of a professional use exemption, there were no objections in the post-meeting comments to the decision reached by the February 2008 NDPSC Meeting on the scheduling of fluorides. A Member, however, remained concerned about increasing the scheduling exemption for toothpastes from 1000 ppm to 1500 ppm. The Member argued that there was no need in the general community for these higher strength toothpaste as:

- Widespread water fluoridation in Australia and the associated halo effect (fluoride from water supplies also being incorporated into food and beverages) meant that the general public was already receiving significant amounts of fluoride.
- 1500 ppm toothpastes were available in Europe, but water in Europe was not generally fluoridated.
- Unnecessary increases in fluoride use could lead to increases in fluorosis, particularly for children.
- Was concerned that sole reliance on a label against use in children would be ineffective without the additional need to purchase from a pharmacy. Asserted that 1000 ppm < toothpastes ≤ 1500 ppm should be Schedule 3 products so that pharmacist advise could combat any public perception that increased fluoride equated with a "better" product.
- Legitimate access by particular at-risk groups, such as the elderly, would still be provided for by Schedule 3.

The Member's concerns were duly noted by the rest of the Committee.

The Committee, however, continued to support the general supply of 1000 ppm < toothpastes ≤ 1500 ppm as it had concluded that mandatory labelling was sufficient to address the fluorosis risk, noting that the above issues were diligently reviewed by the February 2008 NDPSC Meeting. A Member also recalled advice to the February 2008 NDPSC Meeting that concerns regarding use of toothpaste by children leading to fluorosis appeared to have also been addressed by the segmentation of the toothpaste market, with 70–80 per cent of pre-school children using a low fluoride children's toothpaste. Members therefore confirmed the February 2008 resolution to allow an exemption for toothpastes containing ≤ 1500 ppm fluoride (with certain labelling requirements). Members did, however, agree that the Committee could keep an eye on toothpaste strengths (particularly for use by children) and that the issue could be reconsidered should a problem emerge.

A Member noted that the February 2008 decision to not support a professional use exemption was a deliberate move in response to the toxicity risk arising from high concentration products. The Committee noted, however, that there had been no identified increased risk associated with the use of high fluoride products by dental professionals that might warrant an up-scheduling to Schedule 4. Members also noted that there was no indication of distribution or diversion outside the established supply chains to dental professionals. The Committee therefore agreed that a professional use exemption would be appropriate. Members further agreed that it would be logical for this exemption to apply to all strengths of fluoride products, not just the high strengths (>5500 ppm) requested by some post-meeting comments.

Members therefore considered various possible professional use exemptions. There was general agreement that restricting an exemption to "for in-surgery use" was not appropriate as use pattern should be a matter of profession practice. A Member suggested that an exemption for either "dental professionals" or "dentists" may suffice. However, the February 2008 NDPSC Meeting's concern that "dental professionals" would be too broad was reiterated, while a Member noted that registered dental hygienists/therapists should also qualify for the exemption but would not if it was restricted to "dentists". The Committee therefore agreed that "supplied to registered dental professionals" would appropriately identify those dental health workers who should qualify for the exemption.

The Committee also noted, however, that an exemption for supply to "registered dental professionals" would not apply to RANs, GPs or health workers associated with dental health programs (particularly in remote areas). While this could be addressed through mechanisms available within individual States and Territories (as was the February 2008 NDPSC Meetings position) the Committee generally agreed that a scheduling exemption should also be considered. A Member noted that such programs (to apply high strength varnishes) were already operating in the community with no particular problems or issues. A Member suggested, and the Committee agreed, that adding "by approval of an appropriate authority" to the exemption would provide the desired flexibility to allow jurisdictions to approve access by dental health programs (noting the definition of "appropriate authority" in the SUSDP), particularly in rural and remote areas, without the need to comply with Schedule 4 controls.

RESOLUTION 2008/53 – 24 (Variation to Resolution 2008/52-2)

The Committee decided to vary the Schedule 2 and Schedule 3 fluoride amendments from the February 2008 NDPSC Resolution (2008/52-2) by exempting fluoride preparations for human use when "supplied to registered dental professionals or by approval of an appropriate authority".

Schedule 2 - Amendment

FLUORIDES – Amend entry to read:

FLUORIDES for human use:

(a) in preparations for ingestion containing 0.5 mg or less of fluoride ion per dosage unit; or

(b) in liquid preparations for topical use containing 1000 mg/kg or less of fluoride ion, in a container with a child-resistant closure:

(i) for therapeutic use when compliant with the requirements of the *Required Advisory Statements for Medicine Labels* **except** in preparations containing 220 mg/kg or less of fluoride ion, in packs containing not more than 120 mg total fluoride when fitted with a child-resistant closure and compliant with the requirements of the *Required Advisory Statements for Medicine Labels*; or

(ii) for non-therapeutic use when labelled with warnings to the following effect:

(A) Do not swallow; and

(B) Do not use [this product/name of product] in children six years of age or less,

except in preparations containing 220 mg/kg or less of fluoride ion, in packs containing not more than 120 mg total fluoride, when fitted with a child-resistant closure and labelled with warnings to the following effect:

(A) Do not swallow; and

(B) Do not use [this product/name of product] in children six years of age or less,

except in preparations containing 15 mg/kg or less of fluoride ion or preparations supplied to registered dental professionals or by approval of an appropriate authority.

Schedule 3 - Amendment

FLUORIDES – Amend entry to read:

FLUORIDES for human topical use:

(a) in liquid preparations containing 5500 mg/kg or less of fluoride ion, in a container with a child-resistant closure **except** when included in or expressly excluded from Schedule 2; or

(b) in non-liquid preparations containing 5500 mg/kg or less of fluoride ion **except**:

(i) in preparations for therapeutic use containing 1500 mg/kg or less of fluoride ion and, when containing more than 1000 mg/kg fluoride ion, compliant with the requirements of the *Required Advisory Statements for Medicine Labels*;

(ii) in preparations for non-therapeutic use containing 1500 mg/kg or less of fluoride ion and, when containing more than 1000 mg/kg fluoride ion, labelled with warnings to the following effect:

(A) Do not swallow; and

(B) Do not use [this product/name of product] in children six years of age or less; or

(iii) in preparations supplied to registered dental professionals or by approval of an appropriate authority.

11. OTHER OUTSTANDING MATTERS FROM PREVIOUS MEETING

11.1 CODEINE AND IBUPROFEN COMBINATIONS

PURPOSE

The Committee considered the scheduling of codeine and ibuprofen combinations.

BACKGROUND

At its June 2005 Meeting, the Committee first discussed the scheduling of codeine and ibuprofen, after a member of the public raised concerns about the bi-layer tablet which was reportedly being cut in half by addicts in order to easily access the codeine component. Given that the product was reformulated at that time, the Committee agreed that concerns of abuse had been resolved.

At the June 2007 NDPSC Meeting, a jurisdictional representative Member informed the Committee that pharmacists had again raised concerns about the apparent increasing incidence of abuse of codeine and ibuprofen tablets. It was understood that codeine in these products could be easily separated from ibuprofen simply by dissolution in water. XXXXX.

The Committee then considered the scheduling of this combination at the February 2008 Meeting, however the results of the XXXXX investigation into dissolution of the combination were not yet available. Thus, the Committee agreed to foreshadow consideration for the June 2008 Meeting as this would give time for the testing to be completed and results received. The Committee also agreed to garner information regarding the prevalence of abuse of these combinations from a number of different experts and drug and alcohol information centres.

The current definition of 'compounded' was derived from Article 3 of the International Convention on Psychotropic Substances: "... compounded in such a way that it presents no, or a negligible, risk of abuse and the substance cannot be recovered by readily applicable means in a quantity liable to abuse, so that the preparation does not give rise to a public health and social problem." The inclusion of a definition of 'compounded' was first agreed at the August 1991 DPSSC meeting.

There are currently 2 codeine and ibuprofen combination analgesics included on the Australian Register of Therapeutic Goods (ARTG).

DISCUSSION - SUBMISSIONS

The current SUSDP definition of 'compounded' is as follows: "in relation to a substance means combined with one or more other therapeutically active substances in such a way that it cannot be separated from them by simple dissolution or other simple physical means". The Committee recalled that the original concern brought to their attention regarding codeine and ibuprofen combination products was whether or not they fit this definition, particularly in relation to the term 'simple dissolution'.

The Committee recalled the following from the February 2008 Meeting:

- A Minute received from XXXXX detailed their correspondence with XXXXX on the issues of dissolution of the combination and reports of abuse with the product.
- In response to the correspondence, it was asserted that codeine phosphate had substantially higher solubility in water than any of the analgesic actives with which it was combined and therefore it would always start to dissolve more quickly than the other active ingredients. It was claimed that if the formulation were to be altered to change this, it could jeopardise the ability to meet the dissolution requirements of both active ingredients, potentially compromising the efficacy of the product.
- With regards to the question of abuse, data was provided which indicated that the number of adverse event reports and the reporting incidence for codeine and

ibuprofen products was less than that for paracetamol/codeine products. The report stated that there was no clear evidence available to indicate that there was a regulatory failure leading to compromised consumer safety of this product.

- A submission was received from XXXXX detailing anecdotal reports received from pharmacists of patients buying large amounts of codeine and ibuprofen combinations.
- The Committee noted that there had been a case report of abuse of codeine and ibuprofen combinations published in the Medical Journal of Australia and that a report of adverse events related to abuse had been received by ADRAC.
- As the dissolution testing had not been finalised by XXXXX and in order to allow time for further information on abuse patterns to be garnered, the Committee agreed to foreshadow consideration of this combination for the June 2008 Meeting.

The December 2007 MCC meeting considered a recommendation from Medsafe about whether it was appropriate for combination codeine products containing more than 30mg codeine in unlimited pack sizes to be available as pharmacy only medicines. It was noted that Medsafe had provided some suggestions regarding pack size limits in order to harmonise more closely with Australia on access to this substance. It was suggested that all codeine combinations containing 12 mg or less codeine (Pharmacy Only) be limited to packs of 50 dosage units or less and for combinations containing more than 12 mg and up to 30 mg codeine (Restricted) that the pack size be limited to 12 dosage units. The MCC deferred further consideration of this matter to its 39th Meeting.

A Minute was received from XXXXX detailing the results of dissolution testing of codeine when in combination with ibuprofen or paracetamol or aspirin. The following results were found:

- Testing of a total of 8 products was conducted, 3 paracetamol/ codeine, 3 aspirin/ codeine and XXXXX 2 XXXXX codeine and ibuprofen preparations. Testing was carried out in 250mL water at ambient temperature (21 – 23°C) using paddles to stir the solution. Samples were taken at 5, 10, 15 and 30 minutes and were analysed by HPLC.
- Analysis of samples showed that the dissolution of paracetamol was relatively similar to that of codeine and there was no significant difference between the amount of paracetamol and codeine released. Aspirin/ codeine combinations showed a greater disparity between products (due to differences in formulation), however the dissolution profile of aspirin was still such that the bulk of it was dissolved at a similar rate to the codeine except in the one product.
- The two codeine and ibuprofen products showed similar dissolution profiles, with 10 per cent of ibuprofen dissolving after 5 minutes compared with 80-90 per cent of the codeine component. It was stated that this was not unexpected, given the relative solubilities of the two substances.
- The three paracetamol/ codeine combinations were also subjected to a low temperature separation (‘codeine enrichment’) procedure that was sourced from an

internet site. The results of this separation technique showed that a ratio of paracetamol: codeine extraction of between 4 and 5:1 (i.e., 4 to 5mg of paracetamol extracted for every 1mg codeine).

- It was concluded that, while codeine phosphate was much more soluble than other analgesics at room temperature, in terms of absolute dissolution under the conditions of this study, paracetamol and aspirin still had sufficient solubility for the bulk of the active to dissolve.
- Regarding ibuprofen, it was concluded that it was very easily separated from codeine by dissolution in water at room temperature, with only 10 per cent of the ibuprofen dissolving compared with approximately 90 per cent of the codeine. It was noted that this difference in dissolution profiles could further be manipulated by lowering the pH of the dissolution medium as ibuprofen has a very low solubility below pH 6.
- For the low temperature extraction method it was stated that, as the original ratio of paracetamol to codeine in tablets is generally between 30 and 50mg paracetamol to 1mg codeine, the extraction of 4 to 5mg of paracetamol to 1mg of codeine represents a 10-fold increase in the relative concentration of codeine.
- Overall, it was stated that water extraction of codeine from codeine and ibuprofen combination tablets was a practical method of obtaining codeine, but that this method was less feasible for paracetamol or aspirin/ codeine combinations.

Further information was obtained regarding the methods used in the above dissolution testing. It was stated that the testing was carried out using standard pharmacopeial dissolution testing methods, however, the conditions used (volume and temperature of water and sampling times) were designed to emulate the most likely conditions that members of the public would use to extract codeine. It was further noted that there are no current BP dissolution requirements for codeine/ analgesic combination tablets and codeine and ibuprofen tablets do not have a USP monograph either.

The Committee noted that there may be alternative methods of creating a product formulation available which can be used to either increase the solubility of the ibuprofen or decrease the solubility of the codeine component in these combination products. For example the codeine component may be able to be chelated to reduce its solubility or the ibuprofen component micronised to increase its.

XXXXX sent a Minute to the NDPSC Secretariat outlining an ADRAC review of serious adverse events XXXXX. The Committee noted that XXXXX was launched mid 2001 and, of the two codeine and ibuprofen combinations, has approximately 80 per cent market share with codeine and ibuprofen combinations. Since this meeting two further, fatal reports had been received and these were the first fatal reports on the ADRU database. These reports were poor in their information and insufficient data was available to draw a certain cause of death. At its meeting XXXXX expressed concern about the apparent misuse of such combinations and also about large pack sizes being for sale over the counter.

Following the February 2008 NDPSC Meeting, all State and Territory Members were asked if they could provide information on the abuse/ misuse of codeine and ibuprofen combinations in their jurisdiction. The following information was obtained:

- SA – provided notice of 3 patients starting treatment under the opioid substitution program (OSP) for codeine addiction. 2 of these patients had been misusing codeine and ibuprofen combinations. The report mentions another 2 patients who had been (or potentially been) taking high doses of this combination product and had developed ADRs. The SA report also refers to the March 2008 Pharmacy Board of SA newsletter which contained a brief article on the increase in the number of patients presenting with perforated ulcers. It was noted that many of these patients had admitted to consuming large amounts of codeine and ibuprofen combinations.
- ACT – no information to report.
- NT – it was stated that this did not seem to be an issue at the present time and there was no data to present.
- WA – stated that there was no source which specifically monitors the abuse of codeine and ibuprofen combinations, noting that the WA Drugs and Alcohol Office only classifies patients addicted to opiates under 'heroin' or 'other opiates'. It was noted, however, that there had been a number of presentations to major teaching hospitals of case reports of GI problems as a result of excessive intake of this combination. An outline of two of these cases was provided, with both of these patients taking approx 50 Codeine and ibuprofen tablets/ day. It was also stated that the Pharmaceutical Services Branch of WA Health was aware of another patient who had started on a program to deal with codeine dependence after they had been taking up to 75 Codeine and ibuprofen tablets/ day. It was contended that, if this patient had chosen to obtain their codeine via a codeine/ paracetamol combination, the outcome may have been fatal. The WA Member suggested that, as the problem was with the codeine part of the combination causing dependence and, thus, overuse, the Committee really should look at the inappropriate use of all codeine combination products as focusing on codeine and ibuprofen combinations alone may give an unbalanced view of the issue.
- Further information was provided from Next Step, the WA government addiction treatment service. This included a case report of a patient taking up to 72 tablets/ day for an 18 month period who had been diagnosed with multiple gastric erosions. Patient was detox'd and commenced on buprenorphine. The Next Step doctors commented that they felt they were only seeing the tip of the iceberg relating to dependency on OTC codeine analgesics and provided information about the behaviours they see with their patients, including that ingestion of 40 or more tablets/ day is not unusual and that, generally, such patients did not attempt to separate the codeine from the other analgesic agent.
- VIC – provided a number of case studies referred to the Victorian Department of Human Services by an addiction medicine specialist working with a network of 6 public hospitals in greater Melbourne. Over an 18 month period there were 23 cases

of the abuse of codeine and ibuprofen combinations reported. A breakdown of age and gender are provided. It was noted that the average intake was 36 tablets/ day and the average duration of use was 3 – 5 years. Out of the 23 patients, 11 GI complications, 4 hypokalemia, 2 renal failure, 2 peripheral oedema and 1 death were recorded. 6 patients recorded no ADRs. 8 patients were initiated on treatment, 7 were lost to follow up and 7 referred back to their primary carer.

- Two reports from the Victorian State Coroner were provided. The first report detailed the subject taking between 48 and 60 codeine and ibuprofen tablets/ day but that with treatment had reduced the number in the months preceding his death. The day prior to death, the patient had increased intake of the tablets and was found deceased the next day. Post-mortem examination found a perforated peptic ulcer with associated peritonitis and 3L of fluid in the abdominal cavity. Acute nephrotic tubular necrosis was also described. The second report involved the death of a patient who had regularly been taking 30 tablets of codeine and ibuprofen a day, but two days prior to death had taken 60 tablets and went to bed. The patient became increasingly unresponsive and was found dead in bed two days later. The coroner determined that the levels of medication in the blood at death did not exceed normal therapeutic use and were not life threatening. The cause of death was not ascertained and it was stated that there was no evidence the self medication had caused death.
- There were also six additional case reports provided by the Victorian Department of Human Services detailing abuse of codeine and ibuprofen combinations and the treatment the patients are receiving for such. All patients were recorded as taking between 20 and 80 codeine and ibuprofen tablets a day.
- NSW – No information provided.
- TAS – provided the results of a telephone interview of pharmacists from 20 of the 130 pharmacies around Tasmania. The results showed 8 pharmacists supported a Schedule 2 and 3 pack size reduction (to 12 and 50 dosage units respectively), 5 pharmacists supported a change to Schedule 3 pack size only, 2 supported removal from Schedule to into Schedule 3 only, 1 supported a change to Schedule 4 and 4 supported no change to the current scheduling. It was also noted that some of the pharmacists surveyed kept the Schedule 2 product behind the counter or only held small packets (24 doses) which were kept in the dispensary. Pharmacists stated they felt that the issue of misuse of codeine and ibuprofen combinations was overtaking that of misuse of codeine/ paracetamol combinations.
- Anecdotally there were no reports forthcoming on codeine and ibuprofen and generic adverse events from Emergency Medicine Departments in the three major public hospitals in Tasmania. It was likely that the databases in these departments were probably inadequate to reliably identify reports at this level of detail.
- A case report was received of a patient being admitted to an opioid treatment program for codeine dependency. The patient had been taking up to 75 codeine and ibuprofen tablets/ day four days a week.

- Information was also provided about 3 circulars sent to pharmacies in Tasmania between November 2007 and May 2008 notifying them of 2 individual patients involved in drug seeking behaviour for codeine and ibuprofen combinations.
- QLD – Provided late information on 6 patients who had been taking between 30 and 80 codeine and ibuprofen tablets/ day. Five of these patients had reported GI related adverse events and a number had gone on to treatment for opioid dependence. A case was also reported of a patient using approximately 70 codeine and ibuprofen tablets/ day and splitting the codeine layer from the ibuprofen layer. The Committee noted that this is likely to be an old report as the bi-layer formulation of codeine and ibuprofen was discontinued in 2005.

A submission was received from XXXXX outlining a review of a series of 23 case studies of patients misusing codeine and ibuprofen combinations. The following points were made:

- It was stated that XXXXX first became aware of a problem with misuse of this combination in 2006-07 after seeing an increase in the number of patients seeking treatment for opioid dependence with the use of this combination. It was noted that a number of these patients were seen on hospital wards after admission for serious GI injuries or electrolyte disturbances. It was further stated that, despite the misuse of codeine containing analgesics being well characterised, the misuse of this combination was novel as it was resulting in serious physical harm (other than due to opioid dependence) to patients.
- Three concerns were mentioned; that codeine was available with an NSAID as an OTC preparation; the relatively high dose of codeine and large pack sizes available may make it particularly attractive to opioid dependent patients and the fact that patients seemed to be easily able to obtain large quantities of the combination from community pharmacies.
- A description of the methodology used in recording the case reports was given. There were 23 cases recorded in an 18 month period with the numbers of male and female patients being equal. Just over half the cases were in patients less than 35 years of age.
- Most patients consumed between 24 and 48 tablets/ day which contains between 307.2 and 614.4mg codeine and 4.8 and 9.6g ibuprofen (4 – 8 times the recommended OTC dose). The highest intake was 72 tablets/ day and duration of use ranged between 6 months and 10 years, with an average of 3 – 5 years.
- 14 patients had no previous history of illicit drug use, 8 had taken cannabis previously, 6 were current users of which 2 were current injecting drug users. It was found that 15 of the patients had started using the combination for its approved indications. Further, it was noted that 11 patients had a history of mental illness.
- There were a range of complications identified from the misuse of this combination, the most common being GI related i.e., bleeds, perforated ulcers etc (11), followed by hypokalemia (4), renal failure (2) and peripheral oedema (2). There was 1 death

recorded. 7 patients recorded no complications other than dependence. These complications were all serious medical emergencies and could all be attributed to use of high doses of ibuprofen.

- It was noted that 8 of the patients had been stabilised on methadone or buprenorphine treatment, 7 declined treatment and the remaining 7 were referred back to their primary carer.
- XXXXX
- It was stated that the description of these case reports indicated that the profile and behaviour of these patients was unlike other illicit drug users in that most patients started taking the combination for its approved indications and then self-escalated to doses above those recommended. It was theorised that this escalation may have occurred due to tolerance to the codeine component and the patient increasing the dose to seek continued pain relief. It was also postulated that, given this, it may not be appropriate to combine an analgesic which may be quite toxic in high doses with an amount of codeine which is sub-therapeutic for moderate pain (the effective treatment of which occurs between 30 and 60mg).
- It was noted that the numbers of tablets taken per day seemed to correlate with pack size. It was stated that the Committee may need to consider reducing pack sizes, especially the 72 dose pack, given the indication is for temporary relief of pain. It was stated that decreasing the pack size would make it more difficult for patients taking large numbers of tablets to obtain these and may also encourage them to seek help.
- It was observed that just under half the case reports identified had a history of mental illness and it was asserted that this was a population group which may have difficulties in self-medicating safely. It was further stated that their illness may expose them to an increased risk of substance addiction. For this patient group, then, it was postulated that ready access to OTC codeine may make it difficult for them to control their medication use without risk.
- It was stated that it was the authors' experience that patients with dependence problems relating to OTC analgesics would be reluctant to disclose or discuss their problems. The author felt thus, that these case reports may represent only the tip of the iceberg with relation to this issue. It was stated that, by raising awareness of this issue with healthcare practitioners a more structured data collection may be able to be developed which may ultimately result in a reduction in the morbidity and mortality associated with misuse of this combination. It was noted currently that there were no other studies in the literature relating to the misuse of this combination.

XXXXX provided a lengthy submission for the consideration of the Committee recommending that codeine and ibuprofen combinations should be rescheduled to Schedule 4 and that pack size should be limited to 18 tablets. The key points of the submission are summarised as follows:

- OTC codeine and ibuprofen combinations have the highest codeine content of any of the OTC codeine combination analgesics (except for XXXXX which was only

available in packs of 12). Codeine was a drug of addiction and OTC codeine had been subject to misuse for many years. Ibuprofen was among the leading ADR causing drugs, even when it is taken at recommended doses.

- As people develop a tolerance to codeine, they would escalate their dose to get the same effect. When codeine was combined with ibuprofen, the amount of ibuprofen ingested was also increased and this, given the dose dependant nature of the gastric toxicity of the substance, can produce serious and life-threatening gastric injury. High levels of ibuprofen ingestion can also lead to anaemia, renal failure and hypokalemia.
- There appeared to be a high prevalence of mental health disorders in substance abuse patients and it was postulated that this may limit their capacity to safely self-medicate with these combination products.
- 77 individual case reports of dependence on OTC codeine and ibuprofen combinations were documented as part of this submission. These cases detailed numerous occurrences of serious and life-threatening injury and one death due to the misuse of this combination. It was stated that these 77 cases may be indicative of a much larger problem which could be better clarified if time and circumstances allowed. The Committee noted that the information presented in these case reports was identified as confidential.
- During the collection of these case reports, many of the practitioners involved described the frequently overwhelming morbidity experienced by the patients that had presented to them. It was stated that if it were not for the interventions instituted by intensive care units or emergency departments, more of these patients would have died due to their misuse of this combination. It was stated that many of the practitioners who had dealt with the case report patients expressed concern that codeine and ibuprofen combinations should continue to be available as an OTC medicine.
- It was stated that it was believed that it was not fair to expect pharmacists to have to identify drug seeking behaviour and thus deny access to such persons. Many of these patients do not fit the stereotypical profile of a drug dependant person with some of them being employed in well regarded occupations and having no previous history of substance abuse. Thus, it would have proven difficult to identify them as drug dependant or exhibiting drug-seeking behaviours. It was noted that in many of the cases the patient started out using codeine and ibuprofen for its registered indication and then escalated their dose to high levels. It was stated that this evidence suggested that this was a hidden population of patients not previously described and that they were not readily identifiable by pharmacists or pharmacy staff.
- It was stated that the current controls on codeine and ibuprofen combinations had failed to control the misuse/ abuse of this combination. It was noted that the average daily dose taken in the 77 case reports was 50 tablets, which equates to more than two packets of 24 tablets/ day and that this level of use was often sustained over a period of months or years. This equates to almost 10g of ibuprofen/ day and far exceeds the recommended daily dose of OTC (1.2 grams) or prescription (2.4 grams) ibuprofen.

- It was maintained that in the US, codeine was not available as an OTC medicine except in some low dose mixtures or linctuses.

XXXXX provided a submission addressing criteria 1(e) dosage and formulation and 1(g) abuse potential of Section 52E of the Act. The following points were made:

- (e) It was stated that a distinction between levels of compounding as a means of separating higher and lower risk medications is not an effective way of discouraging illicit diversion. It was stated that criminals will find more sophisticated ways of extracting the substance and reference was made to the alteration of pseudoephedrine formulations which was done to discourage diversion to methamphetamine production and had little effect.
- (g) It was stated that codeine and ibuprofen combinations provide effective pain relief at an appropriate level of access and that up-scheduling these based on anecdotal evidence would disadvantage the majority of consumers who use these medications legitimately. It was stated that running an education campaign on the correct use and side effects when misused of this combination would be a better approach. It was also stated that such a campaign would help to increase awareness of the problem and also help identify patients who may be affected. It was asserted that restricting access of this combination based on recreational use would only serve to push users to find another substance to abuse.
- It was noted that a similar issue (availability of OTC codeine analgesics) was considered by the UK Committee on the Safety of Medicines in 2005. The recommendation of the committee was that codeine remain available as an OTC combination analgesic, that warning statements be established for product labels and that there be agreement on responsible promotional activities.
- It was asserted that, from the submitter's own sales data of codeine containing OTC analgesics, there was no evidence to suggest any illicit activity surrounding the use of codeine-containing medicines. It was further stated that this was unlike that which was observed with pseudoephedrine.

XXXXX provided a comment in which it opposed the proposed rescheduling of codeine and ibuprofen combinations as there was little documented evidence of the abuse of such. It was further stated that the risk/ benefit profile of the combination had not changed.

XXXXX provided a submission in which it stated that interested parties had not had access to all the relevant information the Committee had considered previously and urged the Committee to take no decision on the scheduling of codeine and ibuprofen combinations until there had been time for all parties to consider this information. The following points were made:

- There was little evidence which had been presented to the Committee so far which would justify the up-scheduling of this combination and, further, there was not enough evidence even to justify further enquiry into the matter. It was contended that this view was supported by the Committee requesting that data on this matter be

obtained and presented to it. It was asserted that until the data foreshadowed in the February Record of Reasons was presented, no scheduling decision should be taken. Concerns were raised about this data which was being sought and whether it would be published and peer-reviewed. It was also asserted that this information would need to be reviewed by interested parties and submissions made on it before any scheduling decision could be taken. To not allow this placed interested parties at a major disadvantage in making full, detailed submissions to the Committee on this issue. It was stated that the Committee should publish all the data presented to it and invite submissions on it before making any decisions. It was stated that, by doing this, the Committee would be adhering to the administrative law principle of hearing all parties (AG v Quin (1990) 170 CLR 1 at 53 (per Dawson J)).

- It was contended that data presented to the Committee in February 2008 showed that the issue of misuse of these combinations was not an urgent problem and that there was not widespread or increasing abuse of such products. It was stated that, even if the Committee did feel that there was an urgent problem, under law it must adhere to the procedures as set out in the *Therapeutic Goods Regulations 1990*. The Committee noted that XXXXX were referring here to the provision under S42ZCB that if the Committee thought this was an urgent matter, they were required to make a scheduling decision on the matter without gazetting beforehand if gazetting is not practicable.
- It was asserted that the February 2008 Record of Reasons did not clearly identify who the Committee members who presented information regarding anecdotal concerns of abuse of codeine and ibuprofen combinations were and what the nature of the information conveyed to them was. It was stated that this anecdotal information provided about the misuse of codeine and ibuprofen combinations had no probative value as there was no information provided as to how the increase in abuse was measured and the data itself was not presented. It was contended that this provided no basis for the Committee to decide the concerns expressed were real. It was stated that the evidence available to industry showed that, while there had been a significant increase in sales of these combinations over the past five years, there had been no increase in the amount of ADRs reported (from their already low levels). A table detailing this was provided. It was stated that the number of ADRs reported was low, especially when considered against the number of doses consumed and that if there was any misuse, it was not showing up or being reported as ADRs.
- It was stated that member companies were contacted to ascertain the extent of addiction problems and that the data provided did not lead one to believe that there was such issue. Mention was made of concerns surrounding a hidden addiction problem, as detailed in a media article considered by the Committee. It was asserted that if there was such a hidden problem it was one that neither police nor health authorities were aware of. It was also contended that the jurisdictional member who raised the issue had no information from their health department colleagues to validate such a claim. The Medical Journal of Australia (MJA) article describing two case reports of ADRs associated with codeine and ibuprofen misuse the Committee considered at its February Meeting was discussed and it was asserted that, rather than

showing evidence of widespread abuse, the article actually showed the limited nature of any concrete evidence about abuse of these combinations. It was further stated that it can not be inferred from the RoR which press reports were considered by the Committee but that it was clear that they were taken at face value. It was stated that most of the reports in the media at the time had little credibility and that the information presented in them, especially the news.com.au (*Australia's secret drug scourge* by Mark Schliebs January 08, 2008, also see Sydney Morning Herald article *Don't put painkiller on prescription, say pharmacists*, Kate Benson Medical Reporter, January 10, 2008) article which mentioned an Australian online forum which had 7000 addicts registered, could not be verified. It was asserted that the information on there being 7000 addicts in the community was clearly at odds with the data from ADRAC which only detailed 49 ADR cases between 2002-06 and, further, if there was such a large problem how was it able to remain hidden from police or health authorities. It was contended, given the above, that the Committee had no data before it to warrant further consideration this matter.

- XXXXX questioned the matters taken into account under S52E of the Act. It was stated that despite there being no evidence of extensive abuse of the combination the Committee felt that matter (g) the potential for abuse of the substances should be taken into account. It was further asserted that the Committee felt that it was not necessary to take into account S25E 1(a), (b), (c), (d), (e) The Committee recalled that it did state that S52E 1(e) was a matter of concern and (f). It was stated that, given sales data, the public see benefit in the access to this substance and, further, that as sales tend to be to older consumers there should be enquiry into this pattern of use as well as the need for access and purposes of use of this combination for older patients. It was contended that matters (a) and (b) under Section 52E 1 require that the Committee undertake a formal and robust analysis of cost/ benefit and that, as had already been pointed out, the information presented to the Committee would not provide enough information for this to take place. It was submitted that the Committee should consider all matters under S52E (1) relevant to the discussion on the scheduling of this combination.
- It was stated that the Committee had, by not consulting with industry, not undertaking a cost-benefit analysis and by not considering the costs of increased regulation and inconvenience to consumers, failed to abide by the principles of good regulation.

XXXXX provided a submission which it stated was in addition to that provided by XXXXX. XXXXX noted that it has marketed XXXXX since January 2005 and that it was opposed to a scheduling decision being made at the June 2008 Meeting given the lack of data to justify such a decision. The following points were made:

- Based on the evidence presented in the February 2008 RoR, there was no justification to reschedule codeine and ibuprofen combinations. ADRAC data showed that there was an average of 7.5 ADRs for this combination a year, despite the combination becoming increasingly popular. A table was provided showing that over the period 2002-2007 sales of codeine and ibuprofen had increased while sales of codeine/

paracetamol have declined slightly. It was asserted that this data showed patients had found benefit with codeine and ibuprofen formulations that they had not found with codeine/ paracetamol products.

- An article from the March 2008 Australian Journal of Pharmacy was quoted in which a number of codeine addicts were surveyed as to their preferred codeine product. 79 per cent preferred OTC codeine and ibuprofen combinations while OTC codeine/ paracetamol was the choice of only 6 per cent. The same article suggested that the availability of large pack size of codeine and ibuprofen combinations may be in part driving this. It was stated that if this anecdotal evidence was indicative of actual abuse, then pharmacists needed to be encouraged to provide appropriate counselling and dispensing to patients. It was stated that, despite the increase in sales, there was little quantitative data available to determine the meaning of the anecdotal evidence currently available.
- The issue of the compounding of codeine and ibuprofen was discussed as being a secondary consideration to the concerns surrounding potential abuse as it did not appear that extraction of codeine was the preferred means by which the implied abuse was occurring. It was noted that a core feature of product registration in Australia is compliance with the requirements under the British Pharmacopeia (BP), including the requirement to pass dissolution testing. [The Committee recalled it had received advice that there are no current BP dissolution requirements for codeine analgesic combinations.] It was noted that codeine had a higher solubility than any other analgesic it was combined with and, thus, it would always dissolve more quickly. It was stated, however, that using methods to reduce the solubility of codeine may affect a product's ability to meet the necessary dissolution requirements.
- It was noted that there was no evidence or information on the illicit diversion and extraction of codeine from codeine/ other analgesic combinations presented at a May 2008 Australian Crime Commission forum. It was stated that this indicated that if there was a 'hidden' network of codeine diversion, the State and Federal police were unaware of it. It was stated, therefore, that given this along with the fact that the Committee had no hard data on the illicit diversion and extraction of codeine from these combinations, this aspect of codeine and ibuprofen products required no further consideration.
- It was asserted that no scheduling decision should be made at the June Meeting, that full access to any data received be given to all interested parties and that they be given time to assess said data and make a considered submission on it.

XXXXXX provided a submission in which it objected to the rescheduling of codeine and ibuprofen combinations until it has had time to work with stakeholders to ensure the combination can be used appropriately with the maximum benefit to the wider community in terms of accessibility to it. XXXXXX broke its concerns down into three issues:

- 'Compounded' – it was noted that codeine extracted from codeine containing analgesics can either be used to make homebake heroin or for direct oral ingestion. It

was asserted that, due to the complexity of manufacture, the scale of homebake production was relatively small and tends to be for personal use. It was stated that the extraction of codeine from all codeine combination analgesics was similar for all combinations and the method was discussed. It was stated that, as codeine was more soluble than all simple analgesics, the issue of the definition of 'compounded' applies to all codeine containing analgesics. Thus, if codeine and ibuprofen combinations were considered not to meet the definition, neither should any other codeine combination product. XXXXX had conducted its own solubility testing which it stated confirmed that the solubility of all simple analgesics compared to codeine was similar with the codeine being far more soluble than other analgesics.

- It was stated that, in order to identify the extent of the extraction of codeine from combination analgesics, XXXXX talked to a number of government agencies monitoring illicit drug use, including XXXXX. It was stated that these discussions confirmed that there was little concern surrounding homebake production in the community and that OTC codeine was low on the list for preferred starter materials for homebake.
- The definition of 'compounded' and compliance with this had not been discussed with ASMI members since a 2003 submission to the TGA to alter the formulation of a bilayer codeine and ibuprofen tablet. It was asserted that the TGA appeared to have been satisfied with the adherence of the new codeine and ibuprofen and all codeine/ paracetamol combinations with this definition. It was stated that, while the definition of 'compounded' was intended to protect the community, up-scheduling of all codeine containing analgesics would place an undue burden on the healthcare system.
- Abuse/ Misuse potential – It was acknowledged that there was a small amount of misuse of codeine containing analgesics, but it was asserted that there was no quantitative data relating to this level of abuse. XXXXX stated that the limited data it was able to collect showed that patients taking excessive quantities of codeine combinations for recreational use would take paracetamol as well as ibuprofen containing combinations. The data also showed that most consumers only buy one packet of codeine and ibuprofen at a time. Due to the hepatotoxicity of paracetamol, the amount patients can take is self-limiting, however, much larger amounts of codeine and ibuprofen combinations can be taken and it was this which has come to the attention of the Committee.
- It was stated that OTC codeine containing analgesics were developed to provide relief from strong pain without having to visit a doctor and that it had been the policy of the Australian Government for years to encourage well educated consumers to self-select medications for their health needs. This reduced the cost to the community and healthcare system.
- Taking OTC codeine combinations as directed for treatment of short-term pain does not lead to addiction as this does not give the patient the high which is experienced after taking larger doses of codeine. This lack of high may be what drives some patients who have previously taken large doses of codeine to take more than the recommended dose. It was also noted that tolerance to codeine does develop over

time and that for addiction to occur, misuse must take place over a lengthy period. XXXXX acknowledged that over time it had heard anecdotes of misuse of its product, however these were infrequent and unverifiable.

- PSUR data from 1994 – 2007 was supplied and it was asserted that the incidence of ADRs for codeine and ibuprofen was low with 28 cases of abuse/ misuse recorded globally from 2002 – 2007. It was contended that the level of ADRs for codeine and ibuprofen was no greater than that for codeine/ paracetamol.
- XXXXX supplied a chronology of events of potential abuse/ misuse cases it had been made aware of since 2006, starting with an ADR report from the MHRA which concluded that the total number of events of abuse were small; anecdotal reports of misuse from the Department of Human Services (DHS) in Victoria were received in mid 2007; in late 2007 XXXXX was made aware of a series of 23 case reports about misuse/ abuse of codeine and ibuprofen combinations; in December 2007 there were a number of UK and Australian media reports relating to the death of a patient from using excessive amounts of the combination and a web forum where hundreds of codeine and ibuprofen addicts discussed their addiction; an article was published in the MJA in January 2008 detailing 2 case reports of GI bleeding from recreational codeine and ibuprofen use (it was noted that these 2 cases were included in the ADRAC data); in April 2008 XXXXX contacted Emergency Departments in 36 major hospitals Australia-wide in an effort to quantify the aforementioned anecdotal data about an increase in codeine and ibuprofen abuse. It was stated that this was ongoing research, however initial results indicate that ED doctors are more concerned with codeine/ paracetamol combinations. It was asserted that this was borne out by data collected from Australian poisons information centres.
- XXXXX asserted that it had, on numerous occasions, requested copies of the data referred to by the DHS and on the 23 case reports, however this data was never provided.
- It was agreed that it seemed likely there was a low level of misuse of all codeine containing analgesics in Australia, including when in combination with ibuprofen. However, it had proven difficult to quantify the extent of the problem. XXXXX stated that, in such instances the opinion and observances of medical professionals must be given greater weight and, to this end, a number of healthcare professionals were quoted from media articles regarding their opinions that there was little evidence of such abuse, that if such evidence did come to light there were other options than rescheduling to Schedule 4 or 8 and that the majority of the general public who use these substances legitimately should not have OTC codeine combinations removed from their access.
- The risks of codeine misuse must be balanced against the effect a change on their scheduling would have for the wider community. Making codeine and ibuprofen combinations prescription only would inconvenience the great majority of the community who use the combination as recommended while ‘protecting’ only a small number of patients from potentially causing themselves harm. It was asserted that any scheduling change made at this stage would be based on anecdotal evidence only and

it would push the small minority to maintain their habit with the much more toxic codeine/ paracetamol or codeine/ aspirin combinations. It may also serve to cause them to doctor-shop for prescription strength products.

- XXXXX refuted the statement from the February 2008 RoR that excess use was not seen with codeine/ paracetamol combinations as users were aware of the risks of excess paracetamol. It was stated that the results of a Neilsen research survey conducted in May 2008 with 1400 adults found that there was very low awareness of side effects related to the incorrect use of analgesics. It was quoted that 50 per cent of adults were unaware of any side effects from the incorrect use of paracetamol and 74 per cent were unaware that incorrect use of paracetamol may affect the liver.
- It was stated that there was a far larger percentage of the community suffering alcohol or tobacco addiction, yet these issues were dealt with through a variety of means including consumer education and appropriate regulation.
- The new warning statement from the TGA which is required to be applied to all OTC NSAID preparations was discussed ("Do not use for more than a few days at a time unless a doctor has told you to. Keep to the recommended dose. Excessive use can be harmful"). It was noted that this will be on codeine and ibuprofen packets from October 2008 and will provide consumers better information on the health risks associated with excessive use of ibuprofen.
- Recognition of risk and need for response – XXXXX acknowledged that while the level of misuse of codeine and ibuprofen was currently very small, there was a genuine concern amongst some members of the healthcare community and general public. XXXXX stated that to help combat this it intends to develop an eduction program for all pharmacy staff which would help educate consumers about their pain, how to manage it appropriately and what to do if it persists and also to identify consumers showing drug seeking behaviour and help them to manage such situations.
- A large scale study was in preparation and should be commissioned by September 2008 and report by the end of 2009. This study would be an independent, prospective epidemiological study based in major emergency departments in Australia looking at the incidence and issues associated with abuse of codeine containing analgesics. It was requested that the Committee contribute to the design of this study and not make any changes to scheduling until the results of it were received.
- It was noted that there has been concerns about the level of advertising of codeine and ibuprofen. XXXXX stated that all advertisements for such products had been approved through the correct channels and that the in-store promotions and TV advertising adhere to the ASMI code of practice. It was asserted that there was no evidence that TV advertising leads to short-term sudden peaks in consumption and purchasing patterns are generally consistent. XXXXX

XXXXX provided a submission noting that there were two separate but related issues the Committee needed to consider:

- With regards to the definition of 'compounded', XXXXX stated that this was an issue which needs to be resolved carefully. It was believed that rescheduling to Schedule 8 on the basis of differences in dissolution rates of the two actives would not be a sensible outcome as the combination was clearly intended for the management of short-term, self-limiting conditions.
- Relating to misuse/ abuse of the combination it was noted that there were two main ways such a product could be misused either via the extraction of the codeine for the manufacture of homebake or intentional overuse by direct ingestion of the combination. It was stated that data from the Illicit Drug Reporting System (IDRS) showed that homebake use was uncommon. It was further noted that the IDRS data showed that the pattern of codeine use had remained stable over the last few years and that the most commonly identified products for misuse were paracetamol/ codeine combinations.
- There had been some information from pharmacists in certain jurisdictions on the possible misuse of this combination, however it was believed that this was not a widespread problem and that in most cases pharmacists had been involved in providing appropriate interventions. It was further stated that despite there being a small amount of data published on the misuse of these combinations, this did not appear to be indicative of a wider problem.
- It was stated, on the evidence currently available, there appears to be no real issue with the misuse of this combination and that the current scheduling remains appropriate and, further, that consumers must continue to have timely access to these products. However, if the misuse of codeine and ibuprofen was demonstrated to be a real issue, then the Committee may wish to consider limiting the availability of large pack sizes, revising the upper limit of codeine for Schedule 2 or working to standardise the scheduling of codeine across all jurisdictions. It was also stated that an education campaign to pharmacists and pharmacy staff about the misuse of codeine may be warranted.

XXXXX provided a submission stating that the current scheduling of codeine and ibuprofen combinations should be maintained. Further it stated that the issue of 'compounded' medicines should be resolved between pharmaceutical companies and the regulator. The following supporting points were made:

- Codeine and ibuprofen combinations play a vital role in the treatment of mild – moderate short term pain for which a visit to a doctor was not required. Pharmacists have a long history of helping patients to access such medications appropriately and it was a matter of public heath that people require access to appropriate levels of analgesia in a way which does not cause them to suffer unnecessarily. Changing the scheduling of codeine and ibuprofen combinations may cause this to occur. XXXXX supported the duty of care role of pharmacists and was encouraging of any measures, including education campaigns, which would contribute to the quality use of this combination. It was noted that a pilot program educating consumers on the risks of OTC analgesics was currently being conducted.

- There were two separate issues the Committee much consider, firstly the issue of product formulation and then the issue of misuse. It was stated that all formulation issues should be dealt with in liaison between the TGA and manufacturers, rather than by the NDPSC. If this product was found not to meet the definition of 'compounded', then careful consideration would need to be given to the issue by the TGA and stakeholder groups to ensure that inadvertent restriction of access to the affected products did not occur.
- It was stated that the Committee had little solid evidence of an abuse/ misuse problem in front of it and that XXXXX had been unable to find published literature or other hard data suggesting that there was a widespread problem. It was asserted that reports of this occurring, especially in the media, appear to have been overstated and sensationalised.
- The criteria under S52E were addressed as follows:
- (a) Both codeine and ibuprofen are well tolerated at therapeutic doses and their ADR profiles are well characterised.
- (b) The risks and benefits associated with these substances were well characterised as is the combinations' place in the treatment of mild to strong pain. It was stated that, as the type of pain this combination was indicated for was often acute it must be attended to quickly to avoid adverse outcomes and allow people to function in their daily lives. Further, the NDPSC had previously determined that the risk/ benefit profile of ibuprofen was such that it was suitable for general sale and that the risk/ benefit profile of codeine was such that it is contained in many different schedule 2 medicines.
- (c) Both codeine and ibuprofen are well tolerated at therapeutic doses and the use of any substance in excessive quantities would cause ADRs. It was noted that concerns were raised in the RoR for Meeting 52 that use of codeine and ibuprofen combinations may lead to perforated gastric ulcers as per the MJA article. It was noted that there were confounding factors as the first case had a history of alcohol abuse and a thorough history for the second case was not provided, thus, the role of factors other than ibuprofen could not be discounted.
- (d) Codeine and ibuprofen combinations had a long history of use and sales of the products had remained stable for the last 12 months, despite heavy advertising. It was also stated that an increase in sales did not equate to an increase in abuse. XXXXX stated that, despite a comprehensive search, it had been unable to locate any data suggesting widespread abuse or misuse of this combination. It was stated that in the absence of any hard data it would be inappropriate for the Committee to consider the information contained in the media reports credible. It was further asserted that feedback from members had suggested that misuse of these combinations was uncommon and able to be managed in the pharmacy setting. It was suggested that ensuring uniform scheduling across all States and Territories for OTC codeine combinations may be an appropriate initial response to any issues of misuse.

- It was stated that information from the National Drug and Alcohol Research Council (NDARC) showed that the misuse of codeine was not a large issue and the medication of choice for abuse was XXXXX, a codeine/ paracetamol combination. NDARC had stated that it did not support making codeine and ibuprofen combinations prescription only.
- (e) The discussion around the definition of 'compounded' and whether the combination meets this was noted. XXXXX asserted that this was a technical issue of the definition alone as no concern appears to have been raised that the codeine component was being separated out of the combination for illicit use. It was stated that the data from NDARC and other sources backed this up. Further, the issue of the definition of 'compounded' would most likely affect all combination analgesics containing codeine as all simple analgesics have different solubilities to codeine. It was asserted that on this basis it was possible that all codeine containing combination analgesics would be classed as Schedule 8 medicines, which was not in the best interest of the Australian public and it was a matter of public health that these combinations remain available in Schedules 2 and 3. XXXXX stated that, as the results of the solubility testing being conducted had not been made available for public comment, it would be inappropriate for the Committee to act on this information at this stage. Furthermore, the issue of formulation should be dealt with by the regulator and the manufacturer rather than the NDPSC.
- (f) Codeine and ibuprofen combinations are an important tool in the OTC analgesic range as it is indicated for pain that can not be managed by simple analgesia alone. The indications for use were described and it was noted that these were all short term conditions which may cause moderate pain but for which a doctor's visit was not required. It was stated that people in pain need access to appropriate analgesia which does not cause them unnecessary suffering and that including this combination in Schedule 4 or 8 would place people under unnecessary hardship and distress when their pain could easily be dealt with otherwise. It was asserted that all key stakeholders have opposed the suggested rescheduling.
- A number of scenarios were given where it was contended that codeine and ibuprofen combinations were the only suitable option for patients, including a significant number of patients who are unable to take paracetamol for a variety of reasons. It was stated that as ibuprofen is an antiinflammatory agent codeine and ibuprofen combinations were also more suitable for treatment of conditions such as dysmenorrhoea, rheumatic pain and muscular/ soft tissue pain.
- The codeine content of the Schedule 3 medicine XXXXX was discussed, noting that this product contained 12mg codeine (as 15mg codeine phosphate), which was more than the 10mg of codeine contained in the codeine and ibuprofen combinations. It was asserted that this product would be a more attractive target for misuse due to its higher codeine content. XXXXX stated that the argument that paracetamol toxicity limited the misuse/ abuse of codeine/ paracetamol combinations was not borne out by the NDARC data referred to above.

- (g) Use of codeine and ibuprofen combinations at the recommended dose and duration was not habit forming and prolonged use of the combination was not considered appropriate in a pharmacy setting. Patients using this medication regularly should be referred to medical care for investigation of the underlying cause of their pain. It was noted that XXXXX were undertaking a consumer education campaign to ensure community understanding of the quality use of this medicine.
- A number of additional matters were discussed by XXXXX:
- It was asserted that the impact on the public health system from rescheduling this combination would be significant, putting more strain on emergency departments and general practitioners.
- Pharmacists have a duty of care role in the community and are ideally placed to identify misuse/ abuse of substances as they are in a position to detect purchasing patterns which may imply inappropriate medicine use. If this was detected then pharmacists and their staff were required to refuse sale and refer the patient for assistance.
- The standards that pharmacists and staff must adhere to in supplying medications to patients were discussed, stating that they ensure consumers are offered appropriate advice or referral if required and reduces the risk of abuse/ misuse of medicines.
- It was stated that while there was no current evidence pointing to a significant problem with the use of codeine and ibuprofen combinations, if such evidence did come to light, a public education campaign would be the most appropriate response in the first instance. XXXXX welcomed the opportunity to help organise such a campaign. The consumer education pilot program on OTC analgesics currently being tested by XXXXX was discussed. It further was stated that there were other options open to the Committee than rescheduling if a problem was identified. These included reducing pack size, movement of stock out of self-selection areas and increased recording requirements on sales (but not the use of Project Stop for this purpose.)

XXXXX provided the same submission stating that there should be no change to the scheduling of codeine and ibuprofen combinations. The following points were made:

- The issue of ‘compounded’ formulations affects all codeine combination analgesics, thus a better approach for dealing with this issue would be directly between the manufacturer and the TGA.
- Codeine and ibuprofen combinations are an important part of the OTC range of analgesia options. Their availability as OTC medicines was appropriate to the management of a range of short-term conditions which may otherwise require unnecessary medical intervention.
- There was little evidence, other than a few anecdotal reports, to indicate the abuse of this combination was widespread. It was stated that there had been no reports of abuse from consultant pharmacists conducting comprehensive medication reviews in the community, indeed these reviews had shown that use of the combination was well

managed by the consumer in consultation with their pharmacist. Given this, it was illogical to alter the scheduling to restrict the public's access to a clinically effective treatment. It was stated that altering the scheduling would create an unnecessary burden on the public health system.

- It was asserted that changing the scheduling of codeine and ibuprofen combinations would be seen as a challenge to the ability of pharmacists to differentiate the need for and advise patients on the use of this combination.
- As pharmacists play a key role in helping to educate patients about their medications and work to provide appropriate access to them, it was suggested that an education campaign specifically targeted at codeine and ibuprofen combinations should be developed rather than scheduling the combination more restrictively. It was stated that this would help to provide greater information to consumers about the use of such products while providing pharmacists a practical tool to assist them in the management of consumers.

XXXXX have provided submissions in which it was stated that there were two issues to be considered.

- With regard to 'compounded' it was felt a clear and unambiguous statement regarding the definition of 'compounded' was required. Concern was expressed that if codeine and ibuprofen combinations fail to meet the definition of 'compounded', other OTC codeine combinations may also fail to meet this. Concerns were also raised that rescheduling to Schedule 8 may result in misuse of single ingredient analgesic products.
- Concerning the abuse/ misuse issue, it was stated that the problem may relate the availability of large pack sizes of the combination. It was stated that the pack of 72 tablets provides 2 weeks treatment at the maximum daily dose. It was suggested that the combination be rescheduled to Schedule 3 only with a reduction in pack size limits. It was stated that this would allow a pharmacist to be involved in the sale of this combination and, thus, the safety of the public would be better served.

XXXXX provided a submission in which it raised the following points:

- Care needed to be taken when interpreting the results of the case report published in the MJA as it was a small sample size and most likely that the ibuprofen caused the gastric problems, not the codeine. It was stated, however, that such reports were of concern.
- There was little evidence that, when used appropriately, OTC codeine containing analgesics cause adverse events. However, codeine and ibuprofen combinations were particularly open to misuse due to their high codeine content and the lack of toxicity in overdose when compared to codeine/ paracetamol combinations.
- Given this combination was currently not on prescription, rescheduling to Schedule 8 would be an extreme move. Instead rescheduling to Schedule 3 or Schedule 4 should be considered.

- It was stated that the amount of codeine phosphate in Schedule 2 codeine and ibuprofen combinations is 12.8mg (in packs of 12 or 24), which was higher than that in Schedule 2 codeine/ paracetamol combinations (8mg). It was stated that, as 12.8mg is close to the Schedule 3 codeine/ paracetamol codeine phosphate allowance of 15mg, then codeine and ibuprofen should be rescheduled to Schedule 3. The Committee noted that the Schedule 3 entry for codeine allows for 12mg of codeine (cf codeine phosphate). 12mg of codeine (MW = 317.4) is equivalent to 15.36mg of codeine phosphate (MW = 406.4).
- A number of other options were mentioned including limiting pack size, limiting codeine content and monitoring access via a program such as Project Stop.

XXXXX provided a submission in which it opposed the proposal to reschedule codeine and ibuprofen to Schedule 8. The following points under S52E were made:

- (a) The toxic effects of overdoses of both codeine and ibuprofen were discussed. It was stated that OTC codeine combination analgesics had a long history of safe use when used as per directions and a study (Jick et al, 1987) was quoted stating that the frequency of hospital admission for perforated ulcer was not measurably affected by concurrent use of NSAIDs during 30 million person days. It was stated that the 3 recent reports of ADRs in patients occurred under conditions of gross misuse.
- (b) It was noted that tolerance may develop with prolonged use, but that the combination was well known for its benefit in reducing strong pain and inflammation for conditions which do not require a doctor's visit.
- (c) It was stated that all medicines would have adverse effects if misused and some potential hazards were detailed.
- (d) IMS sales data from May 2006 to June 2007 showed that 629,400 units of XXXXX were sold in this time. This made it the leading brand. The Committee noted that it was not stated whether this referred to the leading codeine and ibuprofen combination or leading OTC analgesic combination.
- (e) The dosage recommendations for codeine and ibuprofen combinations were detailed.
- (f) OTC codeine was not included in Schedules I or II of the WHO Single Convention on Narcotic Medicines or Schedules I or II of the WHO Convention on Psychotropic Substances and there was little evidence to suggest that it presented a substantial risk of abuse or misuse. Therefore, codeine and ibuprofen combinations did not meet the classification requirements for a Schedule 8 medicine. It was noted that in June 2002 the Committee rescheduled pseudoephedrine from Schedule 2 to Schedule 3 on the basis that pharmacist intervention would help minimise the illicit diversion of the substance while maintaining access for legitimate users. It was stated that given this rationale, it seemed excessive to reschedule codeine and ibuprofen to Schedule 8 and, further, to do so would place an excessive burden on the general public's ability to access a medication which is indicated for conditions which do no require a doctor's visit.

- (g) While some studies looking at the potential for misuse of OTC codeine had identified that this may occur, all had concluded that patient and physician education or further research into the issue was required. Further, a study conducted in 2000 (Almarsdottir and Grimsson) found that the assumption that increased access to OTC codeine leads to misuse of them was incorrect. It was agreed that there had been a small number of anecdotal reports of misuse of codeine and ibuprofen combinations causing serious ADRs in patients but it was asserted that these have occurred after gross misuse of the combination. It was stated that the MJA article reported that there had been 26 ADRs reported for codeine and ibuprofen to ADRAC and that, in the light of sales of 629,400 packs of codeine and ibuprofen between May 2006 and June 2007, this represented a very small percentage of abuse/ misuse and ADRs.
- (h) The registered indications for OTC codeine and ibuprofen combinations were stated.

XXXXX provided a comment in which it reiterated previous comments it had made to the NDPSC stating that there were serious risks with the use of NSAIDs and that these substances should not be freely available through supermarkets. The Committee noted this was not related to the current issue under consideration, codeine and ibuprofen combinations are either Schedule 2 or Schedule 3 medicines.

A number of public comments were received from people requesting that codeine and ibuprofen combinations not be made Schedule 8 as it would place an undue burden on legitimate users.

A submission from XXXXX recommended that the combination be removed from Schedule 2 and that a pack size limit of 12 be imposed on the Schedule 3 entry.

XXXXX provided a submission in which it was suggested that Project Stop (or a similar system) could be used to track sales of codeine and ibuprofen combinations in much the same way as for pseudoephedrine.

DISCUSSION – RELEVANT MATTERS UNDER 52E

Members noted the following information provided to the Meeting by XXXXX:

- The Australian Medicines Handbook stated that codeine should be prescribed only with extreme caution to patients with a history of drug abuse or dependence, alcoholism, emotional instability.
- In July 2005 the MHRA issued a guidance proposing that a standard warning be placed on product labels of codeine containing products stating that “taking codeine regularly for a long time can lead to addiction.”
- The 2004 National Drug Strategy Household Survey (NDSHS) showed that 3.1 per cent of Australians had participated in the non-medical use of analgesics in the past 12 months (analgesics included aspirin, paracetamol, codeine etc)

- The current Therapeutic Guidelines for analgesics state that 30mg of codeine is required to produce an analgesic effect and 2 tablets of a codeine and ibuprofen combination contain only 18.9mg codeine. The NPS and a number of international guidance documents also state that doses of codeine below 30mg were likely to be ineffective. However, addiction to codeine can still occur at lower doses.
- Codeine and ibuprofen combination tablets have the highest individual amount of codeine phosphate available of all OTC codeine combination analgesics and a packet of 75 tablets contains 960mg of codeine phosphate. This was compared to a 20 packet of Schedule 4 codeine combination tablets containing codeine 30mg, for a total amount per pack of 600mg codeine phosphate.
- NSAIDs are among the leading sources of ADRs in Australia and the rest of the world. In the USA there are approximately 16,500 NSAID related deaths and greater than 103,000 hospitalisations pa. NSAID gastropathy is the 15th leading cause of death (Wolfe M, et al, *Gastrointestinal Toxicity of Nonsteroidal Antiinflammatory Drugs,* The N Eng J Med 1999;340:1888-1899). In the UK the figures show 10,000 hospitalisations and 2,000 NSAID related deaths pa. (Brown TJ et al. *A comparison of the cost-effectiveness of five strategies for the prevention of (NSAID)-induced gastrointestinal toxicity*. Health Tech Assess 2006;10:No. 38.)
- The risk factors for NSAID gastropathy were presented, noting that prolonged NSAID use and higher NSAID doses were a particular risk. There was a significant dose-response relationship to GI ADRs with the odds ratio increasing to 4.6 at a daily dose of > 1800mg ibuprofen (Lewis et al. *Dose-response…serious GI H'ge… meta-analysis*. Br J Clin Pharmacol 2002;54:320).
- A number of case reports, presented in XXXXX original submissions were re-summarised and the ADRs associated with NSAIDs were reviewed in detail.
- One study, conducted in health young subjects taking 800mg ibuprofen tds, showed that patients experienced GI blood loss within 3 days, with an average blood loss of 78 mL over the 28 days of the study (Bowen B et al. *Time Course and Pattern of Blood Loss with Ibuprofen Treatment in Healthy Subjects*, Clin Gastroenterol Hepatol 2005;3:1075-1082.)
- While there was no risk of addiction to NSAID agents themselves, codeine did have addiction potential, thus the combination of an NSAID with codeine could lead to an increase in gastric and other NSAID related ADRs due to inappropriate use.
- Photographic evidence was provided of price promotion and large, publicly accessible dump-bin amounts of codeine and ibuprofen combinations being available in certain pharmacies.

The Committee agreed that there were two issues to consider with respect to OTC codeine / ibuprofen combinations: Firstly, the issue of formulation and compliance with the SUSDP definition of 'compounded'. Secondly, there was the wider issue of abuse associated with these substances and whether scheduling could reduce both the potential for abuse and the harm arising from excessive ingestion of the other active. A Member

noted that, while the two issues were somewhat inter-related, many people who abuse combination analgesic products did not attempt to separate the codeine from the other analgesic.

Members recalled that Australia is a signatory to the UN Single Convention on Narcotic Drugs and, unless codeine is in a preparation that meets the definition of 'compounded', it falls into Schedule II of the Convention and therefore in SUSDP Schedule 8.

A Member stated that, given the results of XXXXX dissolution testing, there was now reasonable evidence that the currently available formulations of codeine /ibuprofen might not comply with the SUSDP listing for Schedules 2 or 3, in that the component drugs could be separated by simple dissolution. It was also noted that the cold water extraction techniques mentioned did increase the yield of codeine obtained from codeine/ paracetamol preparations. However, the Member stated that the Committee did not schedule products, rather it scheduled substances, and the issue of whether a product was compliant with a particular Schedule was a matter for the sponsor and the registration authority, not the NDPSC. Another Member stated that the results of this dissolution testing should be made available to industry to allow comment on them.

A Member pointed out that Australia is not the only signatory to the two treaties and that the combination of codeine and ibuprofen was available OTC in other signatory countries (eg, UK, New Zealand) apparently without controversy. It was suggested that it would be worth looking at the definitions of 'compounded' used by these countries in order to ascertain whether they were substantially different. The New Zealand Member stated that the definition of 'compounded' used in New Zealand was derived from the wording of UN Treaty on Psychotropic substances, as was the SUSDP definition. A Member stated that the Committee needed to decide whether the issue of products not meeting the definition of 'compounded' was an issue for the regulator, or whether the SUSDP definition of 'compounded' needed to be reviewed. A Member put forward that, as there were differing definitions of 'compounded', it was reasonable for the Committee to set aside consideration of this matter until the issue of the definition of 'compounded' could be investigated further.

In general Members felt that the issue of broader concern was the growing evidence of harm resulting from abuse and misuse of codeine and ibuprofen combinations. A Member stated that although the bulk of the evidence presented to date had been individual case reports, this was likely to be the result of the lack of appropriate reporting systems rather than the absence of a problem of misuse. The Member noted that a number of clinicians consulted by the jurisdictional Members had commented that they felt they were only seeing the "tip of the iceberg" of this problem in their clinical practices. The Member further commented that the characteristics of the abusers in the cases presented suggested that they could be potentially more difficult for pharmacy staff to identify than other drug abusers.

A Member stated that, as mentioned in a number of submissions, there was little evidence that police and other law enforcement agencies were aware of a problem relating to the

abuse/ misuse of codeine and ibuprofen combinations. Another Member stated that this problem may well be hidden as there was little or no illegal activity involved, i.e., the tablets were being obtained and used legally, albeit in excessive amounts. The Member stated that the data provided to the Committee for this Meeting by medical practitioners working in the field of addiction medicine suggested that the problem was real and causing significant harm. However, it was noted that the preliminary data provided by XXXXX, which had been obtained from a number of Emergency Department doctors, suggested that they were potentially more concerned with codeine/ paracetamol combinations than codeine and ibuprofen. It was also noted that XXXXX were conducting a more in-depth study on this matter, but that these results would not be available until the end of 2009. It was agreed that there was a case for undertaking a review of the availability of codeine combination analgesics in general to look at the broader issues relating to the supply of codeine, rather than focussing on codeine ibuprofen combinations alone.

It was noted that many of the submissions received had expressed concern at the anecdotal nature of the information considered at the February Meeting, but it was also noted that these submissions had been written without the information which had been gathered by the jurisdictional representatives or information contained in other submissions to this Meeting. A Member reiterated that, given the current reporting mechanisms in place and the apparent lack of illegal activity involved, the evidence that had been presented to the Committee to date should be considered on its merits. A Member also noted that the submissions from XXXXX had shown that ADR monitoring data had not appeared to show significant problems or an increase in reports for codeine and ibuprofen combinations despite their widespread use and increase in sales. However, the Member noted that this may also be due to reporting mechanisms for ADRs not being routinely used for OTC products.

It was noted that the number of tablets taken (from the case reports) seemed to correlate with the pack sizes available and that, considering the combination was indicated for temporary relief of pain, the maximum allowable pack size could be reduced without inconvenience. The Committee noted that one of the studies provided showed that, in Iceland, increased access to OTC codeine did not result in increased misuse. However it was noted that, at the time of the study, pharmacies in Iceland were restricted to selling one packet of 10 tablets (containing 10 mg codeine per dosage unit) of codeine combination analgesics per customer at a time.

Concern was raised about the practice, occurring in some larger pharmacies, of discounting codeine and ibuprofen combinations and placing them in large “dump bins”. It was noted that in two jurisdictions all codeine combinations, both Schedule 2 and 3, were required to be kept behind the counter, away from self selection aisles. However, this was not the case for other jurisdictions and it was recalled that the NSW scheduling for codeine combinations allowed the larger pack sizes to be sold as Schedule 2 medicines. A Member noted that there was an ASMI code of practice discouraging price promotion and usage of dump bins for analgesic substances. However, it was further

noted that breaches of this code only applied to manufacturers and may not penalize pharmacies undertaking this type of promotion.

Members agreed that reducing pack size limits for OTC codeine to four days therapy (at maximum recommended daily dose) would be a potential means of restricting supply to genuine cases of treatment of short-term pain but that this limit would have to be applied consistently for all codeine combinations.

Another Member recalled the WHO analgesic ladder and stated that the vast majority of the population did seem to get benefit from having access to OTC codeine combination analgesics. The Member felt that rescheduling codeine and ibuprofen to Schedule 3 might be the best way to maintain the balance between legitimate users being able to access the substance, while providing pharmacist intervention to help to reduce the amount of inappropriate use. The Committee considered that including the combination in Schedule 3 might not prevent people from pharmacist shopping. A Member pointed out that people also access codeine inappropriately as a Schedule 4 medicine.

The Committee agreed that a review of the scheduling of codeine, in all combinations, was warranted. It was agreed that the issue of misuse/ abuse of codeine and ibuprofen combinations was only a segment of the overall issue and that it would be appropriate for any review to consider all parts of Section 52(E) as well as giving further consideration to the definition of ‘compounded’ currently used in the SUSDP.

The Committee agreed that a working party, consisting of jurisdictional XXXXX regulatory XXXXX industry XXXXX and pharmacy stakeholders XXXXX, as well as the NDPSC Secretariat, should be set up to further investigate these issues.

The Committee agreed that in the interim there was evidence that abuse/ misuse was occurring with codeine and ibuprofen combinations, and that pending the full review of the scheduling of codeine, consideration of limiting Schedule 2 and 3 pack sizes of codeine and ibuprofen combinations be foreshadowed for consideration at the October 2008 Meeting.

It was noted that the NZMCC would be considering the issue of pack sizes of OTC combination analgesics at its next meeting and that the outcome of this might inform the NDPSC’s October consideration of codeine and ibuprofen pack sizes.

RESOLUTION 2008/53 - 25

The Committee agreed to foreshadow consideration of a reduction in the Schedule 2 codeine and ibuprofen combinations pack size limit and to include a Schedule 3 pack size limit for the October 2008 Meeting. Further, the Committee also decided to form a working party to review the availability of all OTC codeine combination analgesics.

11.2 BORON

PURPOSE

The Committee further considered the scheduling of boron

BACKGROUND

The May and August 2001 NDPSC Meetings agreed to revise the boron Schedule 4 entry to exempt a daily oral dose of 3 mg and to exempt dermal preparations containing ≤ 0.35 per cent to harmonise with the New Zealand (NZ) classification for dermal use. However, the Committee was not prepared to harmonise on other use patterns. This outcome was referred to NZ's Medicines Classification Committee (MCC) for consideration.

The February 2006 NDPSC Meeting:

- Noted that NZ had toxicity concerns regarding the use of high strength boron for nappy rash in babies under occlusive conditions.
- Noted that NZ products only contained boric acid and that boron was not listed as an ingredient in medicines. In contrast, registered ingredients for Australian therapeutic products include either boron or boric acid. A Member also noted that the boron scheduling excluded excipients and that this may need to be reviewed on the basis of the substance's toxicity.
- Recommended that NZ consider harmonising with the scheduling of boron and that MCC consider submitting a proposal to the NDPSC regarding appropriate nomenclature for harmonisation.

The June 2007 NDPSC Meeting agreed that consideration of the scheduling of boron should be deferred pending information from NZ about whether it would be proposing a new exemption cut-off, and the reasons for any such recommendation.

At their December 2007 Meeting, the MCC agreed that boron, including boric acid and borax, should be a prescription medicine except when for internal use in medicines containing 6 mg or less per recommended daily dose; for dermal use other than paediatric use in medicines containing 0.35 per cent or less or when present as an excipient.

The February 2008 NDPSC Meeting, following reconsideration of the issues (including the reasons for the adoption by New Zealand of a 6 mg cut-off for internal use), agreed to foreshadow the following amendments to the Schedule 4 boron entry (including capture of all paediatric use as Schedule 4) to allow stakeholders a further opportunity to comment, and to help identify any potential unintended consequences:

- Broadening the entry, particularly regarding topical use, by amending from an inclusive to an exclusive form.

- Increasing the internal use cut-off from 3 mg to 6 mg.
- Capturing all dermal paediatric use in Schedule 4 (i.e. remove the current allowance for dermal paediatric use, when not a dusting powder and ≤ 0.35 per cent, to be unscheduled).
- Removing the exemption for antifungal preparations for dermal use (i.e. these will be captured in Schedule 4).
- Adding the expression "including boric acid and borax" and changing 'milligrams' in part (a) to 'mg'.

Schedule 4 – Foreshadowed amendment

BORON – Amend entry to read:

BORON, including boric acid and borax, for human therapeutic use **except**:

(a) in preparations for internal use containing 6 mg or less of boron per recommended daily dose;

(b) in preparations for dermal use containing 0.35 per cent or less of boron, other than preparations other than preparations for paediatric or antifungal use; or

(c) when present as an excipient.

The February 2008 NDPSC Meeting also agreed that the June 2008 NDPSC consideration of boron could also revisit the appropriateness of the excipient exemption.

DISCUSSION - SUBMISSIONS

Members recalled the following from the December 2007 MCC discussions:

- It appeared from literature that there was a reasonable amount of data available to demonstrate that there were few, if any, adverse effects observed in doses at 6 mg per maximum recommended daily dose (RDD) (6 mg was sought by the NZ complementary medicines and dietary supplements industry). In addition, information had been provided to demonstrate that dietary boron appeared to assist arthritis and osteoporosis. Areas with low boron levels in food tended to have higher incidence of these conditions. Areas with high levels tended to have a much lower incidence. It also appeared that climate factors affected boron levels in food (levels tended to be higher in dry climates than in wet).
- It was noted that a boron RDI had not yet been established for NZ. Internationally, limits ranged from 3 mg in Australia to 14 mg in the US. The Expert Working Group on Minerals and Vitamins in the UK had recommended 6 mg per day.

- MCC concluded that there were no toxicological issues relating to a daily intake of up to 6 mg in dietary supplements and agreed to recommend that this limit should be put into effect using the previously proposed wording (see below). The cut-off point for external use should remain at 0.35 per cent.

Recommendation

- That boron, including boric acid and borax, should be a prescription medicine except when:
  - for internal use in medicines containing 6 mg or less per recommended daily dose.
  - for dermal use other than paediatric use* in medicines containing 0.35 per cent or less.
  - when present *as an excipient.*

*The MCC Secretary noted that it was necessary to exclude paediatric use from the 0.35 per cent exemption for dermal use in order to maintain the current prevention of the use of such products in young children. The Committee noted that the Schedule 4 boron entrycurrently only captures paediatric dusting powders (at all concentrations) and that other paediatric dermal use products at ≤ 0.35 per cent were currently not scheduled.

Members recalled the following from the Members discussion at the February 2008 NDPSC Meeting:

- The following matters under 52E(1) were considered particularly relevant to the consideration: (a) toxicity and safety; (b) risks and benefits; (c) potential hazards; (d) extent and patterns of use; and (f) the need for access, taking into account its toxicity compared with other substances available for a similar purpose.

General

- Members agreed that the Schedule 4 boron entry should be restructured (to the suggested exclusive form) for clarity.

Internal Use

- A Member asserted that there were not strong toxicity concerns and that the 3 mg internal use cut-off was conservative. Another Member noted that there was agreement in most studies that the tolerable daily intake (TDI) was ~20-30 mg (for an adult), and the real issue was the variation in application of a safety factor by the NDPSC and the New Zealand MCC. Members generally agreed that the 3 mg internal use cut-off could be increased to 6 mg in order to harmonise with New Zealand while still maintaining a safety factor (albeit reduced). It was also noted that there were currently products marketed in New Zealand with 6 mg boron which did not appear to have resulted in reports of harm.

Antifungal Use

- The Committee noted that there were safer alternatives to boron antifungals available, and that it was appropriate to no longer exclude such products from Schedule 4. A

Member noted that this Schedule 4 status would strongly encourage consumers to move to the safer alternatives.

Paediatric Use

- A number of Members asserted that it was no longer appropriate to allow paediatric use of boron outside of Schedule 4. However, Members also recalled the evaluation report's assertion (below) that this risk had been overstated because there was only a low absorption of boron compounds through skin.
- The Committee also noted that there were currently unscheduled paediatric products on the market.

Excipient Use

- A Member reiterated a previous concern about the exemption for excipient use, noting that the toxicity of boron regardless of whether it was present as an excipient or active.
- Another Member asserted that this may not be an issue as TGA's regulation of excipients would act to limit the level of excipient boron allowed. The Committee, however, noted advice that boron compounds appeared to be used at relatively high strengths in some products e.g. boric acid as a buffer in eye drops. The Committee agreed that the June 2008 NDPSC consideration of boron could also revisit the appropriateness of the current excipient exemption.

Members also noted the following from the boron evaluation report considered at the February 2008 NDPSC Meeting:

- Included a review by the evaluator of:
  - A report by the Committee for Veterinary Medicinal Products (CVMP) from the European Agency for the Evaluation of Medicinal Products (EAEMP).
  - A 2005 Human and Environmental Risk Assessment (HERA) report.
  - The 2001 review by the National Nutritional Foods Association of New Zealand (NNFANZ), which was a collation of three scientific reviews (below) and an earlier WHO review (also considered by all these reviews):
    - National Academy of Science (NAS) 2000 boron risk analysis.
    - UK Expert Group On Vitamins And Minerals (EGVM) 1999 review.
    - International Programme On Chemical Safety (IPCS) 1998 assessment of Boron.

  The February 2008 Meeting noted that these last 3 reports were first considered by the May 2001 NDPSC Meeting when it established the TDI that was the basis for the current Schedule 4 internal use exemption cut-off.
- Prior to the 1940s boron was used for the treatment of a variety of conditions including amenorrhoea, malaria, epilepsy, urinary tract infections and exudative pleuritis. The generally accepted single oral lethal dose were 2-3 g boric acid for infants, 5-6 g for children and 13-30 g for adults. Symptoms of acute effects included

nausea, vomiting, gastric discomfort, skin flushing, excitation, convulsions, depression and vascular collapse. With multiple exposure > 1 g/day a variety of symptoms were possible, singly or together, and included dermatitis, alopecia, loss of appetite, nausea, vomiting, diarrhoea and focal or generalised nervous system irritation or convulsions. Daily oral doses usually ranged from 1 to 14 g. Normally, complete recovery would occur following withdrawal of treatment. Boron for treatment of these conditions is now obsolete and there is no condition for which boron for internal oral use is an indication. The lowest recorded dose for causing symptoms in adults was 2 g/day.

- The main medicinal uses for boron were as boric acid and borax. Both compounds are moderately water soluble and upon ingestion are present in the alimentary tract, mainly as the undissociated mononuclear boric acid. This is readily absorbed and widely distributed to all tissues, being freely excreted in the urine within 24 hours. The levels in all tissues and plasma are comparable except that those in bone tend to be higher at 2-3x plasma levels. Except for this labile storage in bone, boron does not accumulate. Boric acid is not metabolised in the body and is completely excreted unchanged. Although there was 100 per cent absorption of boric acid from the alimentary tract, it was only poorly absorbed through intact skin, at about 0.4 per cent. Substantial absorption is said to be possible, however, through severely damaged skin.
- The mechanism of toxicity of boron in mammals is not understood, and no biochemical function in which the element plays a part has been identified. There was evidence, however, that boron is an essential element, based on positive responses to boron supplementation studies.

Animal Toxicity Studies

- Single oral dose rat LD_{50}'s for boric acid and borax: 2660-4100 mg/kg and 4500-6000 mg/kg respectively. For dogs > 3980 and > 6150 mg/kg respectively. These doses represented the same dose equivalent of boron (696 mg/kg). A feature of the oral toxicity in dogs was vomiting shortly after dosing at the lowest dose tested (26 mg/kg bw). These figures were consistent across all species tested (rats, mice and dogs).
- Dermal toxicity was > 2000 mg/kg and the compounds were not irritant to the skin or eyes and are not causes of hypersensitivity.
- Repeated dose toxicities in these species were consistently characterised by effects on the testis. Animals receiving doses of up to 88 mg/kg of boron in the diet or drinking water over 90 days developed testicular atrophy, weight loss, rapid respiration, inflamed eyes, swollen paws, and desquamation of the skin of the paws.
- Genetic toxicity tests were consistently negative and compounds were not carcinogenic.
- The most significant studies were those concerning toxicity to reproduction. The NOAEL for a 3 generation study in rats indicated 17.5 mg boron/kg/day for testicular pathology. These lesions were reversible except where testicular germ cells were

affected and atrophy occurred. The NOAEL for a similar study in dogs was 10.2 mg boron/kg/day and for mice 27 mg boron/kg/day.

- Boric acid was tested for developmental toxicity in the rat, mouse and rabbit. Non maternally toxic doses given on gestation days 0 to 20 in the rat caused reduction in foetal body weights and minor skeletal variations which, with the exception of short rib XIII, had reversed 21 days post natal. The NOAEL for the study in rats provided the lowest exposure dose of 9.6 mg boron/kg/day and an LOAEL of 13.7 mg boron/kg/day. This NOAEL of 9.6 boron mg/kg/day provided the data for the calculation of risk assessments of boron compounds at the present time.

ADI

- The allowable daily intake (ADI) was derived on the basis of the NOAEL of 9.6 mg/kg/body weight/day (the reproductive toxicity end point). The pharmacokinetic behaviour of boron in both humans and rats is similar, although the urinary excretion rates in rats is higher, and the toxicity features across the various animal species used in toxicity tests were consistent.
- Uncertainty factors variously proposed in relation to the NOAEL have varied from 25 to 60. The factor usually employed in extrapolation from animals to man for non essential elements is 10 and in the National Academy of Science risk analysis (NAS), the factor used for intra species variation was 3, giving a final uncertainty factor of 30. So the ADI would be 0.32 mg/kg/day. For a 70 kg adult, this would amount to 22.4 mg boron/day.
- Boron is widely distributed in the diet and drinking water. In the same document, the median intake of dietary and supplementary boron in North America was estimated to be 0.85 to 1.5 mg/day. Other limits calculated by other sources confirm this normal exposure level, such as 1.2 mg/day from the IPCS report, 1.5 mg/day from the UK TDS Report and an ADI of 19.2 mg/day by the ECETOX Report of 2005. However, the NAS risk analysis indicates the daily normal intake of boron to be up to 5 mg.
- There are currently no indications for the use of boron as an active for internal use. An intake from nutritional sources can frequently surpass 3 mg/day, the current Schedule 4 exemption cut-off. The evaluator asserted that there was no justification for an entry in Schedule 4 relating to boron as a therapeutic agent for oral internal use.
- In pharmaceuticals, boric acid is used as an excipient preservative, antiseptic, water softener, pH adjuster, emulsifier, neutraliser, stabiliser, buffer or viscosifer. Excipients in the Schedule 4 entry are exempt from scheduling. If the concentration of excipient boron provides for an intake of boron above the ADI of around 20 mg boron/day for adults, whether by oral, percutaneous or pervaginal absorption, then the product may have to be scheduled, based on an estimated intake assessment for the particular product.

Non oral exposure

- Preparations for vaginal use are listed in the Schedule 4 entry. It would have to be presumed that in these formulations boron would be 100 per cent absorbed, as in the

alimentary tract, and if this was in excess of 1g boron/day, symptoms of toxicity might occur. Whether this was likely would depend on the formulation of the product. It would take ~13 g of a vaginal gel containing 9 mg/g boric acid (1.5 mg/g boron) to supply boron at the level of the ADI, and about 660 g for a toxic dose.

- Honey and boric acid/borax mixtures, given to infants (10 kg bw) deliver 0.55 to 2 g boric acid (i.e. 0.09 and 0.35 g boron) per day and these have been followed by transient CNS effects such as convulsions and seizures.
- Absorption across intact skin is negligible, including in infants. The exposure estimate of a 10 kg infant to a 0.35 per cent formulation would be ~0.0028 mg boron over 24 hours. Since no more than 0.4 per cent of the applied boron would be absorbed, even in children with nappy rash, then a boron level in a formulation of 0.35 per cent appears to be excessively conservative, since at least 90 mg would have to be absorbed in this period for clinical signs of toxicity to occur. In any case, the ADI for boron for infants is 3 mg/day and this figure is also well above the estimated quantity absorbed from the single application of a 0.35 per cent formulation.

External Exposure to Boron from Consumer Cleansing Products

- Boric acid concentrations are typically 1 per cent for laundry products and 2 per cent for automatic dishwashing liquids. The worst case exposure estimates of absorption in relation to hand laundry washing and dish washing were 0.0001 μg/kg/day and 0.00015 ug/kg/day respectively for the two product types. These figures are insignificant in relation to the ADI for exposure to boron of 20 mg/day.

Conclusions

- It would appear that the present Schedule 4 entry was unnecessarily conservative. Boron has been employed in one form or another as a therapeutic agent for over 150 years. Since traditional medicinal uses of boric acid and borax have been abandoned, there have been very few, if any, reports of boron toxicity to hospital poison centres. Despite the use of an animal reproductivity end point for adverse effects, there are no indications that humans have suffered adverse reproductive outcomes, despite the widespread use of boron in laundry detergents and washing up fluids. The element is widely distributed in foods and beverages, in many cases accounting for the whole of the ADI.
- Boric acid is readily absorbed from the alimentary tract, but not from the skin, and is readily and completely excreted, mostly within 24 hours. It does not accumulate in the body and may even turn out to be an essential element for optimal mammalian growth. It is not mutagenic or carcinogenic, and although it is a consistent cause of testicular injury at high exposures, no such problems have so far been identified in humans. Neurological disturbances, if they occur, as all forms of toxicity appear to be completely reversible, even teratological abnormalities in the rat appear to become normal postnatally.

- Recommended that the Committee agree to harmonise with NZ. Members noted that this recommendation was made prior to the December 2007 MCC Meeting which recommended changing the NZ classification.

Members also recalled the following from the June 2007 NDPSC Meeting:

- Members were advised that the main issue with the 3 mg internal use cut-off was the additional safety factor applied by the Committee in 2001. A Member noted that the safety margin accounted for boron exposure from multiple sources, including diet and complementary medicines, and these sources needed to be kept in mind. Another Member noted that there was also the possibility of accumulation, given boron's diphasic excretion pattern.

Consideration of MCC Recommendations

- While the SUSDP [human therapeutic] entries referred to boron, NZ classified boron as boric acid. MCC considered that "boron, including boric acid and borax" should cover all possibilities.
- MCC asserted that the Schedule 4 entry was atypical in that inclusions were listed. MCC asserted that this had obviously been designed to prohibit products available at the time and was contrary to the usual listing of exclusions rather than inclusions. MCC recommended the use of the normal cascade effect for the Schedule 4 boron entry and list only those medicines which were excluded from Schedule 4. The June 2007 NDPSC Meeting noted that there were both inclusive and exclusive entries in the SUSDP, and although the exclusive entries predominate, there was no policy against inclusive entries.
- MCC also questioned the need for an exemption for antifungal preparations. MCC agreed that, not only were there better antifungal products available, but also that absorption of boron would occur through broken skin and that this use should be discouraged. It was recommended that NDPSC consider removing the exemption for the use of boron as an antifungal from the schedule entry.

Members also noted the following from previous NDPSC considerations:

<u>February 2006</u>

- There were no adverse reactions associated with boron reported in Australia or New Zealand since 2000. A review of New Zealand's SMARTI yielded 7 eye preparations (5 General Sale (GS) and 2 Pharmacy Only) and one GS vaginal gel containing 9 mg/g boric acid. These products listed boric acid as "other" ingredient which suggested use as an excipient. The boric acid concentrations in the eye preparations ranged between 6-18 mg/mL. Eye preparations containing boron active at any concentration are Schedule 4 in Australia (unless present as an excipient, which would currently qualify for an exemption).

August 2001

- The Committee amended the Schedule 4 boron entry at the May 2001 NDPSC Meeting to exempt internal preparations containing 3 mg per recommended daily dose on the basis that this provided a suitable margin for dietary intake of boron, covered existing products and would not exceed the TDI. The TDI was derived from developmental effects in a rat study using a 25x safety factor. The Committee agreed that this was a very low safety factor for this kind toxicological end-point and that limiting the maximum daily dose to 3 mg had provided an additional margin of safety.
- It was not considered appropriate to support doses close to a TDI when that was related to a possible developmental effect. This was in contrast to the margin of safety that would be associated with a no-effect level and establishment of an ADI.
- Post-meeting correspondence drew attention to the conclusions regarding the TDI of the USFDA (0.4 mg/kg/day) and EU Expert Committee on vitamins and minerals who accepted the same TDI as the US and quoted the WHO safe and acceptable intake range for adults of 1-13 mg/day. A stakeholder noted that the proposed maximum daily intake of 3 mg/day was very low by comparison with these values and requested that the cut-off be set at 10 mg/day for the maximum daily adult dose.
- It was noted that the Committee had moved from a position of not exempting any non-excipient use of boron in internal preparations, to exempting preparations up to a maximum recommended daily dose of 3 mg boron. This recognised the existing products on the market while maintaining a reasonable safety factor for products that were of doubtful efficacy in relation to the claims made for boron.
- The Committee agreed that 0.35 per cent boron was the appropriate figure for harmonising with the New Zealand exemption of external products containing 2 per cent or less of boric acid. The Committee did not agree to extend the exemption to internal preparations as this would erode the safety factor for a toxicological end-point based on developmental effects.

May 2001

- The Committee noted that boron had a TDI of 0.4 mg/kg bw/day. The TDI was derived from a NOAEL of 9.6 mg/kg bw/kg for decreased foetal body weight in a rat developmental study and using a 25x safety factor. The TDI equated to 28 mg/day for a 70 kg person, while the estimated mean dietary intake of boron was around 1.2 mg/day, which was low in comparison to the TDI. The February 2008 NDPSC Meeting noted that the evaluator's report discussed above made an alternative finding from this data.

XXXXX provided a comment in which it noted the Committee's considerations.

A comment was received from XXXXX stating that its interest mainly lay with non-therapeutic uses of boron and noted that the current consideration was primarily around human therapeutic use. It was stated, however, that as XXXXX would make post-meeting

comment if the outcome of the February meeting resulted in a change other than that foreshadowed.

Consideration of this item was foreshadowed at the February 2008 Meeting as there were discussions on inadvertently capturing products that may be widely used XXXXX. The Committee noted that there were no pre-Meeting submissions received from pharmaceutical companies and felt that this suggested that the pharmaceutical industry were not concerned about the proposed amendment.

DISCUSSION – RELEVANT MATTERS UNDER 52E

A Member felt that the Committee had been fairly conservative in its recommendation to exempt 6 mg or less per recommended daily dose of boron from scheduling given that the ADI for boron is 20 mg/ day.

Members discussed the use of boron as an excipient ingredient, noting that it was used in a large number of products as a buffer agent or for other physical properties. Members noted that, due to the widespread use of boron as an excipient ingredient, removing the exemption for this might have a large regulatory impact. Members agreed that there were few concerns with the toxicology of boron at the levels it would likely be used at as an excipient and that the Committee had previously considered this issue in detail at a number of meetings.

RESOLUTION 2008/53 -26

The Committee decided to:

- Broaden the entry, particularly regarding topical use, by amending from inclusive to an exclusive form.
- Increase the internal use cut-off from 3 mg to 6 mg.
- Capture all dermal paediatric use in Schedule 4 (i.e. remove the current allowance for dermal paediatric use, when not a dusting powder and ≤ 0.35 per cent, to be unscheduled).
- Remove the exemption for antifungal preparations for dermal use (i.e. these will be captured in Schedule 4).
- Add the expression “including boric acid and borax” and changing ‘milligrams’ in part (a) to ‘mg’.

Schedule 4 – Amendment

BORON – Amend entry to read:

BORON, including boric acid and borax, for human therapeutic use **except**:

(a) in preparations for internal use containing 6 mg or less of boron per recommended daily dose;

(b) in preparations for dermal use containing 0.35 per cent or less of boron, which are not for paediatric or antifungal use; or

(c) when present as an excipient.

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

12.1 SUSDP, PART 4

12.1.1 OSELTAMIVIR

PURPOSE

The Committee considered a proposal to include oseltamivir for the treatment and prevention of influenza type A and B in Schedule 3.

BACKGROUND

Oseltamivir is an oral prodrug of oseltamivir carboxylate which selectively blocks the viral surface enzyme neuraminidase, thereby preventing the release of virus particles from infected cells and is active against influenza A and B viral neuraminidase. Oseltamivir is readily absorbed from the gastrointestinal tract after oral doses and is extensively metabolised in the liver to the active entity, oseltamivir carboxylate. At least 75 per cent of an oral dose reaches the systemic circulation as the carboxylate. Binding to plasma proteins is about 3 per cent for the carboxylate and 42 per cent for the parent drug. Oseltamivir has a plasma half-life of 1 to 3 hours. The carboxylate is not metabolised further and is eliminated in the urine.

The October 2004 NDPSC meeting considered an application that oseltamivir be rescheduled to Schedule 3. The Committee agreed to defer making a decision on this issue until the February 2005 meeting to allow input from XXXXX to be received.

The Committee further considered the proposal at the February 2005 NDPSC meeting with consideration to the comments received from XXXXX. The Committee considered that further information was required regarding the prophylactic use of oseltamivir and the potential for development of resistance. The Committee thus agreed to defer making a decision on this issue until this data was available and XXXXX were able to make a final recommendation.

At the July 2005 meeting, the Committee was advised that the Medicines Classification Committee (MCC) had received an application for reclassification of oseltamivir from

prescription to restricted medicine for the treatment and prophylaxis of influenza in adults and adolescents. The MCC decided to retain the current scheduling for oseltamivir. The Committee agreed to defer the matter until the final recommendation from XXXXX had been received.

The Committee re-considered the application at the October 2005 meeting with regard to the further information provided by XXXXX. The Committee agreed that the current scheduling of oseltamivir was appropriate given:

- the concerns relating to the development of resistance to the drug,
- concerns regarding the likelihood of misdiagnosis by pharmacists without accurate point-of-care tests or physical examination during non-pandemic periods.

At the February 2006 NDPSC meeting the Committee considered whether States and Territories had appropriate mechanisms to allow pharmacists to supply Schedule 4 substances without prescription during either a localised outbreak or influenza pandemic. The Committee noted that such powers do exist at State, Territory and Commonwealth levels.

At the 34th MCC meeting in June 2006, the MCC considered a further application for reclassification of oseltamivir from prescription to restricted medicine. The MCC recommended that pharmacists should be able to sell oseltamivir between the months of May and September for the treatment of influenza but not for prophylaxis.

The October 2006 NDPSC meeting considered the issue of the harmonisation of the scheduling of oseltamivir with New Zealand, as oseltamivir was able to be supplied as a Pharmacy Only medicine (Schedule 3) during influenza season in that country. At this Meeting, the Committee agreed that Australia was currently harmonised with New Zealand on the scheduling of oseltamivir given that the only change to the New Zealand classification was an exemption to do with supply of the medication and that such Australian mechanisms of supply set down by jurisdictions had been duly explored at the February 2006 NDPSC Meeting. Thus it was concluded that the current scheduling of oseltamivir remained appropriate.

DISCUSSION - SUBMISSIONS

XXXXX

Members recalled the mechanisms that jurisdictions either currently have in place, or are in the process of implementing, to allow over-the-counter supply of oseltamivir in an influenza epidemic or pandemic:

- VIC: There is currently a Bill before the Victorian parliament which proposes to amend the *Drugs, Poisons and Controlled Substances Act 1981*. The Bill proposes that in the event of a public health emergency the Secretary would have the power to make an order that authorises a specified class or classes of persons to possess, use

and supply poisons and controlled substances, including Schedule 4 poisons. It is envisaged that this power may be delegated to the Chief Health Officer and that the class or classes of person may include registered nurses, pharmacists and employees of municipal councils.

- NSW: It is proposed to amend the NSW *Poisons and Therapeutic Goods Regulations 2002* so that a person or a class of persons other than a medical practitioner can prescribe a restricted substance. Such a person or class of persons will need to be approved by the Director General who will be able to apply conditions to the approval if required. In pandemics it is proposed that nurses will approved and they will be restricted to prescribing only a very small range of drugs (eg oseltamivir) for the period of the pandemic. It is anticipated that the amended regulation will commence around August 2008.
- ACT: There are mechanisms in place (Standing Orders issued by the Chief Health Officer if/when required) in the ACT for the distribution of oseltamivir in an emergency situation.
- WA: Amendments are planned. XXXXX.
- QLD: The *Health (Drugs and Poisons) Regulation 1996* contains provisions that enable specific health professionals (pharmacists, registered nurses and paramedics) to administer or supply oseltamivir or zanamivir under a drug therapy protocol in a declared public health emergency. In addition ambulance officers are also authorised to administer and supply these substances in a declared public health emergency.
- NT: Section 42 of the Poisons & Dangerous Drugs Act, which relates to medical kit provision, will be used allow oseltamivir distribution in case of pandemic. Under this section the NT is able to authorise registered health practitioners named on the various Board registers to administer oseltamivir.
- SA: Section 18 of the *Controlled Substances Act 1984* confers the power to issue a licence to a person for the supply and administration of Schedule 4 drugs such as oseltamivir or zanamivir if issuance of a licence is considered appropriate. However, as licensing would not be a practical option in the event of a pandemic, it is proposed that the *Controlled Substances Act 1984* will be amended to allow the Minister (with delegation to the Chief Medical Officer) to specify individuals or professions who are able to supply Schedule 4 drugs (e.g. oseltamivir or zanamivir) without a prescription during a declared emergency such as a pandemic influenza outbreak. Supply and administration would be in accordance with a standing order for the supply and administration of oseltamivir or zanamivir for treatment or prophylaxis against pandemic influenza.
- TAS: Regulation 61 of the *Tasmanian Poisons Regulations 2002* and Section 14 of the *Public Health Act 1997* provide for nurses to be authorised to supply a Schedule 4 substance in a public health emergency. The Poisons Regulation was applied on the 28th December 2005.

The Committee recalled that listing in Schedule 3 means that the direct intervention of a pharmacist is required for supply of the drug to a consumer and also the pharmacist must establish the therapeutic need for the substance. Therefore, in an epidemic or pandemic situation, mechanisms other than Schedule 3 would still need to be invoked for appropriate supply to occur to patients without lengthy delays.

Members also recalled that there were concerns raised at both the October 2004 and October 2005 considerations regarding the potential for misdiagnosis of serious illnesses, such as pneumonia, as influenza. It was recalled that early stages of bacterial pneumonia can mimic early stages of influenza and it was felt that this warrants physical examination by a medical practitioner prior to diagnosis. Such misdiagnosis could lead to serious health consequences for the patient including delays in treatment, hospitalisation and even death. Concern was also raised about potential logistical issues of a patient's spouse/ carer presenting at a pharmacy rather than the patient themselves and such a situation making correct diagnosis extremely difficult. It was felt that this, as well as patients coming in having already self-diagnosed influenza, would potentially put pharmacists under undue pressure to prescribe the product when it may not be appropriate.

There had been some media coverage regarding the NDPSC's consideration of this matter, including articles in Pharma in Focus and Pharmacy News.

A PubMed search of the literature relating to the development of resistance to oseltamivir in seasonal influenza A, influenza B and avian influenza was undertaken by the Secretariat. A 2005 position statement from the Neuraminidase Inhibitor Susceptibility Network (NISN) (*Neuraminidase Inhibitor Susceptibility Network position statement: antiviral resistance in influenza A/H5N1 viruses*, Hayden F et al, Antiviral Therapy 10:873–877) stated that there was no evidence that avian H5N1 strains had developed resistance to neuraminidase inhibitors (NIs) and that the likelihood of resistance developing was much less than that documented with amantadine. NISN also looked at a number of studies documenting oseltamivir resistance in influenza A (H1N1 and H3N2), noting that resistance appeared to develop in 16 – 18 per cent of patients. It was stated, however, that some of these patients may have received sub-optimal doses, which may, in turn, lead to optimal conditions for the development of resistance. NISN stated that further studies in this area were needed to determine the potential for the development of resistance. A further study from NISN (*Detection of Influenza Viruses Resistant to Neuraminidase Inhibitors in Global Surveillance during the First 3 Years of Their Use*, Monto A, et al, Antimicrobial Agents And Chemotherapy, July 2006, p. 2395–2402 Vol. 50, No. 7) looked at the development of resistance to NIs over the first three years of their use. NISN noted that over the period of 1999 – 2002, 2287 isolates of influenza were tested for resistance. Of these only 8 (0.33 per cent) had a > 10 fold decrease in susceptibility to oseltamivir and none of the patients the isolates were taken from had been treated with NIs. It was noted that of the resistant isolates, one was isolated in 1999 – 2000, three in 2000 – 2001 and four in 2001 – 2002 and that this was not a significant increase over the survey period. The authors concluded that the presence of these resistant isolates in treatment naïve patients may indicate that a low level of naturally

occurring resistant variants exist. NISN, however, did recommend continued surveillance on this matter, especially in areas of high NI use.

A number of more recent studies (published in 2007 and 2008) looking at NI resistance in seasonal human influenza were also found. Two studies (*Influenza virus susceptibility and resistance to oseltamivir*, Aoki FY et al, Antivir Ther. 2007;12(4 Pt B):603-16 and Neuraminidase inhibitor resistance in influenza viruses, Reece PA, J Med Virol. 2007 Oct;79(10):1577-86) concluded that the overall level of resistance to oseltamivir in seasonal influenza is low (reporting 5.4 per cent and 18 per cent in children respectively). Aoki et al stated that a higher incidence of resistance had been reported in two Japanese studies, but also noted that a different dosing schedule to the standard Western one had been used in participants. Reece stated that the concentration of NI at the infection site type, strain, virulence of infection and nature of the patients' immune response all play a part in the development of resistance and further stated that early initiation of NI treatment is important in minimising the development of resistance. Hatakeyama et al (*Emergence of Influenza B Viruses With Reduced Sensitivity to Neuraminidase Inhibitors*, Hatakeyama et al, JAMA, April 4, 2007—Vol 297, No. 13 1435) looked at the development of oseltamivir resistance in influenza B strains in Japan during the 2004 – 2005 influenza season. The authors stated that 7 out of 422 (1.7 per cent) isolates from untreated patients and 1 out of 74 children (1.4 per cent) treated with oseltamivir tested showed a reduced sensitivity to oseltamivir. From this the authors concluded that resistance to oseltamivir in influenza B does not arise as frequently as in influenza A. The authors also found it of note that, of the 7 reduced sensitivity isolates found, 4 were from infection in a community setting and 3 from contact with infected siblings and stated that this suggests person to person transmission rather than spontaneous emergence. The authors also state that, as Japan has a high use of oseltamivir, it may be that the resistance developed so far is due to the widespread use of the substance and that continued surveillance on this issue is essential. The authors further state that their findings show that oseltamivir may not be as effective against influenza B as influenza A. Hurt and Barr (*Influenza Viruses With Reduced Sensitivity To The Neuraminidase Inhibitor Drugs In Untreated Young Children*, Hurt AC, Barr IG, CDI Vol 32 No 1 2008) looked at the NI sensitivity of 1098 influenza isolates obtained from Australasia, Asia, the Pacific region and South Africa between 2001 and 2006. The authors found that only 2 (0.2 per cent) of the isolates tested (a H1N1 and a B strain) showed a significant reduction in sensitivity to NIs, noting that one of the strains showed the same resistance mutation as had been observed in mutants following oseltamivir treatment. The authors commented that both of the strains had been isolated from untreated children in the less than 2 year age group. A recent study published in Nature (*Crystal structures of oseltamivir-resistant influenza virus neuraminidase mutants*, Collins PJ et al, Nature, doi:10.1038/nature06956) found that the reason some oseltamivir resistant isolates were still sensitive to zanamavir was due to an alteration in a binding site for oseltamivir which does not affect the binding of zanamavir.

With regards to avian influenza, a number of journal articles have recently been published looking at the development of resistance within these viruses to oseltamivir. A

study conducted by Hurt et al (*Susceptibility of highly pathogenic A(H5N1) avian influenza viruses to the neuraminidase inhibitors and adamantanes,* Hurt AC et al, Antiviral Res. 2007 Mar;73(3):228-31. Epub 2006 Nov 10) between 2004 and 2006 found that of 55 avian (H5N1) influenza isolates tested, the majority were fully sensitive to NIs. 2 strains were noted to show increased resistance. Another study, comparing the sensitivity of clade 1 and clade 2 H5N1 viruses from Cambodia and Indonesia was conducted by McKimm-Breschkin et al (*Reduced Sensitivity of Influenza A (H5N1) to Oseltamivir,* McKimm-Breschkin JL et al, Emerging Infectious Diseases Vol. 13, No. 9, September 2007). The authors compared the sensitivity of the clade 1 2004 Cambodian virus to the 2005 virus as well as to the 2005 clade 2 Indonesian virus. All isolates were obtained from poultry. The authors found that, for the Cambodian clades, the 2005 isolates demonstrated a 6-fold reduction in susceptibility to oseltamivir when compared to the 2004 isolates. It was concluded that, as the sequence variations did not correlate to any known mutations, the decrease in sensitivity was due to genetic drift rather than exposure to oseltamivir. Further, the authors also found that compared to the clade 1 Cambodian isolates, the clade 2 Indonesian isolates demonstrated a 30-fold decrease in sensitivity to oseltamivir. The authors concluded that this was an issue of special concern as it may lead to sub-optimal dosing in persons infected with this isolate which, in turn, may lead to the selection of viruses with a high level of resistance. It was also noted that the clade 2 virus had spread from Indonesia to parts of Europe and Africa. Ferraris and Lina (*Mutations of neuraminidase implicated in neuraminidase inhibitors resistance*, Ferraris O, Lina B, Journal of Clinical Virology 41 (2008) 13–19) conducted a review of all the mutations currently implicated in NI resistance and stated that most mutations to one NI will induce cross resistance to another. They also noted that framework mutations which lead to a decrease in NI susceptibility will generally not lead to a decrease in the transmissibility of the virus, whereas catalytic mutations will adversely affect the transmissibility.

The latest (27 March 2008) report on oseltamivir resistance from the WHO stated that a total of 711 out of 4992 (14 per cent) influenza A isolates tested in the period last quarter 2007 to 27 March 2008 showed resistance to oseltamivir.

A submission was received from XXXXX in support of the rescheduling of oseltamivir to Schedule 3. The following points were made:

- Seasonal influenza is a world-wide public health problem and in Australia thousands of people were infected each year, with approximately 3000 deaths resulting. It was stated that despite vaccines being available not everyone takes them and there is also some failure experienced by patients who are vaccinated. It was stated that antiviral drugs such as oseltamivir terminate the influenza infection by blocking neuraminidase and, thus, spread of the virus in the body.
- The symptoms of influenza infection were discussed and it was stated that oseltamivir treatment is best started 6 to 12 hours (but up to 48 hours) after the onset of symptoms and that it is effective against both influenza A and B. It was further stated that most people are not able to see a doctor immediately, perhaps waiting 2 or 3 days and this

delay renders oseltamivir almost useless given the narrow window for initiating therapy. It was contended that making oseltamivir available from a pharmacist would provide more timely treatment of infected persons and reduce the spread of the disease in the community.

- The October 2005 NDPSC decision on the rescheduling of oseltamivir was noted and the concerns of the Committee regarding diagnostic and resistance issues were addressed. It was stated that a submission from XXXXX will answer the concerns of the Committee about correct diagnosis of influenza. The availability of accurate, but low sensitivity quick diagnosis tests was discussed and it was stated that these would be of benefit to the pharmacist in making their diagnosis. It was stated that the small number of false negatives given by such tests would leave those patients no worse off than previously but that the majority of patients would benefit from the use of them.
- With regards to the concerns surrounding resistance, XXXXX asserted that if oseltamivir was used indiscriminately or inappropriately (eg, by someone with the common cold) resistance would not develop. It was stated that influenza virus mutants resistant to oseltamivir may be selected if the virus replicates in the presence of the drug, however, the likelihood of this occurring was the same whether the substance is prescription or OTC. It was stated that recently a number of H1N1 oseltamivir resistant isolates had been found but that these were still sensitive to zanamivir. The Committee noted that no data was provided in the submission relating to this claim. Regarding the concern surrounding oseltamivir resistance in seasonal influenza and the implications of this in a pandemic, it was asserted that as it was most likely that a pandemic would be caused by a new virus there should be little resistance to oseltamivir with this virus.
- It was noted that the Committee previously had concerns about patients with a bacterial infection being wrongly prescribed oseltamivir and, thus not seeking help from a doctor. It was asserted that this was not very different to what would occur currently when a patient who thinks they have the flu goes and buys OTC cold and flu tablets instead of going to the doctor for a course of antibiotics. It was also contended that a pharmacist prescribing oseltamivir would inform the patient to see their doctor if the condition did not improve.
- Mention was made of the practise of healthy patients stockpiling oseltamivir either by purchase over the internet or by obtaining a doctors' prescription. It was stated that personal stockpiling would be lessened if oseltamivir was available in pharmacies for rapid supply to those who need it.
- The Committee's October 2005 request to see the exploration of arrangements for appropriate access to oseltamivir in the instance of a seasonal outbreak or pandemic is discussed. It was stated that either of these instances would lead to panic in the community and that the long term availability of oseltamivir in pharmacies would help alleviate this as people would be "trained" in its use. Public education about these substances was also asserted to be essential in reducing the impact of influenza on the community.

XXXXX briefly addressed the criteria of S52E of the Act as follows:

- (a) – It was noted that oseltamivir does not inhibit any mammalian neuraminidases and the main side effects are discussed. The occurrence of neuropsychiatric events was also mentioned but it was noted that influenza itself can result in similar symptoms. It was asserted that a pharmacist could advise of such potential side effects as well as a doctor.
- (b) – The risks of using oseltamivir are very small and allergic reactions which might occur are most likely due to excipient ingredients rather than oseltamivir. It was stated, however, that the benefits of reducing influenza virus replication were great both for the individual and community but that these benefits were only manifest if early treatment is available.
- (c) – Despite suggestions to the contrary, there was no evidence that excreted oseltamivir moving into the sewage system has the ability to cause resistance of H5N1 avian influenza in ducks.
- (d) – June, July and August would be the months of greatest demand for oseltamivir and the level of demand would vary from year to year. However, influenza can occur all year round, so oseltamivir should be available OTC all year also.
- (e) – The dosage and formulation of oseltamivir were stated.
- (f) – The current anti-viral treatments for influenza were discussed, noting that resistance to the M2 ion channel inhibitors (eg amantadine) develops readily. It was stated that while zanamivir was a more effective agent than oseltamivir, there were problems with its delivery, therefore oseltamivir was the substance of choice to be made available OTC.
- (g) – There was little potential for abuse with oseltamivir.
- (h) – The indications for oseltamivir were discussed.
- For further information regarding the toxicity, safety, risks and benefits of oseltamivir, XXXXX pointed to a 28 page document that XXXXX submitted to the USFDA.

XXXXX provided a draft statement for the consideration of the Committee. The information is summarised as follows:

- Pre 2007 – High level resistance to oseltamivir had principally been due to a mutation which substitutes a tyrosine for a histidine at a particular residue (H274Y) of the neuraminidase molecule. Resistance had been measured at up to 4 per cent of adults and 16 per cent of children with H1N1 infection and treated with oseltamivir. It was stated that, in the UK during the period 2005-07, 25 per cent of the viruses isolated from children had the H274Y mutation. It was noted that such mutations do not emerge until day 3 – 6 of treatment and that virus shedding is no longer detected after day 7 – 10. It was further noted that this mutation had also appeared in H5N1 infected patients treated with oseltamivir.

- Despite this, the incidence of oseltamivir resistant H1N1 circulating in the community was low and prior to the introduction of oseltamivir into clinical practice no studies had detected the presence of the H274Y mutation. In the 2004 – 2007 European influenza seasons resistance was only detected in 0.4 per cent of H1N1 isolates. Similarly in Japan there were no resistant isolates detected in 2004-05, 2 per cent in 2005-06 and <1 per cent in the 2006-07 season. It was stated, however, that studies conducted in Japan in the 2006-07 season suggested that some low-level transmission of H274Y mutated H1N1 virus did occur.
- 2007 – 2008 Given the above data, the level of oseltamivir resistant H1N1 virus detected in the Northern Hemisphere winter was unprecedented. The majority of these strains were closely related to the vaccine strain A/Solomon Islands/3/2006, however there was an increasing number of A/Brisbane/59/2007-like virus detected. It is noted that the increased frequency of resistance of H1N1 viruses was first detected at the end of 2007 in Europe (24 per cent resistance) and North America (14 per cent). All of the resistant isolates carried the H274Y mutation which resulted in a 400-fold or greater decrease in susceptibility to enzyme inhibition assays. The proportional distribution of the resistant isolates varied widely in Europe with Norway showing 70 per cent resistance, the UK 10 per cent and other countries showing no resistance. It was noted that Canada showed a higher proportion of resistance (20 per cent) than the US as a whole (11 per cent), but that there was considerable variation between US states. Levels of resistance were much lower in Asia with 11 per cent of isolates form Hong Kong found to be resistant while only 2 per cent from Japan were. It was stated that the impact of this increased resistance in Southern Hemisphere countries is yet to be determined.
- It was noted that viruses with the H274Y mutation maintain full susceptibility to zanamivir and amantadine and that, further this was a mutation specific to the N1 subtype viruses.
- The origin of the resistant viruses is unknown despite their recent emergence. It was postulated that this may be due to spontaneous emergence of naturally resistant variants which have no competitive disadvantage or selective drug pressure during oseltamivir treatment. It was stated, however, that current evidence shows that selective drug pressure is not what is driving the spread of this resistant virus as none of the resistant isolates from Europe or North America were taken from patients treated with oseltamivir. Further, it was noted that there was very little use of oseltamivir in Europe and that in Japan, where oseltamivir is used extensively, there were relatively low levels of the H274Y mutation identified.
- It was stated that phylogenetic analysis of the most recently isolated oseltamivir resistant H1N1 viruses show that most of them fall within the A/Brisbane/59/2007-like group. Despite this there was some diversity between the sequences of the oseltamivir resistant neuraminidases and it was postulated that this diversity, together with the co-circulation of sensitive and resistant viruses and seeming lack of correlation of resistance with drug use is evidence that different resistant variants emerged independently and in the absence of drug pressure. It was thought that these

viruses have overcome previous reductions in fitness and transmissibility but why this may be the case was unknown. Additionally, it did not appear that the 2007-08 resistant viruses differed in their virulence from the oseltamivir sensitive ones. Further investigation into this was ongoing.

- The transmission of these viruses which have seemingly developed in the absence of selective drug pressure was of particular importance from a public health perspective. It appeared that oseltamivir would be unlikely to be effective for prevention or treatment of infections caused by strains carrying the H274Y mutation. The results of an animal study were quoted where treatment with oseltamivir did not reduce respiratory viral titres in oseltamivir resistant H1N1 infected animals. The H274Y mutation had also been associated with an increase in viral load in human patients but it did not generally appear that patients experienced prolonged illness.
- There had been a number of animal studies documenting the effect that the H274Y mutation has on the ability of H1N1 and H5N1 subtype viruses to infect and transmit. For the H1N1 virus, the results have varied from study to study and it appeared that the replicative fitness of the virus was dependant on its genetic background. Most studies did show that there was some reduction in fitness of the mutated virus but it was possible that other changes to the neuraminidase may compensate for this. The results from the H5N1 animal studies suggest that virus with the H274Y mutation may retain the same pathogenicity as the wild-type virus, but it should be noted that, as with the H1N1 virus, this may vary with genetic background.
- The clinical and public health implications of oseltamivir resistance in H1N1 virus were discussed. It was noted that oseltamivir resistance had no effect on vaccine efficacy and that H1N1 infections are generally associated with lower morbidity and mortality than H3N2 infections. Despite this, severe disease and complications can occur in vulnerable patients infected with H1N1.
- It was acknowledged that oseltamivir would not be effective for prophylaxis against H1N1 H274Y mutated strains, but it was asserted that these strains have only made up a small proportion of the overall circulating virus in the 2007-08 influenza season. It was noted that oseltamivir resistance in seasonal influenza was currently confined to H1N1 viruses and that a broad change in the pattern of use of antivirals did not seem warranted at this time.
- The H1N1 H274Y mutated strains remain susceptible to both zanamivir and the adamantanes and these remain useful tools for the treatment of the disease. It was noted, however, that zanamivir cannot be given to young children and may be difficult to administer in the elderly. Although there had been no dual resistance to NIs detected to date, given that the emergence of resistance was of particular concern in immunocompromised hosts, monitoring of the situation was required.
- Further surveillance should help to provide a clearer picture of the patterns of spread of resistance in the H1N1 virus and may help to predict future trends. It was noted that H1N1 strains are usually not the dominant ones circulating in an influenza season and it was questioned how well these oseltamivir resistant strains would be able to

compete and circulate during the next influenza season. It was stated that the data from this may drive the need for regional antiviral use recommendations.

- With regard to the H5N1 subtype it was noted that the NA sequence differs from the H1N1 subtype by about 20 per cent. It was postulated that study of the genetic background of H1N1 H274Y mutated strains would help to predict the sustainability of this mutation and, thus help to predict the likelihood of this mutation occurring more commonly in the H5N1 subtype.

XXXXX provided a submission in which it was stated that oseltamivir satisfied the requirements for a Schedule 3 medicine and should be rescheduled. A large number of references were provided as part of this submission. The following points were made in support of down scheduling:

- In 2005 the Committee was concerned about the ability of pharmacists to correctly diagnose and manage seasonal influenza infections. It was noted that the New Zealand MCC considered the same issue in 2006 and felt that although there may be some potential for delay in the treatment of more serious diseases, the same delay would occur when seeking other OTC cold and flu products. The MCC agreed that pharmacy access to oseltamivir ensures rapid access to the medication which is necessary for effective treatment. It was noted that New Zealand was the only country in the world which has put such a mechanism for oseltamivir access in place and it was stated that it was important to review the experience of this in order to determine if down scheduling in Australia was appropriate.
- A study was conducted by Pharama Projects and Auckland University in which community pharmacists were interviewed in order to assess their thoughts on the mechanism for supply, including whether they felt it led to inappropriate use of oseltamivir. It was stated that generally the mechanism for supply was viewed favourably and that there were no serious safety concerns related to it. Pharmacists felt that barriers to supply still existed in the form of the face to face prescribing requirement and that this impeded the full public health benefit of OTC availability of oseltamivir being realised. It was stated that a further relaxing of the conditions of supply would present no safety concerns.
- It was stated that the criteria for diagnosing influenza was the same for GPs as for pharmacists and that the criteria of cough, fever and fatigue were specific and sensitive for diagnosing influenza.
- Another concern of the Committee in 2005 was how a change in the mechanism for seasonal supply of oseltamivir would affect pandemic supply. It was stated that clear Government communication about pandemic preparedness, government stockpiling and changes to manufacturing capacity to ensure both seasonal and pandemic supply had served to ease these concerns. It was asserted that the New Zealand study results showed that there was very little evidence of patients stockpiling oseltamivir for pandemic purposes and, additionally, sales of oseltamivir as an OTC medicine were low in 2007. It was stated that this was due to a mild influenza season and proved that pharmacists were responsible in their diagnosing and dispensing. It was also asserted

that the UK method of allowing accredited pharmacists to dispense oseltamivir during the influenza season to at-risk patients again highlighted the ability of pharmacists to deliver this important service.

- The issue of development of resistance was also noted as a concern of the Committee during its 2005 consideration. It was acknowledged that data from the 2007-08 European influenza season had shown that some strains of H1N1 carry a mutation conferring resistance to oseltamivir and it was stated that the WHO were collecting data to determine how widespread the resistance was. WHO data from last quarter 2007 to May 5 2008 show that 15 per cent of H1N1 isolates were resistant to oseltamivir.
- Following the detection of this increase in resistance, an interim risk assessment was released by the European Centre for Disease Protection and Control (ECDC) and the WHO also authored a document providing further guidance and information on this issue. These include:
  - Evidence that resistant viruses can be transmitted between patients.
  - Current information does not suggest that the increase in resistance was due to drug pressure.
  - Patients infected with resistant virus display the same symptoms and course of illness as those infected with wild-type virus.
  - Resistance was confined to H1N1 virus and there was a large amount of regional variation in the levels of resistance.
  - It was possible that the resistant strains will not become more common and will be overwhelmed by fitter wild-type viruses.
  - H1N1 was not a pandemic threat and thus, WHO and ECDC recommendations about the use of oseltamivir have not been altered.
- It was noted that no resistance had been reported in New Zealand and two resistant isolates reported in Australia to date. It was asserted that it was of particular relevance that the reported resistance is limited to H1N1 which is a seasonal virus and that, since 1988, there have only been 3 seasons where H1N1 was the predominant circulating influenza A strain. Thus oseltamivir would be an effective treatment option for most patients presenting with seasonal influenza. Further, it was stated that illness produced by H1N1 infection was less severe than for other sub-types, thus it was important that the majority of patients have rapid access to a safe and effective treatment option.
- It was noted that there were a number of organisations which monitor global resistance to NIs including NISN, WHO collaborating centres, ECDC and the CDC. It was stated that, given this, it was unlikely that any increase in resistance to oseltamivir would go unnoticed.
- It was noted that the PI for oseltamivir had recently been updated to include information relating to the occurrence of neuropsychiatric events. These changes

came about after a review by the USFDA Paediatric Advisory Committee on the safety and ADRs associated with oseltamivir. It was stated that they reflected observations from a growing body of data, which showed no evidence of a causal relationship between oseltamivir and the reported events. The data showed that these neuropsychiatric adverse events also occurred in influenza patients who were not taking oseltamivir and it was noted that the USFDA committee stated that they had an "increasing level of comfort in the evidence that NP events may be more likely a manifestation of influenza than of the drug or the interaction of drug and disease, although uncertainty still exists."

XXXXXprovided a submission in which it stated it had consulted with experts in antimicrobial resistance and noted that there were concerns about the risk of increasing resistance. It was stated that, given this it would be a concern if oseltamivir where rescheduled to Schedule 3.

XXXXX provided a submission in which it stated its support for the inclusion of oseltamivir in Schedule 3 as pharmacists are ideally placed to provide the substance for early initiation of therapy. However, XXXXX stated concerns about previous occasions where a substance had been down-scheduled but no product had been marketed at the lower schedule. Therefore, XXXXX stated that the down-scheduling of oseltamivir should only take place if the sponsor had committed to marketing a Schedule 3 product and developed suitable material to train pharmacists and educate consumers on its supply.

XXXXX provided a comment stating that it had no objection to the proposed rescheduling.

A submission was received from the XXXXX stating that it supported the inclusion of oseltamivir in Schedule 3 for the following reasons:

- The vaccination rate in at risk individuals is approximately 45 per cent, therefore there needs to be treatment available when patients become infected with influenza. Access to oseltamivir needs to be timely as treatment needs to be initiated within 48 hours after symptom onset for it to be effective. The accessibility of community pharmacists means that consumers will have the ability to seek and access treatment within this timeframe. Further, if a pharmacist believed there was a more serious, underlying condition they would be able to refer the patient for medical assessment.
- Oseltamivir is well tolerated with the most common side effects being nausea and vomiting.
- Oseltamivir meets the NDPSC criteria for a Schedule 3 medicine as it is substantially safe for use, has a low incidence of serious ADRs and low abuse potential or potential for harm from misuse. It is indicated for a short duration of treatment and the condition for treatment is readily recognisable by a pharmacist.
- If oseltamivir was included in Schedule 3, then Appendix H listing was also warranted on the basis that this would help to raise public awareness of health risk factors and consequences related to influenza, it would ensure consumers were

informed about different treatment options for influenza and it would inform consumers about the need and benefit of seeking early treatment.

- XXXXX stated that it would support the development of an evidence based education program for pharmacists and asked that reasonable time be given from the date of decision to implementation of the new scheduling in order to allow this program to be developed and pharmacists trained.
- The collection and monitoring of data if oseltamivir is rescheduled was strongly advocated as it was believed that oseltamivir was a good candidate for conducting a post-rescheduling surveillance study focussed on the quality use of the medicine.

A submission was received from XXXXX objecting to the proposed rescheduling of oseltamivir. The following points were made:

- Neuraminidase inhibitors should not be promoted as an alternative to vaccination as they have a limited role in treatment as a post-exposure agent. It was asserted that by making oseltamivir available OTC it would reduce the impact of the more effective vaccination option. Vaccination should remain the first-line strategy in combating morbidity and mortality from influenza.
- In healthy adults neuraminidase inhibitors are not recommended for the treatment of seasonal influenza as they have a benefit of reducing the duration of illness by only 1 to 1.5 days. It was stated that increased access to medications often leads to increased demand, in this case it was postulated that having oseltamivir available OTC sends a message to consumers that if they had flu-like symptoms they should take the medicine. This was not in line with the quality use of medicines in Australia.
- It was asserted that the concerns expressed by the Committee in 2005 about the rescheduling of oseltamivir had not changed. Influenza infection was difficult to differentiate from other influenza-like illnesses and was unable to be diagnosed on clinical grounds or a 'tick the box' approach alone. It was stated that while pharmacists are trained to dispense medicines they are not appropriately trained in diagnosing patients. Only medical practitioners have the training to make correct diagnoses, understand the risks and benefits of prescribing and provide monitoring of the ongoing use of the medicine. It was contended that unnecessary use of oseltamivir due to misdiagnosis was not a quality use of medicines.
- While the risk of development of resistance to neuraminidase inhibitors was currently rare, there was still a risk that overuse of oseltamivir could decrease its usefulness. This risk must be weighed against the benefit of increased access.
- It was stated that there had been a substantial number of reports of neuropsychiatric events and deaths associated with the use of oseltamivir in children. It was noted that Japan has the highest incidence of use of oseltamivir in the world and it was postulated that down-scheduling oseltamivir in Australia may increase the risk of it being used inappropriately in children and, thus, increase the risk of adverse events being experienced. The Committee was also reminded of its February 2008 decision to restrict the use of cough and cold preparations in children <2 The Committee noted

this decision only related to sedating antihistamines, not all cough and cold medicines.

XXXXX provided a lengthy submission referencing a large number of documents. XXXXX supported the rescheduling of oseltamivir to Schedule 3. The following points were made:

- It was stated that early access to oseltamivir produced a 38 per cent reduction in the severity of symptoms, a 55 per cent reduction in the use of antibiotics for secondary infections and a 30 per cent reduction in the duration of illness. These clinical outcomes would only be achieved if a patient commenced on treatment within 48 hours, thus currently, it is essential that patients seek advice from their GP as soon as possible. Given the shortfall in the number of doctors, especially in rural and remote areas, patients may suffer an increase in waiting times in winter, thus delaying access to treatment. Making oseltamivir a Schedule 3 substance would enable pharmacists (following professional guidelines) to recommend oseltamivir to patients displaying signs and symptoms of influenza. It was also asserted that allowing pharmacists to recommend oseltamivir would help to reduce the spread of influenza and help to reduce the economic burden of influenza infection on the community.

The criteria for inclusion of a medicine in Schedule 3 and matters to be considered under S52E were addressed as follows:

- Abuse potential – oseltamivir has a low potential for abuse.
- Potential for harm from inappropriate use – oseltamivir has a wide therapeutic index and few drug interactions and it is not an inhibitor of cytochrome P450 (CP450). It was asserted that there are two situations in which oseltamivir may be inappropriately used, firstly when used outside the 48 hour window for treatment and secondly when given for symptoms of viral infections other than influenza. In order to minimise the likelihood of inappropriate use if oseltamivir were rescheduled, it was proposed that protocols be developed to aid pharmacists in the diagnosis of influenza, and that these include instances when patients should be referred for medical attention. It was noted that recently XXXXX had been involved in the successful development of supply protocols for Schedule 3 emergency hormonal contraception and that this demonstrated that the pharmacy profession had the ability to appropriately supply oseltamivir. Further, research had shown that in areas experiencing high rates of influenza, a simple case definition differentiating between influenza and common cold symptoms had a level of clinical accuracy. Pharmacists would advise patients to seek medical attention if their symptoms did not improve once treatment had finished or if they suffered any adverse events.
- Low incidence of adverse events/safety – oseltamivir has a low level of well characterised side effects, the most common of which are nausea and vomiting. Recently there had been some reports, originating from Japan, of neuropsychiatric events occurring in children and adolescents. These events often had a rapid onset and resolution, generally consist of delirium and abnormal behaviour and there had been

fatalities reported. It was asserted that when compared with the levels of use of oseltamivir are relatively uncommon and that the same types of events can occur in the early stages of influenza. Preliminary animal research showing that alcohol can help oseltamivir enter the CNS was referred to, but it was noted that this had not yet been shown to have a causal link in humans. It was also noted that the oseltamivir PI was recently updated to include information on these effects. It was suggested that, as these effects had been seen primarily in young people, the Committee may wish to consider restricting Schedule 3 sales to patients over the age of 18.

- Pharmacist management of interactions – oseltamivir has few interactions with other drugs, low plasma protein binding and its gastric absorption is unlikely to be affected by drugs which alter gastric pH. Although it is metabolised in the liver, moderate hepatic impairment has no effect on the metabolism of it. Further, oseltamivir is not metabolised by the CP450 system, does not interact with cimetidine, paracetamol, amoxicillin or oral contraceptive agents.
- Therapeutic index/toxicity – oseltamivir has a wide therapeutic index, with doses of 1000mg daily being well tolerated. For patients with renal failure dose adjustment was only required when creatinine clearance dropped below 30mL/ min. It was noted that patients with severe renal failure would be under strict medical care.
- Risk of masking underlying conditions – influenza symptoms are similar to those for respiratory syncytial virus (RSV) which is a cause of serious respiratory infection in children < 13 years which can lead to serious morbidity and mortality. RSV infection is generally mild and self limiting in patients > 13 years, therefore the Committee may wish to limit a Schedule 3 listing of oseltamivir to patients over 13 years of age.
- Pharmacist management of contraindications and safety – oseltamivir is only contraindicated for patients who have hypersensitivity to any components of the product. As pharmacies are open extended hours and pharmacists are in a position to provide advice to patients without need for an appointment, they are in a key position to facilitate access to oseltamivir within the 48 hour window for effective use. Pharmacists were also able to recognise when medical assessment is required and refer patients if necessary.
- Indications for use – influenza is generally a self-limiting disease which is rapidly spread among close contacts via aerosol transmission. Symptoms generally last from 3 to 7 days and peak viral shedding occurs 24 to 36 hours after the onset of symptoms. Most people only take symptomatic relief for the illness but, despite these treatments making the person feel better, they do not limit the spread of the disease or reduce the likelihood of secondary infection. It was asserted that the treatment strategy for influenza was the same whether a patient saw a medical practitioner or pharmacist and that diagnosis was based on clinical symptoms and prevalence of influenza in the community. A kit designed to raise awareness about seasonal influenza had recently been distributed to pharmacists. This kit provided information on prevention, limiting and managing influenza infections. Pharmacists would be able to use a simple case definition, included in oseltamivir dispensing protocols, to diagnose and manage patients with influenza in the pharmacy setting.

- Risks and benefits – there appeared to be few risks to oseltamivir use given its safety profile, however the benefits of treatment were significant, with studies showing a 38 per cent reduction in the severity of symptoms, a 55 per cent reduction in the use of antibiotics for secondary infections and a 30 per cent reduction in the duration of illness. From a public health perspective increased access to oseltamivir would offer a large number of benefits including reductions in the number of deaths from influenza; in the spread of influenza; in the use of antibiotics for both secondary infections and inappropriately; in the pressure on primary healthcare services; in the rates of hospitalisation associated with influenza and in the rates of work absenteeism.
- Potential hazards – evidence does not suggest that the increase seen in drug resistance to oseltamivir was associated with increased use of the substance. Further, this resistance was limited to H1N1 strains and these do not carry the potential to cause a pandemic. Thus, oseltamivir was still an appropriate treatment in pandemic situations and it was noted that the WHO had not altered their recommendations relating to the use of oseltamivir in seasonal and avian influenza. There was also little potential for misdiagnosis of influenza if pharmacist protocols are followed.
- Extent and patterns of use – although vaccination is the primary public health method for dealing with influenza it does not provide total protection from the virus and rates of vaccination in people under the age of 65 are quite low. Given this there is a clear role for the use of oseltamivir in the management of seasonal influenza. It was stated that the use of oseltamivir in Australia has been limited due to the need to obtain a prescription for it and commence treatment within 48 of symptom onset.
- Dosage and formulation – this was described.
- Need for access – the earlier a person commences on oseltamivir treatment the shorter their duration of illness and the current need to see a doctor and obtain a prescription for oseltamivir was a barrier to the timely and effective use of the substance. Making oseltamivir a Schedule 3 medicine would help to remove this barrier and ensure that patients were able to be assessed and treated, if required, or referred to a medical practitioner in a timely manner. It was asserted that the improved access to oseltamivir will help reduce the loss of life associated with influenza infection and also help to reduce the considerable morbidity associated with the disease and decrease the need for antibiotic treatment of associated secondary infections. This, in turn, would serve to reduce to economic burden of influenza infection to the wider Australian community.
- Purpose of use – it was proposed that oseltamivir in Schedule 3 be restricted to the treatment of seasonal influenza A and B in patients over 13 years of age and that it could be supplied to patients or their carers who describe symptoms consistent with the case definition for influenza.
- It was noted that both New Zealand and the UK have established systems which allow the supply of oseltamivir as an OTC medicine and that the experience from these countries has shown that trained pharmacists, using well developed protocols can successfully and safely provide oseltamivir to patients. Further, it would provide

healthcare practitioners experience in the use of this substance which would be of value in a pandemic situation.

A submission was received from XXXXX in support of XXXXX submission. The following points were made:

- Even if the widespread use of oseltamivir to treat seasonal influenza caused these viruses to become resistant, oseltamivir would still be effective against any new strain of pandemic influenza virus that arose.
- It was noted that it had recently been discovered that the mechanism for resistance in H5N1 avian influenza was the same as in H1N1 seasonal influenza. It was stated that, despite this, it was unlikely that resistance in H1N1 strains would automatically mean H5N1 strains would also be resistant as they were two distinct virus stains. It was acknowledged, however, that widespread use of oseltamivir to treat H5N1 avian influenza may eventually result in resistance developing, but it was stressed that this was not related to any resistance which may develop in H1N1 strains.

XXXXX provided a submission stating that it supported any responsible measure to make neuraminidase inhibitors more readily available. XXXXX. The following points were made:

- Oseltamivir is a safe and effective treatment for reducing the duration and severity of influenza, however this benefit is only obtained if treatment was started within 48 hours of onset of symptoms and a number of studies are quoted relating to this. One study (outlined in the Tamiflu PI) showed that starting treatment within 36 hours lead to a reduction in infection duration of one third and lessened the severity of illness by 40 per cent. A 2008 Cochrane review was cited which showed the efficacy of oseltamivir in healthy adults to be 61 per cent at the 75mg dose. The authors of this study concluded that oseltamivir should not be used in seasonal influenza but, rather, should be used as a public health measure in epidemic or pandemic influenza. A further Cochrane review in children was discussed, noting that NIs were shown to be effective in reducing illness duration and complications from influenza in healthy children.
- The issue of resistance was discussed, noting that reports of resistance to oseltamivir had been increasing and that concerns had been raised about widespread use contributing to this. It was stated that the issue of resistance needs to be considered in pandemic planning and monitored closely. A number of studies were quoted showing that, in healthy adults, resistance ranges between 0 and 0.5 per cent, but that in children it can be as high as 4 per cent. It was noted that this estimate of higher incidences in children included a number of recent publications which had shown resistance as high as 18 per cent, albeit at low levels and having no influence on the course of the illness. One theory for this increase in resistance was that insufficient doses of oseltamivir were being used and the virus was not being eradicated. This statement was supported by reference to another study conducted in children in the

US which showed no evidence of resistance when doses were tailored to age and weight.

- It was noted that there was an increase in H1N1 resistance in the Northern Hemisphere 2007-08 influenza season, with some strains showing up to 70 per cent resistance to oseltamivir. It was asserted, however, that studies had shown that there was little evidence of the spread of resistant H1N1 in the community. It appeared that these strains had the ability to be transmitted and cause clinical disease similar to oseltamivir susceptible strains. The origin of these strains was unknown and it was not clear whether they would persist through the summer or if they would spread more widely. It was noted that the WHO was currently assessing the spread and extent of oseltamivir resistant influenza, but to date no changes had been made to any WHO recommendations on treatment of influenza with oseltamivir.
- It was asserted that the current consideration that oseltamivir treatment only be initiated when there was a reasonable certainty that a patient has come into contact with the influenza virus was an economic one as there were no concerns with resistance developing in patients who were not actively infected. However, it was desirable to have tests which could aid in diagnosis and assist in making decisions about antiviral use. It was noted that there were some point of care tests available, but that these were of low sensitivity and not widely available. A study was quoted as showing that clinical judgement and knowledge of local influenza conditions were of similar use in influenza diagnosis. It was stated that, given this, when influenza was a likely cause of infection, the benefits of starting the patient on oseltamivir were worthwhile.
- It was stated that the Committee should also take into account the fact that any healthcare practitioner prescribing oseltamivir would need to be able to identify complications of influenza and advise on appropriate treatment. Also, it should be noted that data from Western Australia had shown that, in the absence of fast and reliable diagnostic tests, GPs accurately diagnosed influenza in 57 per cent of cases. Further, it was stated that the Committee would need to consider that there was minimal impact on patients taking oseltamivir when it was not required and that there were benefits to patients (eg in lessening time off work) having access to oseltamivir as a treatment option.
- Given that rapid access to treatment was important, it should be remembered that influenza season was a particularly busy period for medical practitioners and there had been anecdotal reports of patients having to wait a number of days to see a doctor. Patients who had to wait such lengthy periods of time were missing out on the potential benefits of oseltamivir treatment.
- The side effect profile of oseltamivir was discussed, noting that it was well characterised and generally well tolerated. It was noted that the Australian PI for oseltamivir was updated in February 2008 to contain information about potential neuropsychiatric events which resulted from the above-mentioned ADRs seen in Japan. It was noted that a causal link has yet to be established. A number of reasons for these ADRs occurring more frequently in Japan were advanced including higher

rates of oseltamivir use, differing methods of ADR reporting and differing manifestations of influenza in Japan compared with the US.

A submission was received from XXXXX requesting that oseltamivir be rescheduled to at least Schedule 2. XXXXX stated that, in the case of a pandemic, medical officers may be in short supply and patients need access to oseltamivir early in their illness. It was also stated that the product had been proven to be safe.

XXXXX provided a submission in which it stated that the risks of OTC availability significantly outweigh the benefits which may be obtained and, thus, rescheduling is not supported. This position was taken due to the large potential for overuse of oseltamivir during winter and the possibility that this may generate transmissible resistance.

XXXXX provided a submission in which it supports the rescheduling of oseltamivir to Schedule 3. XXXXX also provided a statement in favour of rescheduling. The following points were made:

- Last year in the ACT there were 390 laboratory confirmed cases of influenza, 4,644 in Queensland and 10,577 Australia wide. It was noted that the Queensland Government estimated that approximately 10 per cent of staff were affected by the illness each year. It was stated that the economic cost of influenza to business and the community through employee absenteeism and associated loss in productivity and other costs was estimated at approximately $2 billion dollars in 2007 and $400 million in Queensland alone.
- It could be difficult to get an appointment to see a doctor in the winter in a timely manner and this can impact on the effectiveness of oseltamivir as it must be taken within 48 hours of symptom onset and, thus, limit the benefit the patient receives from it. It was asserted that if oseltamivir were available OTC it would allow more patients access to it within the critical 48 hour timeframe. This would lead to an associated reduction in the amount of employee absenteeism from work due to the virus, reduce the spread of the virus to co-workers and, thus, a significant saving to the cost of the infection to business would be achieved. It was also asserted that it would reduce the cost of influenza to the health system.

DISCUSSION – RELEVANT MATTERS UNDER 52E

A Member asked whether treatment with oseltamivir impacts on patient mortality. It was noted that the sponsor's clinical trial data showed a 24 to 36 hour decrease in symptom duration but that there was no clear data showing a reduction in mortality, even in high-risk patients. It was noted that there were approximately 3000 deaths from influenza seen each year.

Members generally agreed that patients who were classified as "high-risk" were likely to be under medical management and thus be expected to have access to oseltamivir. It was further noted that they were also the group which should be targeted for influenza

vaccination. However, another Member noted that oseltamivir was indicated for all patients with seasonal influenza, not just those in high-risk groups.

Members discussed the likely public health impact that Schedule 3 availability of oseltamivir would have on vaccination rates. A number of Members felt that it was possible that Schedule 3 availability of oseltamivir would potentially decrease the level of vaccination in the community, or create the perception that NIs might be an alternative to vaccination. The Committee noted that vaccination is currently only approximately 70 per cent effective, however effectiveness increases with successive years of vaccination. A number of Members recalled the National Prescribing Service (NPS) had issued a position statement on the use of neuraminidase inhibitors entitled the *"Role of the neuraminidase inhibitors oseltamivir* XXXXX *and zanamivir* XXXXX *in seasonal influenza."* Members recalled that this statement set out guidelines for the use of these substances and strongly recommended that, due to the small absolute benefit seen with NI treatment, their use should be avoided in seasonal influenza in otherwise healthy individuals. Members also noted that the NPS statement maintained that NIs should only be used in laboratory confirmed cases of influenza and that influenza infection could not be accurately diagnosed on clinical grounds alone.

Members also noted that the NPS document also stated that NIs are not an alternative to vaccination for preventing influenza and its complications and, further, that vaccination remained the first-line strategy for reducing morbidity and mortality from influenza in high-risk groups. The NPS statement acknowledged that some high-risk groups may not develop full immunity with vaccination and that NIs might be considered. A Member reiterated that these high-risk patients should already be under medical supervision and, thus, there would be little benefit to them from oseltamivir being a Schedule 3 medicine. Members agreed that vaccination should remain the first line strategy for the prevention of influenza.

The Committee noted that seasonal influenza could be a serious public health hazard to some populations within the community and that increased availability of NIs might help to lessen this risk. However, the Committee acknowledged any medical practitioner could write a prescription for a high-risk patient and instruct them to fill it at the onset of any flu-like symptoms. A Member noted that in the United Kingdom certain, licensed pharmacies were able to provide oseltamivir to high-risk patients without a prescription. However, it was noted that these pharmacies must have been certified and must also collect dispensing data.

Members recalled there was also the risk of misdiagnosis of serious illness. A Member stated that pneumonia and influenza can often present with similar initial symptoms and that a physical examination was essential to exclude the possibility of pneumonia. This alone was a strong argument for not making oseltamivir a Schedule 3 medicine.

A Member expressed concern that down-scheduling of oseltamivir could also lead to underreporting of cases of influenza in the community, despite influenza being a Notifiable Disease.

Members discussed the information presented on the levels of resistance to oseltamivir. A Member noted that the level of resistance to oseltamivir appeared to be increasing and an increase, globally, in drug exposure may lead to a further increase in resistance. Another Member stated that it was unknown whether the currently seen Northern Hemisphere H1N1 oseltamivir resistant strains would persist, but agreed that the increasing incidence of resistance was of concern. However, another Member noted that the resistance being seen was mostly due to genetic drift in animal reservoirs and not due to drug pressure. The Member noted that Japan has the highest incidence of use of oseltamivir but that it also has the lowest incidence of resistant isolates. The Member further stated that restricting the use of oseltamivir was unlikely to have any impact on the incidence of genetic drift. Members generally agreed, however, that there was still a degree of uncertainty surrounding the risk and extent of development of resistance to oseltamivir.

A Member stated that it was likely that patients who did not actually have influenza would be provided with oseltamivir and that this would put them at risk of ADRs without any benefit from the substance. Members agreed that although oseltamivir had very few drug-drug interactions and a low potential for harm from inappropriate use, there was still a risk to patients of ADRs from unnecessary use.

Members noted that all jurisdictions either had in place or were in the process of implementing mechanisms to facilitate the supply of oseltamivir when circumstances warranted rapid access.

In summary, the Committee remained concerned about the risk of the development of resistance, and that down-scheduling could potentially lower influenza vaccination rates, including among vulnerable patient groups. The Committee also noted that without appropriate physical examination the risk of misdiagnosis could lead to delays in treatment and potential exposure to adverse effects without the prospect of a significant benefit. Finally, the Committee expressed confidence that all States and Territories had established, or were planning to establish, mechanisms to facilitate rapid access to oseltamivir should circumstances warrant, and thus concluded that, on balance the current scheduling remained appropriate.

RESOLUTION 2008/53 - 27

The Committee decided that the current scheduling of oseltamivir remained appropriate.

13. MATTERS REFERRED BY THE REGISTRATION PROCESS FOR PRESCRIPTION MEDICINES

13.1 NEW SUBSTANCES (NOT SEEN BEFORE BY THE NDPSC)

13.1.1 RALTEGRAVIR

PURPOSE

The Committee considered the scheduling of the new medicine raltegravir.

BACKGROUND

Raltegravir is in a new pharmacological class of antiretroviral agents known as HIV integrase inhibitors. It prevents viral replication by inhibiting viral DNA insertion into the host's cellular genome. Specifically, raltegravir prevents integrase insertion essential for endonucleolytic processing of the viral DNA ends and the subsequent strand transfer or integration of viral and cellular DNA. Humans lack the integrase enzyme and therefore toxicities due to integrase inhibition are not expected.

The December 2007 ADEC Meeting recommended approval of a submission from Merck Sharp & Dohme (Australia) Pty Ltd to register ISENTRESS tablets containing the new chemical entity raltegravir 400mg for the indication:

> *In combination with other antiretroviral agents is indicated for the treatment of HIV-1infection in treatment-experienced adult patients who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents. This indication is based on analyses of plasma HIV-1 RNA levels up through 24 weeks in two controlled studies of ISENTRESS. These studies were conducted in clinically advanced, 3-class antiretroviral (NNRTI, NRTI, PI) treatment-experienced adults. The use of other active agents with ISENTRESS is associated with a greater likelihood of treatment response [see Clinical Studies (14)].The safety and efficacy of ISENTRESS have not been established in treatment-naïve adult patients or pediatric patients.There are no study results demonstrating the effect of ISENTRESS on clinical progression of HIV-1 infection*.

The recommended dose of raltegravir in adults is 400 mg twice daily.

XXXXX

DISCUSSION - SUBMISSIONS

The Committee noted the Minutes of the December 2007 ADEC Meeting XXXXX.

The Committee noted the following from Micromedex:

- adverse reactions included dizziness, fatigue and weakness;
- efficacy in paediatric patients less than 16 years of age had not been established;
- there were no adequate and well-controlled studies in pregnant women;
- raltegravir would be prescribed by a specialist in HIV medicine.

The Committee noted that raltegravir was classified as a prescription medicine in New Zealand.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that toxicity and safety, risks and benefits, extent and patterns of use, need for access as well as the purpose for which it is to be used (52E(1)(a)(b)(d)(f)(h)) were relevant to consideration of scheduling.

The Committee noted that as there was a recognised need for effective anti retroviral treatments in the face of resistance and toxicity and that use of the substance would require professional oversight, it would be appropriate to include raltegravir in Schedule 4.

The Committee also agreed that the adverse reactions of dizziness and fatigue were of a low level which did not warrant consideration for inclusion in Appendix K.

RESOLUTION 2008/53 - 28

The Committee decided to include raltegravir in Schedule 4 of the SUSDP.

Schedule 4 – New entry

RALTEGRAVIR.

13.1.2 MARAVIROC

PURPOSE

The Committee considered the scheduling of the new medicine maraviroc.

BACKGROUND

Maraviroc is a chemokine receptor antagonist that prevents HIV infection of CD4 T-cells by blocking the CCR5 receptor. The antiviral mechanism of action of maraviroc is exclusively CCR5-mediated by preventing the interaction of HIV-1 glycoprotein (gp)120 and CCR5 necessary for CCR5-tropic HIV-1 to enter cells. It is inactive against the CXCR4 receptor and does not inhibit dual-tropic HIV-1 entry.

The December 2007 ADEC Meeting recommended approval of a submission from Pfizer Australia Pty Ltd to register CELSENTRI tablets containing the new chemical entity maraviroc 150 mg & 300 mg for the indication:

> *In combination with other antiretrovirals, for treatment-experienced adult patients infected with only CCR5-tropic HIV-1 detectable. The indication is based on safety and efficacy data from two double-blind, placebo controlled trials of 24 weeks duration in treatment experienced patients.*

The recommended dose of maraviroc is 300mg twice daily.

XXXXX

DISCUSSION - SUBMISSIONS

The Committee noted the Minutes of the December 2007 ADEC Meeting.

The Committee noted the following from Micromedex:

- adverse reactions include musculoskeletal, hepatic and cardiovascular effects, rash, abdominal pain, cough, fever, dizziness and hypertension;
- safety and efficacy have not been established in paediatric patients;
- there were no adequate and well-controlled studies in pregnant women;
- that maraviroc was a new HIV medicine for use in treatment-experienced adult patients infected with only CCR5-tropic HIV-1 detectable.
- the condition to be treated requires medical diagnosis and monitoring of response;
- that maraviroc would be prescribed by a specialist in HIV medicine.

The Committee noted that maraviroc was not classified in New Zealand.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that toxicity and safety, risks and benefits, extent and patterns of use, need for access as well as the purpose for which it is to be used (52E(1)(a)(b)(d)(f)(h)) were relevant to consideration of scheduling.

The Committee noted that as the use of maraviroc would require correct medical diagnosis and monitoring of both response and side effects, it would be appropriate to include the substance in Schedule 4.

The Committee agreed that the adverse reactions of dizziness was of a low level which did not warrant consideration for inclusion in Appendix K.

RESOLUTION 2008/53 - 29

The Committee decided to include maraviroc in Schedule 4 of the SUSDP and to recommend to New Zealand that it consider a similar scheduling outcome.

Schedule 4 – New entry

MARAVIROC.

13.1.3 NITRIC OXIDE

PURPOSE

The Committee considered the scheduling of the new medicine nitric oxide.

BACKGROUND

Nitric oxide is a member of the respiratory stimulant class. It is a medicinal gas administered by inhalation which acts as a pulmonary vasodilator by increasing intracellular levels of cyclic guanosine 3', 5' –monophosphate.

The October 2007 ADEC Meeting recommended approval of a submission from Delpharm Consultants Pty Limited to register INOmax medicinal gas containing the new chemical entity nitric oxide 800ppm.

INOmax is a gaseous blend of nitric oxide and nitrogen in a ratio of 0.08 per cent and 99.92 per cent respectively at 800ppm. In persistent pulmonary hypertension of the newborn (PPHN), pulmonary vascular resistance is high, leading to hypoxemia secondary to right to left shunting of blood through a patent ductus arteriosus and foramen ovale. INOmax is used to improve oxygenation in these newborns by dilating pulmonary vessels and redistributing blood flow away from areas with low ventilation / perfusion.

The ADEC approved indication is:

> *INOmax, in conjunction with ventilatory support and other appropriate agents, is indicated for the treatment of term and near-term (>34 weeks) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, in order to improve oxygenation and to reduce the need for extracorporeal membrane oxygenation.*

XXXXX

DISCUSSION - SUBMISSIONS

The Committee noted the Minutes of the October 2007 ADEC Meeting.

The Committee noted that nitric oxide:

- is approved in the US and the EU;
- is used in the chemical industry, including as an intermediate for the synthesis of nitric acid from ammonia. It also finds use in the semiconductor industry for various processes;
- 'as is' is of minimal use in today's chemical industry, as reported on the website *courses.washington.edu*. The ammonia oxidation reaction is most commonly used as the first of three sequential reaction steps that convert ammonia into ammonium nitrate, a fertilizer. In the second step, nitric oxide is reacted with more oxygen and water to form nitric acid. In the third step, nitric acid is reacted with ammonia to form ammonium nitrate.

The Committee noted that nitric oxide was not classified in New Zealand.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that toxicity and safety, risks and benefits, extent and patterns of use, need for access as well as the purpose for which it is to be used (52E(1)(a)(b)(d)(f)(h)) were relevant to consideration of scheduling.

The Committee noted that as nitric oxide would only be administered in a medical unit, it would be appropriate to include the substance in Schedule 4.

The Committee also agreed that as nitric oxide did have industrial uses, scheduling should be for human therapeutic use only.

RESOLUTION 2008/53 - 30

The Committee decided to include nitric oxide for human therapeutic use in Schedule 4 of the SUSDP and to recommend to New Zealand that it consider a similar scheduling outcome.

Schedule 4 – New entry

NITRIC OXIDE for human therapeutic use.

13.1.4 ROTIGOTINE

PURPOSE

The Committee considered the scheduling status of the new medicine rotigotine.

BACKGROUND

Rotigotine is a non-ergolinic aminotetralin dopamine-3/dopamine-2/dopamine -1 (D3/Dw/D1) receptor agonist, is effective in the treatment of Parkinson's disease. While the precise mechanism is unclear, it is thought to stimulate D2 receptors within the caudate-putamen in the brain.

The October 2007 ADEC Meeting recommended the approval of the submission from UCB Pharma to register NEUPRO transdermal drug delivery system containing the new chemical entity rotigotine with nominal release rates of 2mg / 4 mg / 6mg / 8mg / 24hr for the indication as monotherapy, or in combination with levodopa, for the treatment of idiopathic Parkinson's disease from early stage to advanced disease.

XXXXX

DISCUSSION – SUBMISSIONS

The June 2008 Meeting of the NDPSC noted Micromedex which reported that patients are to be alerted to possibility of falling asleep during normal activities for up to 1 year after beginning treatment; to avoid activities requiring mental alertness; to rise slowly from sitting/supine position as drug may cause orthostatic hypotension; that drug may cause application site reactions, nausea, dizziness, headache, vomiting, insomnia, syncope, hallucinations or peripheral edema and that patients should not drink alcohol or take other CNS depressants while using this drug.

The Committee noted that the Patient Instructions in Micromedex included a warning that this medicine may make patients dizzy or drowsy and to avoid driving, using machines, or doing anything else that may make the patient feel light-headed when getting up from a sitting or lying position suddenly. The patient is advised to rise slowly from sitting or lying down.

DISCUSSION – RELEVANT MATTERS UNDER 52E

Members felt that, given the side effect profile for rotigotine and its status as a new chemical entity, its inclusion in Schedule 4 was warranted.

This relates to both S52E (1) (b), the risks and benefits associated with the use of a substance; and S52E (1) (c), the potential hazards associated with the use of a substance. The Committee noted that rotigotine was not scheduled in New Zealand.

The Committee further agreed that, as it was probable that rotigotine would always be dispensed and that there was evidence that it causes drowsiness, that it should be included in Appendix K of the SUSDP.

RESOLUTION 2008/53 - 31

The Committee decided to include the new chemical entity rotigotine in Schedule 4 of the SUSDP. The Committee also decided to include rotigotine in Appendix K of the SUSDP.

Schedule 4 – New Entry

ROTIGOTINE.

Appendix K – New entry

Rotigotine

13.1.5 LENALIDOMIDE

PURPOSE

The Committee considered the scheduling of the new medicine enalidomide.

BACKGROUND

Lenalidomide is an immune modulator. It is an analogue of thalidomide, which is currently registered in Australia as monotherapy for *the treatment of multiple myeloma after failure of standard therapies.* Myeloma is a rare disease in Australia and this agent has been designated as an orphan drug for this indication. Besides thalidomide (THALIDOMIDE PHARMION), bortezomib (VELCADE) has also been approved for the treatment of myeloma.

The October 2007 ADEC Meeting recommended that there should be no objection to approval of the submission from Celgene Pty Limited to register Revlimid capsules containing the new chemical entity lenalidomide 5mg, 10mg, 15mg and 25 mg for the indication: for the treatment of multiple myeloma patients who have received at least one prior therapy, and who have progressive disease.

XXXXX

DISCUSSION - SUBMISSIONS

XXXXX

The June 2008 NDPSC Meeting noted that the approved Product Information for Revlimid (lenalidomide) records the following;

- *Lenalidomide is a Pregnancy Category X medicine*;

- a boxed warning *Teratogenic effects: Revlimid (lenalidomide) is structurally related to thalidomide. Thalidomide is a known human teratogen that causes severe life threatening human birth defects. If lenalidomide is taken during pregnancy, it may cause birth defects or death to an unborn baby. Women should be advised to avoid pregnancy whilst taking Revlimid (lenalidomide) and for 4 weeks after stopping the drug;*

- Lenalidomide is available under a restricted distribution program (RevAccess). Only physicians and pharmacists registered with this program can prescribe and dispense the product. Lenalidomide must only be dispensed to patients who are registered and meet all the conditions of the program (detailed in the Product Information) including;

- female patients should use effective contraception, without interruption, four weeks before starting treatment, throughout the entire duration of treatment and four weeks after the end of treatment;

- it is not known whether lenalidomide is present in semen. Therefore all male patients should use condoms throughout treatment duration, during dose interruption and for

one week after cessation of treatment if their partner is of childbearing potential and has no contraception.

A Member noted that lenalidomide did not warrant inclusion in Appendix D paragraph 2, subparagraph (2) point (b), as a dermatologist would not prescribe it. It was agreed that inclusion in Appendix D paragraph 4 would be a better option as this refers only to specialist physicians. It was also noted that a specialist physician would be counselled against the prescription of lenalidomide to a patient when there is a risk of pregnancy.

The possibility of the private importation of lenalidomide, along with the mitigation of this risk by the regulator limiting which specialists can prescribe lenalidomide was noted by the Committee.

The Committee noted that lenalidomide was not classified in New Zealand.

DISCUSSION – RELEVANT MATTERS UNDER 52E

Members felt that, given the concerns surrounding the toxicity and safety of the lenalidomide and the potential for teratogenicity, its inclusion in Schedule 4 was warranted. This relates to both S52E (a), the toxicity and safety of a substance, S52E (b), the risks and benefits associated with the use of a substance, and S52E (c), potential hazards associated with the use of a substance.

Members also felt that lenalidomide should appear in Appendix D paragraph 4, due to the potential for teratogenicity, under S52E (a) the toxicity and safety of the product S52 and (c) potential hazards associated with the use of a substance.

RESOLUTION 2008/53 - 32

The Committee decided to include the new medicine lenalidomide in Schedule 4 and in Appendix D.

Schedule 4 - New entry

LENALIDOMIDE.

Appendix D – Amendment

Appendix D, paragraph 4 – Amend entry to read

4. Poisons available only from or on the order of a specialist physician and for which the prescriber must, where the patient is a woman of child bearing age:

(a) ensure that the possibility of pregnancy has been excluded prior to commencement of treatment; and

(b) advise the patient to avoid becoming pregnant during or for a period of 1 month after completion of treatment.

TRETINOIN for human oral use.
LENALIDOMIDE.

13.1.6 ALGLUCOSIDASE ALFA

PURPOSE

The Committee considered the scheduling of the new medicine alglucosidase alfa.

BACKGROUND

Alglucosidase alfa-rch is a purified form of the lysosomal enzyme acid alfa-glucosidase (GAA) produced by recombinant DNA technology in a Chinese hamster ovary cell line, indicated for the treatment of Pompe disease.

Pompe disease is a rare autosomal recessive disease caused by the deficiency of lysosomal GAA. Pompe disease results in intralysosomal accumulation of glycogen in various tissues, particularly cardiac and skeletal muscles, leading to the development of cardiomyopathy, progressive muscle weakness and impairment of respiratory function. Treatment of Pompe disease with Alglucosidase alfa provides an exogenous source of GAA.

The February 2008 Australian Drug Evaluation Committee (ADEC) Meeting recommended approval of a submission from Genzyme Australasia Pty Ltd to register Myozyme Powder for Injection containing the new biological entity alglucosidase alfa (rch) 52.5 mg for the indication:

> *For the long-term treatment of patients with a confirmed diagnosis of Pompe disease (acid alfa-glucosidase deficiency).*

XXXXX
DISCUSSION - SUBMISSIONS

The Committee noted the Minutes of the February 2008 ADEC Meeting. XXXXX.
The Committee noted the approved Product Information.

The Committee noted alglucosidase alfa was classified as a prescription medicine in New Zealand.

The Committee noted that Micromedex for alglucosidase alfa recorded a black box warning *Life-threatening anaphylactic reactions, including anaphylactic shock, have been observed in patients during alglucosidase alfa infusion. Because of the potential for*

severe infusion reactions, appropriate medical support measures should be readily available when alglucosidase alfa is administered.

On the issue of nomenclature, the Committee noted that the February 2002 NDPSC Meeting included epoetin alfa and epoetin beta in Schedule 4. As part of the trans-Tasman harmonisation process at the October 2006 NDPSC Meeting, the schedule entries for epoetin alfa and beta were deleted and a new Schedule 4 class entry for "EPOETINS" was included.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that toxicity and safety, risks and benefits, extent and patterns of use, need for access as well as the purpose for which it is to be used (52E(1)(a)(b)(d)(f)(h)) were relevant to consideration of scheduling.

The Committee noted that as alglucosidase alfa would be used in a life saving context with medical oversight and that there was an overwhelming benefit v. risk ratio, it would be appropriate to include the substance in Schedule 4.

The Committee agreed that the schedule entry would not require specifying the alfa subtype.

RESOLUTION 2008/53 – 33

The Committee decided to include alglucosidase in Schedule 4 of the SUSDP.

Schedule 4 – New entry

ALGLUCOSIDASE.

13.1.7 TEMSIROLIMUS

PURPOSE

The Committee considered the scheduling of the new medicine temsirolimus.

BACKGROUND

Temsirolimus is an antineoplastic agent. It is an inhibitor of mTOR (mammalian target of rapamycin), an intracellular serine / threonine protein kinase which is a central controller of multiple signalling pathways involved in regulating cell growth, proliferation and apoptosis.

The February 2008 Australian Drug Evaluation Committee (ADEC) Meeting recommended approval of a submission from Wyeth Australia Pty Limited to register

TORISEL Injection Solution containing the new chemical entity temsirolimus 25 mg/mL for the indication *the treatment of advanced renal cell carcinoma*.

XXXXX

DISCUSSION - SUBMISSIONS

- The Committee noted the minutes of the February 2008 ADEC Meeting XXXXX.

The Committee noted the approved Product Information.

The Committee noted that temsirolimus was not classified in New Zealand.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that toxicity and safety, risks and benefits, extent and patterns of use and need for access as well as the purpose for which it is to be used (52E(1)(a)(b)(d)(f)(h)) were relevant to consideration of scheduling.

The Committee noted that as temsirolimus would be administered in specialist medical unit, it would be appropriate to include the substance in Schedule 4.

RESOLUTION 2008/53 - 34

The Committee decided to include temsirolimus in Schedule 4 of the SUSDP and to recommend to New Zealand to consider a similar scheduling outcome.

Schedule 4 - New entry

TEMSIROLIMUS.

13.1.8 IDURSULFASE

PURPOSE

The Committee considered the scheduling of the new medicine idursulfase.

BACKGROUND

Idursulfase is a recombinant form of iduronate-2-sulfatase, produced by recombinant DNA technology in a human cell line. Idursulfase is intended as an exogenous source of enzyme in patients with mucopolysaccharidosis II (MPSII or Hunter syndrome).

MPS is a serious genetic (X-linked) disorder that primarily affects males. It is caused by congenital deficiency of iduronate-2-sulfatase, a lysosomal enzyme involved in the degradation of glycosaminoglycans (GAGs). It is characterised by the accumulation in a wide variety of tissues of the GAGs dermatan sulfate and heparan sulfate.

The TGA Delegate approved the registration of XXXXX containing idursulfase solution concentrate 6 mg in 3 mLs for the treatment of Mucopolysaccharidosis (MPS) II (Hunter syndrome).

DISCUSSION - SUBMISSIONS

The Committee noted that where the TGA was able to obtain the USFDA evaluation, the product would be considered by the TGA Delegate without referral to the Australian Drug Evaluation Committee (ADEC) or Peer Review.

The Committee noted the TGA Delegate's summary. XXXXX

The Committee noted the approved Product Information.

The Committee noted the following from Micromedex:
- black box warning – anaphylactoid reactions which may be life threatening;
- precautions include acute respiratory disease, compromised respiratory function and acute febrile illness.

The Committee noted that idursulfase was not classified in New Zealand.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that toxicity and safety, risks and benefits, extent and patterns of use, need for access as well as the purpose for which it is to be used (52E(1)(a)(b)(d)(f)(h)) were relevant to consideration of scheduling.

The Committee noted that that as idursulfase had a favourable risk benefit ratio and would be administered in a specialist medical setting for the treatment of a rare disease, it would be appropriate to include the substance in Schedule 4.

RESOLUTION 2008/53 - 35

The Committee decided to include idursulfase in Schedule 4 of the SUSDP and to recommend to New Zealand to consider a similar scheduling outcome.

Schedule 4 - New entry

IDURSULFASE.

13.2 FOR INFORMATION (SUBSTANCES ALREADY SCHEDULED)

13.2.1 VILDAGLIPTIN

PURPOSE

The Committee noted XXXXX the new medicine vildagliptin.

BACKGROUND

Vildagliptin belongs to a new class of oral anti-diabetic drugs known as islet enhancers and was developed for the treatment of type 2 diabetes mellitus.

XXXXX

DISCUSSION – SUBMISSIONS

The Committee noted:

- XXXXX
- that vildagliptin was included in Schedule 4 at the June 2007 NDPSC Meeting, through harmonisation;
- that no marketed product is approved for use in Australia;
- that under the therapeutic goods legislation, there are a number of avenues whereby a drug can be accessed, including personal importation, the Special Access Scheme (SAS) and clinical trials.

RESOLUTION 2008/53 - 36

The Committee noted XXXXX the new medicine vildagliptin.

13.2.2 NILOTINIB

PURPOSE

The Committee noted ADEC's consideration of the new medicine nilotinib.

BACKGROUND

Nilotinib is a novel aminopyrimidine – a highly effective competitive inhibitor of the protein tyrosine kinase activity of Bcr-Abl.

XXXXX submission from Novartis Pharmaceuticals Pty Ltd to register TASIGNA capsules (hard) containing the new chemical entity nilotinib XXXXX.

The December 2007 ADEC XXXXX recommended that:

- there should be no objection to approval of the submission for 200 mg for the indication *for the treatment of adults with chronic phase and accelerated phase Philadelphia chromosome positive chronic myeloid leukaemia resistant to or intolerant of prior therapy including imatinib;*

- XXXXX

DISCUSSION - SUBMISSIONS

The Committee noted:

- the minutes of the XXXXX December 2007 ADEC Meeting;
- the approved Product Information;
- that nilotinib was included in Schedule 4 at the June 2007 NDPSC Meeting, through harmonisation.

RESOLUTION 2008/53 - 37

The Committee noted ADEC's consideration of the new medicine nilotinib.

13.2.3 SITAGLIPTIN

PURPOSE

The Committee noted ADEC's consideration of the new medicine sitagliptin.

BACKGROUND

Sitagliptin is one of a new class of antidiabetic agents.

The October 2007 ADEC Meeting recommended:

- approval of a submission from Merck Sharp & Dohme (Australia) Pty Ltd to register JANUVIA tablet containing the new chemical entity sitagliptin (as phosphate monohydrate) 25 mg, 50 mg and 100 mg for the indication:

  For the treatment of diabetes mellitus type 2 in persons 18 years of age and older who have failed dietary measures and exercise:
  - as dual combination therapy with metformin or with a sulfonylurea or with a thiazolidinedione where the use of a thiazolidinedione is considered appropriate.

XXXXX

DISCUSSION - SUBMISSIONS

The Committee noted:

- the minutes of the October 2007 ADEC Meeting;
- the approved Product Information;

- that sitagliptin was included in Schedule 4 at the February 2007 NDPSC Meeting, through harmonisation.

RESOLUTION 2008/53 - 38

The Committee noted ADEC's consideration of the new medicine sitagliptin.

13.2.4 SERTINDOLE

PURPOSE

The Committee noted XXXXX.

DISCUSSION - SUBMISSIONS

The Committee noted:

- XXXXX;
- that sertindole was included in Schedule 4 at the November 2000 NDPSC Meeting, through harmonisation;
- that no marketed product was approved for use in Australia;
- that under the therapeutic goods legislation, there are a number of avenues whereby a drug can be accessed, including personal importation, the Special Access Scheme (SAS) and clinical trials.

RESOLUTION 2008/53 - 39

The Committee noted XXXXX the new medicine sertindole.

13.2.5 LEVOSIMENDAN

PURPOSE

The Committee noted XXXXX the new medicine levosimendan.

BACKGROUND

Levosimendan is a pyridazinone-dintrile derivative which enhances calcium sensitivity of cardiac contractile proteins, opens ATP-sensitive and Ca2+-dependent K+ channels and is a selective phosphodiesterase III (PDE) inhibitor. By these inotropic and vasodilatory actions, levosimendan increases cardiac output without significantly increasing oxygen demand

XXXXX

DISCUSSION - SUBMISSIONS

The Committee noted:

- XXXXX ;
- that levosimendan was included in Schedule 4 at the October 2006 NDPSC Meeting, through harmonisation;
- that no marketed product was approved for use in Australia;
- that under the therapeutic goods legislation, there are a number of avenues whereby a drug can be accessed, including personal importation, the Special Access Scheme (SAS) and clinical trials.

RESOLUTION 2008/53 - 40

The Committee noted XXXXX the new medicine levosimenden.

13.2.6 INSULIN HUMAN (INHALED)

PURPOSE

The Committee noted ADEC's consideration of the new medicine insulin human (inhaled).

BACKGROUND

The October 2007 ADEC Meeting recommended approval of a submission from Pfizer Australia Pty Ltd to register EXUBERA, powder for inhalation containing the new chemical entity insulin human 1mg and 3mg for the indication:

> *For the treatment of adult patients with type 2 diabetes mellitus who failed therapy with oral antidiabetic agents and who require bolus insulin.*

XXXXX

DISCUSSION - SUBMISSIONS

The Committee noted:

- the minutes of the October 2007 ADEC Meeting;
- that until February 2000, insulin had retained a Schedule 3 classification in part because of the need to ensure there was a mechanism to ensure the ready availability of an emergency supply;
- that the February 2000 NDPSC Meeting rescheduled insulin to Schedule 4 on the basis of its pharmacological profile, mechanisms were available to ensure supply in emergency situations and existing procedures reflected a Schedule 4 level of control.

RESOLUTION 2008/53 - 41

The Committee noted ADEC's consideration of the new medicine human insulin (inhaled) and agreed that it should be captured by the Schedule 4 insulins entry.

13.2.7 FLUTICASONE FUROATE

PURPOSE

The Committee considered the scheduling of the new medicine fluticasone furoate.

BACKGROUND

Fluticasone furoate is a new synthetic corticosteroid. It is related to fluticasone propionate, a semi-synthetic trifluorinated glucocorticoid that has local anti-inflammatory activity and a potency of about twice that of beclomethasone dipropionate and which is registered in various topical nasal presentations for the treatment of allergic rhinitis and nasal polyps and in inhaler presentations for the treatment of asthma. Multiple topical nasal steroids are currently registered for the treatment of allergic rhinitis.

The December 2007 ADEC Meeting recommended approval of a submission from (GlaxoSmithKline Australia Pty Ltd) to register Avamys nasal spray containing the new chemical entity fluticasone furoate 27.5µg per actuation for the indication *for the treatment of seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) in adults and children aged 2 years and over*.

XXXXX

DISCUSSION - SUBMISSIONS

The Committee noted that:

- the April 1994 NDPSC Meeting considered (via ADEC) fluticasone propionate and agreed to include it under a new Schedule 4 fluticasone entry;
- the November 2001 NDPSC meeting considered an application to reschedule fluticasone propionate for short-term prophylaxis or treatment of seasonal allergic rhinitis from Schedule 4 to Schedule 3. The NDPSC agreed to a new Schedule 3 entry for this indication. The entry was also amended in November 2001 to include perennial allergic rhinitis;
- the October 2003 NDPSC Meeting considered an application to reschedule fluticasone propionate for the prophylaxis and treatment of allergic rhinitis from Schedule 3 to Schedule 2. The NDPSC agreed to a new Schedule 2 entry for this indication.

There was discussion as to whether or not fluticasone furoate should be captured under the current Schedule 2 and Schedule 4 fluticasone entries, or if it should be included as a separate Schedule 4 entry, being a new medicine.

The Committee noted that there was some clinical evidence to suggest that fluticasone furoate was less potent and not as effective as fluticasone propionate. The Committee also noted that all products are required to go through TGA's approval process.

RESOLUTION 2008/53 - 42

The Committee noted ADEC's consideration of the new medicine fluticasone furoate and agreed that it should be captured under the current Schedule 4 and Schedule 2 fluticasone entries.

13.2.8 HUMAN NORMAL IMMUNOGLOBULIN

PURPOSE

The Committee noted ADEC's consideration of the new biological entity human normal immunoglobulin.

BACKGROUND

Human normal immunoglobulin is derived from pooled human plasma.

The October 2007 and December 2007 ADEC Meetings respectively recommended approval of two medicines containing the new biological entity human normal immunoglobulin:

- Octapharma Australia Pty Ltd registering GAMMANORM injection solution containing human normal immunoglobulin 165 mg/mL for the indications

  Replacement therapy in adults and children with primary immunodeficiency syndromes such as:
  - *Congenital agammaglobunaemia and hypogammaglobulinaemia*
  - *Common variable immunodeficiency*
  - *Severe combined immunodeficiency*
  - *IgG subclass deficiencies with recurrent infections*

  Replacement therapy in myeloma or chronic lymphatic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections.

- Baxter Healthcare Pty Ltd registering KIOVIG solution for injection containing human normal immunoglobulin 10 per cent 2/v for the indications

  Primary Immunodeficiency Disorders (PID) associated with defects in humoral immunity, acting as replacement therapy, including:

– *Congenital agammaglobulinemia and hypogammaglobulinemia*
– *Common variable immunodeficiency*
– *Severe combined immunodeficiency*
– *Wiskott Aldrich syndrome*

Secondary immunodeficiency syndromes including:
– *Myeloma (B-cell chronic lymphocytic leukaemia) with severe secondary hypogammaglobulinemia and recurrent infections.*
– *Paediatric HIV infection*
– *Allogenic bone marrow transplantation*

Immunomodulation:
– *Idiopathic thrombocytopenic purpura (ITP), in children or adults at high risk of bleeding prior to surgery to correct the platelet count.*
– *Guillain Barre syndrome (GBS)*
– *Kawasaki disease*

XXXXX

DISCUSSION - SUBMISSIONS

The Committee noted:

- the minutes of the October and December 2007 ADEC Meetings;
- that the October 2007 NDPSC Meeting included fractionated blood products and equivalent recombinant products in Appendix A of the SUSDP to allow such products to be exempt from the requirements of scheduling;
- that the October 2007 NDPSC Meeting made particular mention of intravenous immunoglobulins and that these were not included in the Appendix A exemption;
- that although derived from pooled human plasma, *human normal immunoglobulin* would be captured by the Schedule 4 entry for immunoglobulins.

RESOLUTION 2008/53 - 43

The Committee noted ADEC's consideration of the new biological entity human normal immunoglobulin and agreed that human normal immunoglobulin should be captured by the Schedule 4 immunoglobulins entry.

14. OTHER MATTERS FOR CONSIDERATION

14.1 HYDROQUINONE

PURPOSE

The Committee noted concerns raised about the scheduling of hydroquinone.

BACKGROUND

Hydroquinone is a reducing agent and it oxidizes to form quinone in air. It is used as a photographic developer, antioxidant, stabilizer in paints, fuels, oils, and polymers, as a chemical intermediate, in pharmaceuticals, and as a skin depigmenting agent. Hydroquinone increases melanin excretion from melanocytes and may also prevent its production. It is used topically as a depigmenting agent for the skin in hyperpigmentation conditions such as chloasma (melasma), freckles, and lentigines (small macules that resemble freckles). Concentrations of 2 to 4 per cent are commonly used; higher concentrations may be very irritant and increase the risk of ochronosis (i.e., the bluish black discoloration of certain tissues to which the substance has been applied).

Hydroquinone was first included in Schedule 4 of the SUSDP in 1969 due to concerns being raised about the promotion and free availability of skin lightening creams which were being targeted to the PNG and indigenous Australian populations. The Committee agreed that, due to the highly toxic nature of this substance and the potential for ADRs, free availability was not warranted and, therefore, it should be included in Schedule 4.

The February 1971 Meeting agreed to amend the Schedule 4 entry for hydroquinone to allow an exemption from scheduling for preparations of hydroquinone containing 2 per cent or less. No discussion for this reasoning was minuted.

At the May 1986 Meeting, the Committee recommended that the exemption from scheduling for 2 per cent preparations should be deleted from the Schedule 4 entry and, thus, all preparations of hydroquinone for human use would revert to Schedule 4. This decision was based on concerns raised regarding the potential for skin lightening creams to be used unknowingly on melanomas and, thus, delay treatment and worsen the prognosis for such patients. The Committee also considered the overall ADR profile for hydroquinone warranted inclusion in Schedule 4. However, this recommendation was not implemented.

Further discussion was undertaken at the May 1987 Meeting, where it was agreed to foreshadow creation of a new Schedule 2 entry for preparations of 2 per cent or less of hydroquinone when for use as a human therapeutic or for cosmetic purposes. An evaluation of data addressed the concerns raised by the Committee previously about the potential for use on melanomas. It was noted that there was only one case report of this and that both dermatologists and oncologists felt that the likelihood of hydroquinone use disguising a melanoma was remote. Members agreed that the safety profile of

preparations of 2 per cent or less hydroquinone warranted inclusion in Schedule 2 with an accompanying Appendix F warning statement entry. This was confirmed at the July 1987 Meeting.

There are currently two products (both creams) on the Australian Register of Therapeutic Goods (ARTG) which include hydroquinone for skin lightening. Both of these products contain hydroquinone at 2 per cent and are indicated for the lightening of age spots, freckles and brown skin blemishes.

DISCUSSION - SUBMISSIONS

XXXXX of the TGA received a letter from XXXXX regarding a media article on the dangers of using hydroquinone cream for skin lightening. The TGA responded to XXXXX and forwarded a copy of this response to the Committee along with a Minute requesting that the Committee give consideration as to whether this substance was still appropriately scheduled.

In August 2006, the USFDA announced a review of the safety of hydroquinone products because of concerns about carcinogenicity with regard to topical use and blue-black skin discolouration with lower concentrations. At this stage, the USFDA had not finalised their review and no further information was available on the issue from the USFDA website.

Hydroquinone had been banned from use as a skin lightening agent in the UK and the EU as of January 2001 (although France appeared to have banned its use in 1998) but it is unclear whether this is for cosmetic or therapeutic proposes. It also appeared to have been banned from use for cosmetic purposes in Japan and South Africa (in 1998).

DISCUSSION – RELEVANT MATTERS UNDER 52E

A Member suggested that it was not uncommon to find hydroquinone containing products which were sourced from overseas being imported into Australia. The Member stated that there was a high demand for skin lightening type products in certain sections of the community. It was noted that these products would have inappropriate labelling for the Australian requirements.

A Member noted that the International Agency For Research On Cancer (IARC) listing for hydroquinone showed that there was inadequate evidence for the carcinogenicity of the substance in humans and that there was limited evidence in animals.

Members recalled that there was a review of hydroquinone safety currently being undertaken by the USFDA and felt that, given this and the fact that it has been banned from use in a number of other countries it may be timely to review the scheduling of hydroquinone. Members agreed that currently there was limited data on the issue of carcinogenicity and toxicity in humans and that it would be appropriate to obtain more information on this before a scheduling decision was made.

RESOLUTION 2008/53 - 44

The Committee noted XXXXX and decided to foreshadow consideration of the scheduling of hydroquinone at the October 2008 NDPSC Meeting.

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

15.1 ITEM DELETED

15.2 GLYCERYL TRINITRATE

PURPOSE

The Committee considered the scheduling of glyceryl trinitrate for use in the treatment of haemorrhoids, including a proposal to up-schedule to Schedule 3.

BACKGROUND

Glyceryl trinitrate (GTN) is a nitrovasodilator used in the management of angina pectoris, heart failure and myocardial infarction. Other indications include inducing hypotension and controlling hypertension during surgery. GTN is believed to exert its vasodilator effect through release of nitric oxide, which causes stimulation of guanylate cyclase in the vascular smooth muscle cells; this results in an increase in cyclic guanosine monophosphate. GTN is also used for the treatment of chronic anal fissure because of its ability to relax the anal sphincter. Topical application of glyceryl trinitrate ointment in concentrations of 0.2 to 0.8 per cent has relieved pain and aided healing of anal fissures.

A search was undertaken by the Secretariat to determine when GTN was first included in the SUSDP. No minuted discussion was located and the first recorded inclusion of it in Schedule 3 was in 1971 and Schedule 2 in 1975.

DISCUSSION - SUBMISSIONS

XXXXX at its February 2008 Meeting, considered a submission to vary the indications for XXXXX (containing 0.2 per cent w/w GTN). In its consideration of this matter, a XXXXX Member commented that despite being Schedule 2, XXXXX was mainly purchased on the advice of a medical practitioner. The concern was raised that consumers could self-select this product without being aware of the large number of contraindications and precautions associated with GTN. It was considered that, due to these contraindications and precautions, GTN for rectal use should be rescheduled to Schedule 3. Members noted that side effects alone are not necessarily a reason to reschedule a substance.

There are currently 4 other OTC medicines (ARTG Nos. 116840, 21847, 22614 and 12033) indicated for the treatment of anal fissure. All of these products contain hydrocortisone and are currently Schedule 2 substances.

A submission was received from XXXXX on behalf of XXXXX supporting the proposal to include GTN in Schedule 3 for rectal use if it was also included in Appendix H. The following points in support of Appendix H inclusion were made:

- Advertising will provide a public health benefit by advising consumers of the availability of a safe and effective treatment for anal fissure, this advertising also means that consumers knowing about the product will have the benefit of a pharmacists advice and counselling,
- All advertising will comply with the requirements of *Therapeutic Goods Advertising Code* (TGAC),
- All claims of efficacy are evidence based and have been evaluated by the regulator,
- None of the indications are prohibited or restricted as per the TGAC and all indications are clear and can be simply communicated via advertising,
- There is a TGA approved CMI available to assist pharmacists in their counselling. It is also included in the primary package for the benefit of patients. Members noted that CMIs are not generally required for Schedule 2 medicines and at the Schedule 2 level there is no other feasible way for a consumer to access a CMI unless it is included in the primary package,
- Directions of use for the product are simple and thus easily explained by the pharmacist to the patient and are also included on the product label and in the CMI.

XXXXX commented that it supported the inclusion of GTN for rectal use in Schedule 3. XXXXX and XXXXX also supported this rescheduling.

DISCUSSION – RELEVANT MATTERS UNDER 52E

A Member stated that an issue of concern with allowing this substance in Schedule 2 was that there may be older patients already on nitrates for angina who access it unwittingly as a treatment for haemorrhoids as it is generally placed with the other Schedule 2 haemorrhoid treatments. Another Member stated that this product was generally only used on the advice of a medical practitioner, but Members agreed that there was a risk that an unaware patient may pick it up and use it without knowing about the interaction with other nitrates or the need for a nitrate-free interval. It was agreed that pharmacist intervention would be able to manage this concern.

A Member stated that there was no real public health need for GTN for rectal use to be included in Appendix H as the product had been around for approximately 30 years and that the public was already aware of it. The Member also stated that given the indications of the product (treatment of anal fissure or use post haemorrhoidectomy) patients would most likely be informed about it by their treating medical practitioner. Another Member

stated that the other Schedule 2 products indicated for anal fissure can be advertised direct to consumers and that was appropriate on grounds of public health benefit to allow the advertising of this substance, if it was included in Schedule 3. Another Member noted, however, that the other Schedule 2 medicines for the treatment of anal fissure all belonged to a different class, i.e., are corticosteroids and did not have the same drug profile as GTN does. Members agreed that there would be little discernable public health benefit from the inclusion of GTN for rectal use in Appendix H.

RESOLUTION 2008/53 - 46

The Committee decided to include glyceryl trinitrate for rectal use in Schedule 3.

Schedule 2 – Amendment

GLYCERYL TRINITRATE **–** delete entry

Schedule 3 – Amendment

GLYCERYL TRINITRATE – Amend entry to read:

GLYCERYL TRINITRATE:

(a) in preparations for oral use; or

(b) in preparations for rectal use.

Schedule 4 – Amendment

GLYCERYL TRINITRATE – Amend entry to read:

GLYCERYL TRINITRATE **except** when included in Schedule 3.

15.3 IBUPROFEN COMBINATIONS

PURPOSE

The Committee noted XXXXX discussions regarding the scheduling of ibuprofen combination products and request for the NDPSC to provide clarification on the Schedule 2 entry for ibuprofen.

BACKGROUND

The June and October 2003 NDPSC Meetings agreed to exempt appropriately labelled small packs of oral ibuprofen 200mg from the requirements of scheduling. The October 2005 NDPSC Meeting amended the Schedule 2 entry for ibuprofen to transfer the warning statements to the *Required Advisory Statements for Medicine Labels* (RASML).

At the February 2006 NDPSC Meeting, the Committee noted a submission from XXXXX relating to an issue raised in the October 2005 XXXXX consideration of a chewable tablet containing 100 mg ibuprofen which was intended for use in children aged 2 to 12. The proposed labelling presented the tablets as unscheduled, as the product complied with the conditions and labelling requirements for the Schedule 2 ibuprofen exemption, including the statement "Unless your doctor has told you to, don't use [this product / name of product] in children 6 years of age or less". The Committee agreed that there was an inconsistency in the Schedule 2 requirements and agreed to foreshadow a decision to amend the ibuprofen Schedule 2 entry to tighten the exemptions for solid-dose products so as to explicitly omit those labelled for use in children aged 6 years or under, for consistency with paracetamol scheduling.

Further consideration of this matter was undertaken at the June 2006 Meeting and the Committee agreed to confirm the foreshadowed decision to amend the Schedule 2 entry for ibuprofen to explicitly state that divided preparations labelled for use in children aged 6 years or under do not qualify for exemption from scheduling.

Phenylephrine in daily doses of 50mg or less in packs containing 250mg or less was exempted from scheduling at the October 2005 NDPSC Meeting. At this Meeting, Members agreed that the safety profile of phenylephrine and long experience of use as a general sale medicine in New Zealand and the UK was such that it warranted exemption from scheduling at a recommended daily dose of 50mg or less. This exemption did not place restrictions on phenylephrine requiring it be single active ingredient.

DISCUSSION - SUBMISSIONS

XXXXX at its February 2008 Meeting, considered an application to register a composite pack product containing two separate liquid filled capsules to be taken together as a single dose. The green capsules contained ibuprofen 200mg and the clear capsules contained phenylephrine 10mg. The applicant asserted that the product would be unscheduled as ibuprofen was the only therapeutically active constituent in the green capsules. XXXXX, however, felt that the product was a Schedule 2 medicine as the ibuprofen was not the only therapeutically active constituent in the product given that phenylephrine was contained in the clear capsules and these were intended to be taken with the green capsules as a single dose. XXXXX agreed with this and stated that the same substances' scheduling should apply regardless of whether the two ingredients are combined in a single capsule or two separate capsules to be taken as a single dose.

Despite its recommendation, XXXXX has requested that the NDPSC provide clarification about the intent of the current Schedule 2 entry for ibuprofen to ensure that the entry unambiguously covers products where two dosage units which contain different ingredients are to be taken as a single dose.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee considered whether this was a similar issue to that which had previously been considered relating to sedating antihistamine products having two separate bottles (one containing the daytime dose and one containing the night-time dose) inside the primary pack. The Committee agreed that this issue was different as both the tablets were contained in a blister platform in the primary pack and not a complete/ separate container (as was the case with the sedating antihistamines presentations).

The Committee discussed whether taking two separate tablets containing different active ingredients as a single dose differed from taking a single combination tablet containing the two ingredients. The Committee agreed that the intent of the two single tablets was the same as the combination tablet, i.e., the two single tablets were required to be taken together as a single dose and, therefore, ibuprofen was not the only therapeutically active constituent in the product concerned. Given this, the product did not meet the requirements for the exemption from the Schedule 2 ibuprofen entry.

RESOLUTION 2008/53 - 47

The Committee noted XXXXX consideration of the scheduling of combination ibuprofen products and confirmed that XXXXX interpretation of the Schedule 2 entry for ibuprofen was correct.

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

16.1 MEDICINES FOR HARMONISATION

16.1.1 DAPTOMYCIN

PURPOSE

The Committee considered the scheduling of the new medicine daptomycin.

BACKGROUND

Daptomycin is an antibacterial agent of a new class of antibiotics, the cyclic lipopeptides. It is a natural substance that has clinical utility in the treatment of infections caused by Gram-positive bacteria; it retains potency against antibiotic-resistant Gram-positive bacteria, including isolates resistant to methicillin, vancomycin and linezolid; it binds to bacterial membranes and causes a rapid depolarization of membrane potential in both growing and stationary phase cells, where the loss of membrane potential causes inhibition of protein, DNA and RNA synthesis resulting in cell death with negligible cell lysis.

The December 2007 New Zealand Medicines Classification Committee (MCC) Meeting classified daptomycin as a prescription medicine.

DISCUSSION - SUBMISSIONS

The Committee noted the minutes of the December 2007 MCC Meeting. In particular, that Cubicin (containing daptomycin):

- is indicated for the treatment of complicated skin and skin structure infections (cSSTI) and for Staphylococcus aureus bloodstream infections (bacteremia) (SAB/IE), including right-sided infective endocarditis, caused by methicillin-susceptible and methicillin-resistant isolates in adults;
- has not demonstrated efficacy in patients with left-sided endocarditis due to Staphylococcus aureus;
- is active against Gram positive bacteria only;
- is not indicated for the treatment of pneumonia.

The Committee noted the following from Micromedex:

- daptomycin is a useful alternative to other agents (eg, linezolid, quinupristin/dalfopristin) for treating infections caused by resistant gram-positive pathogens, including methicillin-resistant Staphylococcus aureus and vancomycin-resistant enterococci;
- there are few options at present for treating these infections;
- daptomycin is an injectable administered by a nurse or other trained health professional

The Committee noted the US Product Information and that XXXXX (daptomycin) is to be administered by IV infusion over a period of 30 minutes. The Committee also noted the US Patient Information Sheet included a special warning that XXXXX may cause serious muscle damage and may affect nerve conduction.

The Committee noted that scheduling daptomycin as a prescription medicine would harmonise with New Zealand.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that toxicity and safety, risks and benefits, extent and patterns of use, need for access as well as the purpose for which it is to be used (52E(1)(a)(B)(d)(f)(h)) were relevant to consideration of scheduling.

The Committeed noted that as use of the daptomycin would require medical oversight and administration by a medical professional in a medical setting, it would be appropriate to include the substance in Schedule 4.

RESOLUTION 2008/53 - 48

The Committee decided to include daptomycin in Schedule 4 of the SUSDP.

Schedule 4 - New entry

DAPTOMYCIN.

16.1.2 IXABEPILONE

PURPOSE

The Committee considered the scheduling of the new medicine ixabepilone.

BACKGROUND

Ixabepilone is the first of a novel class of non-taxane, microtubule stabilizing agents called epothilones and their analogs, which have potent activity in chemotherapy resistant tumour models. It is a semi-synthetic analog of epothilone B that stabilizes microtubule dynamics, resulting in blockade of cancer cells during the mitotic stage of the cell division cycle which leads to apoptosis and cell death;

The December 2007 New Zealand Medicines Classification Committee (MCC) Meeting classified ixabepilone as a prescription medicine.

DISCUSSION - SUBMISSIONS

The Committee noted the minutes of the December 2007 MCC Meeting. In particular that the proposed indications are:

- for the treatment of locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy;
- in combination with capecitabine in patients after failure of prior therapy with a taxane and an anthracycline or for whom further anthracycline therapy is not indicated;
- as monotherapy in patients after failure of prior therapy with taxanes, capecitabine and anthracyclines or for whom further anthracycline therapy is not indicated.

The Committee noted the following from Micromedex:

- ixabepilone is administered intravenously
- black box warning for toxicity in hepatic impairment
- precautions
  - XXXXX (containing ixabepilone) contains 39.8 per cent dehydrated alcohol [may cause dizziness/drowsiness]

- history of cardiac disease
- concomitant capecitabine - increased risk of cardiac adverse events including myocardial ischemia and ventricular dysfunction
- concomitant use with CYP3A4 inhibitors and CYP3A4 inducers
- diabetes mellitus - increased risk of severe neuropathy
- hypersensitivity reactions including anaphylaxis
- myelosuppression, dose dependent - severe neutropenia and thrombocytopenia
- peripheral neuropathy, moderate *to severe*

- USFDA pregnancy category D. There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g. if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

- Patient Instructions for ixabepilone:
  - not to be administered to patients who are pregnant, have neutropenia, thrombocytopenia or severe liver disease;
  - administered in a hospital or cancer treatment centre by a nurse or other trained health professional
  - medicine contains alcohol which may cause dizziness or drowsiness. Avoid driving, using machines or doing anything else that could be dangerous if you are not alert.

The Committee noted that the Prescribing Information for XXXXX (ixabepilone) records that the medicine contains dehydrated alcohol and to avoid activities that may be dangerous, such as driving or operating machinery, if dizzy or drowsy. Fatigue/asthenia is recorded as one of the most common side effects.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that toxicity and safety, risks and benefits, extent and patterns of use, need for access as well as the purpose for which it is to be used (52E(1)(a)(b)(d)(f)(h)) were relevant to consideration of scheduling.

The Committee noted that as use of the ixabepilone would require medical oversight and administration by a medical professional, it would be appropriate to include the substance in Schedule 4.

The Committee agreed that the issue of drowsiness be referred to TGA's Required Advisory Statements for Medicine Labels (RASML).

RESOLUTION 2008/53 - 49

The Committee decided to include ixabepilone in Schedule 4 of the SUSDP.

Schedule 4 - New entry

IXABEPILONE.

16.1.3 LAROPIPRANT

PURPOSE

The Committee considered the scheduling of new medicine laropiprant.

BACKGROUND

Laropiprant (codenamed MK-05424A) is a potent selective antagonist of the prostaglandin D2 (PGD2) receptor, DP1. It suppresses PGD2 mediated flushing associated with administration of niacin.

The December 2007 New Zealand Medicines Classification Committee (MCC) Meeting classified the laropiprant as a prescription medicine.

DISCUSSION - SUBMISSIONS

The Committee noted the following information provided by the MCC Secretariat, which was considered by the December 2007 MCC Meeting:

XXXXX

The Committee noted from the www.drugs.com website that Merck & Co announced on 29 August 2007 that Cordaptive (niacin/laropiprant) formerly known as MK-05424A, had been accepted for standard review by the USFDA; the company is also moving forward with filings in countries outside the US; Cordaptive is an investigational compound containing Merck's own extended-release niaicin and laropiprant, a novel flushing pathway inhibitor designed to reduce flushing often associated with niacin treatment; that data included in the application supported the proposed use of Cordaptive, either alone or with a statin, as adjunctive therapy to diet for the treatment of elevated LDL cholesterol, low HDL cholesterol and elevated triglycerides levels; all are conditions associated with increased risk of heart disease; niacin is widely recognised as an effective lipid-modifying therapy; treatment has been limited as a result of the flushing side effect.

The Committee noted from the www.businessweek.com website that on 28 April 2008 the USFDA rejected Cordaptive with reasons not revealed.

The Committee noted from the www.merck.com website that Merck issued a news release on 28 April 2008 that they had received a "not-approvable" letter from the USFDA for MK-524A (niacin/laropiprant) for the treatment of primary hypercholesterolemia or mixed dyslipidemia; the USFDA had also rejected the proposed US trade name of Cordaptive for the product; it will again be known as MK-524A for

the time being; the product did receive marketing approval for MK-0524A in Europe from the Committee for Medicinal Products for Human Use; Merck will continue to pursue approval within indivudal markets in the EU and around the world.

The Committee noted that no information was available on the USFDA website.

The Committee noted that the European Medicines Agency website (www.emea.europa.eu) reported that on 24 April 2008, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending to grant a marketing authorisation for the medicinal product Trevaclyn (Merck Sharp & Dohme Limited), 1000 mg/20 mg modified-release tablet containing nicotinic acid and laropiprant; the approved indication is *treatment of dyslipidaemia*, (characterised by elevated levels of LDL-cholesterol and triglycerides and low HDL-cholesterol) and in patients with primary hypercholesterolaemia (heterozygous familial and non-familial); the CHMP on the basis of quality, safety and efficacy data submitted, considered that there was a favourable benefit to risk balance for Trevaclyn and therefore recommended the granting of the marketing authorisation.

The Committee noted from the www.merck.com website that Merck issued a news release on 21 May 2008 regarding the discontinuation of ACHIEVE trials (An Assessment of Coronary Health Using an Intima-Media Thickness Endpoint for Vascular Effects), an imaging study evaluating MK-0524A (niacin/laropiprant) in patients with Heterozygous Familial Hypercholesterolemia. Merck said that the trial was not stopped because of the FDA rejection, but because of the patient population being studied. Merck also reported that all other ongoing clinical studies continue unchanged.

The Committee noted that scheduling laropiprant as a prescription medicine would harmonise with New Zealand.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that toxicity and safety, risks and benefits, extent and patterns of use, need for access as well as the purpose for which it is to be used (52E(1)(a)(B)(d)(f)(h)) were relevant to consideration of scheduling.

The Committee noted that as use of the laropiprant would require medical oversight, it would be appropriate to include the substance in Schedule 4.

RESOLUTION 2008/53 - 50

The Committee decided to include laropiprant in Schedule 4 of the SUSDP.

Schedule 4 - New entry

LAROPIPRANT.

16.2 FOR INFORMATION

16.2.1 HARMONISED MEDICINES

16.2.1.1 ASPIRIN

PURPOSE

The Committee noted New Zealand's harmonisation consideration of aspirin (when compounded with caffeine, paracetamol or salicylamide).

BACKGROUND

In considering a TTHWP recommendation for harmonisation, the February 2007 NDPSC Meeting decided that the current scheduling of aspirin when in combination with paracetamol, caffeine or salicylamide remained appropriate due to the risk of nephrotoxicity.

DISCUSSION - SUBMISSIONS

The Committee noted the minutes of the December 2007 New Zealand Medicines Classification Committee (MCC) Meeting. In particular, that as there was only one such compound product on New Zealand market, which the sponsor intended to withdraw, the MCC decided to reclassify aspirin to harmonise with Australia as there would be no regulatory impact.

Classification	Australia	New Zealand
Prescription / Schedule 4	ASPIRIN: (a) when combined with caffeine, paracetamol or salicylamide or any derivative of these substances; or (b) for injection.	Aspirin for injection; when combined with caffeine, paracetamol or salicylamide

RESOLUTION 2008/53 - 51

The Committee noted that aspirin when in combination with paracetamol, caffeine or salicylamide is now harmonised.

16.2.1.2 MEFENAMIC ACID AND NAPROXEN

PURPOSE

The Committee noted New Zealand's harmonisation consideration of mefenamic acid and naproxen.

BACKGROUND

The February 2007 New Zealand Medicines Classification Committee (MCC) Meeting noted that pharmacy-only packs of ibuprofen and diclofenac included labelling with maximum recommended daily doses, but no such limits were applicable for mefenamic acid and naproxen. The MCC deferred consideration.

The June 2007 NDPSC Meeting decided that the current scheduling of mefenamic acid and naproxen remained appropriate as there was no scientific evidence to require a scheduling change and there was no requirement to pursue consistency simply for consistency's sake.

DISCUSSION - SUBMISSIONS

The Committee noted that minutes of the December 2007 MCC Meeting. In particular, that MCC had decided not to pursue this matter in view of the NDPSC's decision.

Classification	Australia	New Zealand
Pharmacy-Only / Schedule 2	MEFENAMIC ACID in divided preparations for oral use in packs of 30 or less dosage units for the treatment of dysmenorrhoea.	Mefenamic acid in solid dose form in packs containing not more than 30 tablets or capsules for the treatment of dysmenorrhoea
	NAPROXEN in divided preparations containing 250 mg or less of naproxen per dosage unit in packs of 30 or less dosage units.	Naproxen in solid dose form containing 250 milligrams or less per dose form in packs of not more than 30 tablets or capsules

RESOLUTION 2008/53 - 52

The Committee noted that mefenamic acid and naproxen are essentially harmonised.

16.2.1.3 IRON

PURPOSE

The Committee noted New Zealand's harmonisation consideration of iron.

BACKGROUND

The February 2007 NDPSC Meeting recommended an upper pack size limit of 750 mg and maximum daily dose of 24 mg for general sale iron products when in undivided dose forms or in solid dose forms containing more than 5 mg per dose form. Oral products which exceeded these limits should be classified as pharmacy-only medicines.

DISCUSSION - SUBMISSIONS

The Committee noted the minutes of the December 2007 New Zealand Medicines Classification Committee (MCC) Meeting. In particular, that MCC had agreed that limiting the dose size to 5 mg for general sale products was not justified, but that limiting the pack size to 750 mg was more relevant. The MCC decided to reclassify iron to general sale when in packs containing not more than 750 mg and not more than 24 mg per recommended daily dose and in parenteral nutrition replacement preparations.

XXXXX

Classification	*Australia*	*New Zealand*
General sale		*Iron in medicines containing 24 milligrams or less per recommended daily dose; in parenteral nutrition replacement preparations*
Pharmacy-Only / Schedule 2	*IRON COMPOUNDS (excluding iron oxides when present as an excipient, in divided preparations containing 10 mg or less of total iron oxides per dosage unit or in undivided preparations containing 1 per cent or less of total iron oxides) for human internal use **except**:* *(a) when included in Schedule 4; or* *(b) when labelled with a recommended daily dose of 24 mg or less of iron:* *(i) in undivided preparations supplied in packs each containing 750 mg or less of iron; or* *(ii) in divided preparations:* *(A) containing more than 5 mg of iron per dosage unit in packs each containing 750 mg or less of iron; or* *(B) containing 5 mg or less of iron per dosage unit.*	*Iron in medicines containing more than 24 milligrams per recommended daily dose*

RESOLUTION 2008/53 - 53

The Committee noted that iron is not harmonised.

16.2.1.4 ZINC

PURPOSE

The Committee noted New Zealand's harmonisation consideration of zinc.

DISCUSSION - SUBMISSIONS

The Committee noted the minutes of the December 2007 New Zealand Medicines Classification Committee (MCC) Meeting. In particular, that the MCC decided to reclassify zinc to general sale when in medicines containing:

- 25 mg or less per recommended daily dose;
- 50 mg or less and more than 25 mg per recommended daily dose when labelled with a statement that the product may be dangerous if taken in large amounts or for long periods or words of similar meaning.

The MCC noted that although this appears to harmonise with Australia, the New Zealand Dietary Supplements Regulations 1985 allowed no more than 15 mg per recommended daily dose to be contained in dietary supplements. Even though zinc in recommended daily dose of up to 50 mg would be classified as general sale, products containing more than 15 mg would require consent before they could be legally supplied as general sale. This is regardless of the requirement for a warning statement on the pack. Products would continue to be non-compliant dietary supplements if they contain more than 15 mg of zinc per recommended daily dose and did not have consent to be marketed as general sale. In effect, the reclassification should have no regulatory effect on current compliant dietary supplements.

The MCC Chair agreed that New Zealand products should carry the same warning statement as required in Australia or words of similar meaning to ensure harmonised labelling on both sides of the Tasman.

Classification	Australia	New Zealand
General sale		Zinc for external use except zinc chloride in medicines containing more than 5%; for internal use in medicines containing 25 milligrams or less per recommended daily dose; for internal use in medicines containing 50 milligrams or less and more than 25 milligrams per recommended daily dose and in packs which have received the consent of the Minister or the Director-General to their distribution as general sale medicines and are sold in the manufacturer's original pack and when labelled with a statement that the product may be dangerous if taken in large amounts or for long periods; except except in parenteral nutrition replacement preparationsin parenteral nutrition preparations
Pharmacy-only / Schedule 2	ZINC CHLORIDE for human dermal use **except** in preparations containing 5 per cent or less of zinc chloride.	Zinc chloride for dermal use in medicines containing more than 5%

RESOLUTION 2008/53 - 54

The Committee noted that zinc is now harmonised.

16.2.1.5 PYRETHRINS

PURPOSE

The Committee noted New Zealand's harmonisation consideration of pyrethrins.

BACKGROUND

In consideration a TTHWP recommendation for harmonisation, the February 2007 NDPSC Meeting decided to include a primary entry for naturally occurring pyrethrins for human therapeutic use in Schedule 2 and for preparations containing 10 per cent or less of naturally occurring pyrethrins to be exempt from the requirements of scheduling as they would pose little risk to the public;

DISCUSSION – SUBMISSIONS

The Committee noted the minutes of the December 2007 New Zealand Medicines Classification Committee (MCC) Meeting. In particular, that as there were no pyrethrin products on the New Zealand Market and previous products had contained less than 2 per cent of pyrethrins, the MCC decided to harmonise with Australia as there would be no regulatory impact.

Classification	Australia	New Zealand
General Sale		Pyrethrins in medicines containing 10% or less
Pharmacy-Only / Schedule 2	PYRETHRINS, naturally occurring, being pyrethrolone, cinerolone or jasmolone esters of chrysanthemic or pyrethric acids, for human therapeutic use in preparations containing more than 10 per cent of such substances.	Pyrethrins in medicines containing more than 10%.

RESOLUTION 2008/53 - 55

The Committee noted that pyrethrins are now harmonised.

16.2.1.6 SITAXENTAN

PURPOSE

The Committee noted New Zealand's harmonisation consideration of sitaxentan.

BACKGROUND

The June 2007 NDPSC Meeting included sitaxentan in Schedule 4.

DISCUSSION - SUBMISSIONS

The Committee noted the minutes of the December 2007 New Zealand Medicines Classification Committee (MCC). In particular, that MCC classified sitaxentan as a prescription medicine, harmonising with Australia.

RESOLUTION 2008/53 - 56

The Committee noted that sitaxentan is now harmonised.

16.2.1.7 PARICALCITOL

PURPOSE

The Committee noted New Zealand's harmonisation consideration of paricalcitol.

BACKGROUND

The June 2007 NDPSC Meeting included paricalcitol in Schedule 4.

DISCUSSION - SUBMISSIONS

The Committee noted the minutes of the December 2007 New Zealand Medicines Classification Committee (MCC). In particular, that MCC classified paricalcitol as a prescription medicine, harmonising with Australia.

RESOLUTION 2008/53 - 57

The Committee noted that paricalcitol is now harmonised.

16.2.1.8 RANIBIZUMAB

PURPOSE

The Committee noted New Zealand's harmonisation consideration of ranibizumab.

BACKGROUND

The June 2007 NDPSC Meeting included ranibizumab in Schedule 4.

DISCUSSION - SUBMISSIONS

The Committee noted the minutes of the December 2007 New Zealand Medicines Classification Committee (MCC). In particular, that MCC classified ranibizumab as a prescription medicine, harmonising with Australia.

RESOLUTION 2008/53 - 58

The Committee noted that ranibizumab is now harmonised.

16.2.1.9 GALSULFASE

PURPOSE

The Committee noted New Zealand's harmonisation consideration of galsulfase.

BACKGROUND

The June 2007 NDPSC Meeting included galsulfase in Schedule 4.

DISCUSSION - SUBMISSIONS

The Committee noted the minutes of the December 2007 New Zealand Medicines Classification Committee (MCC). In particular, that MCC classified galsulfase as a prescription medicine, harmonising with Australia.

RESOLUTION 2008/53 - 59

The Committee noted that galsulfase is now harmonised.

16.2.2 POTASSIUM CHLORIDE

PURPOSE

The Committee noted New Zealand's harmonisation consideration of potassium and potassium chloride.

BACKGROUND

The June 2007 NDPSC Meeting decided to amend the Schedule 4 entry for potassium chloride to only capture preparations with 550 mg or more per dosage unit of potassium chloride. The Committee noted this cut-off would not capture glucosamine sulfate complexed products currently on the ARTG.

The May 2007 New Zealand Medicines Classification Committee (MCC) Meeting decided to seek information about the potassium content of glucosamine sulfate complexed products on the New Zealand Market in order to avoid capturing glucosamine products under the schedule entries for potassium. The Meeting also noted that the reason for classifying potassium chloride separately and more restrictively in Australia was probably not as valid in New Zealand due to cooler climatic conditions. However, the MCC Minutes did not elucidate further as to why this might be the case.

The December 2007 MCC Meeting considered responses from sponsor companies of complementary medicines and dietary supplements containing glucosamine.

DISCUSSION - SUBMISSIONS

The Committee noted the minutes of the December 2007 MCC Meeting. In particular that:

- Australia was able to impose labelling statements on complementary medicines whereas New Zealand legislation did not allow for this. The New Zealand Dietary Supplements Regulations were currently under review with the intention to divide dietary supplements into food-type and therapeutic-type supplements with the therapeutic-type supplements to come under the control of Medsafe;
- use of glucosamine was growing and it was perceived as a safe product in that it was natural. It was not always possible to ascertain the potassium content of glucosamine products in complementary medicines. It would be unlikely that average consumers would realise that such products could contain significant amounts of potassium. In addition, consumers might unknowingly eat foods containing high levels of potassium;
- it was possible that there were already glucosamine products on the market containing sufficient potassium to mean that, technically, they would qualify as pharmacy-only medicines;
- there was general agreement that Medsafe should be asked to prepare an article for Prescriber Update pointing out to doctors that glucosamine products may be a significant source of potassium;
- MCC Members agreed that:
  - a statement of the amount of potassium contained in each dose should be added to the packs of glucosamine sulfate complexed products containing potassium;
  - glucosamine sulfate complexed products containing potassium should carry a warning on the pack that the product should not be used by consumers with kidney problems;
  - complementary medicine glucosamine products which were currently general sale products would default to pharmacy-only medicines unless these two requirements were met;
  - the current cut-off point between general sale and pharmacy-only medicine for oral products containing potassium should remain at 100 milligrams of elemental potassium per recommended dose;
  - the current exceptions for oral rehydration therapy, parenteral nutrition replacement or dialysis products should remain;
  - the complementary medicines sector and the pharmacy profession should be informed of these requirements for glucosamine sulfate complexed products containing potassium.

The Committee noted that the December 2007 MCC Meeting decided not to harmonise with Australia, recommending that:

- potassium should be classified as a pharmacy-only medicine when for internal use:
  - in slow release or enteric coated forms
  - in medicines containing more than 100 milligrams per recommended dose
  - in glucosamine sulfate complexed products containing more than 100 milligrams of elemental potassium per recommended dose except when carrying a label warning against use with kidney problems and a statement of the potassium content per dose
  - except in medicines for oral rehydration therapy, parenteral nutrition replacement or dialysis;

- potassium should be a general sale medicine when:
  - for external use
  - for internal use in medicines containing 100 milligrams or less per recommended dose
  - in glucosamine sulfate complexed products containing more than 100 milligrams of elemental potassium per recommended dose when carrying a label warning against use with kidney problems and a statement of the potassium content per dose
  - in medicines for oral rehydration therapy, parenteral nutrition replacement or dialysis

RESOLUTION 2008/53 - 60

The Committee noted New Zealand's harmonisation consideration of potassium and potassium chloride and that they remain unharmonised with Australia.

16.2.3 STIMULANT LAXATIVES

PURPOSE

The committee noted New Zealand's harmonisation consideration of stimulant laxatives.

BACKGROUND

The June 2006, February and June 2007 NDPSC Meetings considered TTHWP recommendations for the harmonisation of stimulant laxatives, with the June 2007 meeting deciding that the current (non-) scheduling of aloes for internal use, aloin, bisacodyl, colocynth (*citrullus colocynthis)*, ipomoea (*ipomoea* species), jalap resin (*operculina macrocarpa*), sennosides and sodium picosulphate was appropriate and did not require further controls.

The New Zealand Medicines Classification Committee (MCC) has also considered the issue of harmonisation at a number of meetings, with the most recent meeting held in December 2007.

DISCUSSION - SUBMISSIONS

The Committee noted the minutes of the December MCC Meeting. In particular that:

- the NDPSC had reviewed the safety of stimulant laxatives and could see no safety issues to justify moving them to a more restrictive level of access in Australia;
- abuse of products did not appear to occur to the same degree in Australia or to elicit the same degree of concern as it did in New Zealand;
- a comment from the Eating Difficulties Education Network which was strongly against any relaxation of the classification status of stimulant laxatives;
- women of all ages were abusing laxatives, with a pharmacist reporting of a 70 year old woman taking up to 30 tablets per day;
- it could be difficult to know whether or not a consumer was intending to misuse or abuse a product, but guidelines are in place in pharmacies for the sale of laxatives and the opportunity to offer advice at the point of sale;
- pharmacy profession might not be as aware of the abuse or misuse problem in Australia as the products were not scheduled and could be purchased from outlets other than pharmacies.

The Committee noted that the December 2007 MCC Meeting agreed that stimulant laxatives should remain classified as pharmacy-only medicine in New Zealand.

In defence of dot points two and six above, the Committee noted consideration at previous NDPSC meetings. In particular:

- XXXXX commented that the management of eating disorders is multi-faceted and while the abuse of laxatives can be a symptom of the overall disorders, it was not the essence of the disorder nor was it always involved in the disorder. It also commented that patients could purchase large supplies of laxatives at multiple pharmacies, rescheduling would not achieve any real benefit to patients with eating disorders. This view was XXXXX;
- XXXXX had no objection to the scheduling of stimulant laxatives and pointed out that these substances were also sold in complementary and traditional Chinese medicine products. The meeting noted that there was little information on XXXXX website and the fact that XXXXX did not feel able to provide comment on the issue without performing a full literature review probably meant that they were not overly concerned that abuse of stimulant laxatives was a problem in the community;

- XXXXX stated that XXXXX XXXXX did not feel that there was sufficient evidence that scheduling would prevent potential abuse of products containing bisacodyl and sodium picosulfate;
- an extensive canvassing of relevant stakeholder groups failed to reveal concrete evidence of significant problems of abuse or adverse effects with the use of stimulant laxatives in Australia despite their long incidence of adverse events.

RESOLUTION 2008/53 - 61

The Committee noted New Zealand's harmonisation consideration of stimulant laxatives and that they remained unharmonised with Australia.

17. MINUTES OF THE ADVERSE DRUG REACTIONS ADVISORY COMMITTEE (ADRAC)

Item deleted.

18. MINUTES OF THE MEDICAL DEVICE EVALUATION COMMITTEE (MDEC)

Item deleted.

19. INFORMATION ITEMS (PHARMACEUTICALS)

Item deleted.

20. GAZETTAL NOTICES

The Committee noted the pre-June 2008 Gazette Notice No.16 of 23 April 2008.

The Committee noted the post-February 2008 Gazette Notice No.14 of 9 April 2008.

21. AMENDMENTS TO THE SUSDP

21.1 EDITORIAL CHANGES AND ERRATA

21.1.1 DEXTRORPHAN & DEXTROMETHORPHAN - STEREOISOMERS

PURPOSE

The Committee considered an editorial amendment to the scheduling entries for dextrorphan and dextromethorphan with regard to the inclusion of stereoisomers.

BACKGROUND

The issue of the stereoisomers of morphan and methorphan was raised at the October 2007 NDPSC meeting. There are separate entries for stereoisomers of these compounds in the SUSDP:

Morphan:
Dextrorphan in Schedule 4
Levorphanol in Schedule 8
Racemorphan in Schedule 9

Methorphan:
Dextromethorphan in Schedules 4 and 2
Levomethorphan in Schedule 9
Racemethorphan in Schedule 9

DISCUSSION - SUBMISSIONS

The Committee noted that a Member raised the possibility of conflicting schedule entries:

- excluding stereoisomers from the entries for levorphanol and levomethorphan, but not from the entries for dextrorphan, racemorphan, dextromethorphan and racemethorphan, the latter entries (particularly those for dextrorphan and dextromethorphan) could include stereoisomers and thus cause conflict in the scheduling of those substances.

DISCUSSION – MATTERS RELEVANT UNDER 52E

The Committee agreed the Member's that, to obviate the possibility of any such interpretation, entries for dextrorphan and dextromethorphan should have the wording "(excluding its stereoisomers)" added to their scheduling entries.

RESOLUTION 2008/53 - 63

The Committee decided to amend all scheduling entries for dextrorphan and dextromethorphan to include the wording "(excluding its stereoisomers)".

Schedule 2 – Amendment

DEXTROMETHORPHAN – Amend entry to read:

DEXTROMETHORPHAN (excluding its stereoisomers) when supplied in a pack containing 600 mg or less of dextromethorphan and with a recommended daily dose of 120 mg or less of dextromethorphan.

Schedule 4 – Amendment

DEXTROMETHORPHAN – Amend entry to read:

DEXTROMETHORPHAN (excluding its stereoisomers) **except** when included in Schedule 2.

DEXTRORPHAN – Amend entry to read:

DEXTRORPHAN (excluding its stereoisomers).

21.1.2 OVERLAP BETWEEN APPENDIX C AND SCHEDULES

PURPOSE

The Committee considered the issue of overlaps between entries in the Schedules and in Appendix C of the SUSDP.

DISCUSSION - SUBMISSIONS

A Member reminded the Committee that the standard practice has been to word entries in Appendix C of the SUSDP in such a way that they do not overlap with entries for the same substance in any of the Schedules, just as entries in two Schedules are not written to overlap each other. The Member cited the entries for *Azadirachta indica* (neem), clioquinol and phenylenediamines.

The Member advised the Committee that in recent times, there appeared to have been a departure from the practice of avoiding overlaps between the Schedules and Appendix C. The Member cited the Schedule 4 entry for ethylhexanediol and the Schedule 6 entries for Basic Orange 31, methyl methacrylate, formaldehyde and paraformaldehyde.

The Member advised that this presented a practical problem in NSW where control of Appendix C substances is achieved by including them in Schedule 7 of the NSW Poisons List. The NSW Poisons List adopts the SUSDP schedules 1 to 8 entries by reference, with a very few exceptions. If the number of overlaps between the Schedules and Appendix C of the SUSDP continued to increase, there would be an increasing number of scheduling disparities between NSW and other States, and NSW may be forced to reduce its direct adoption of the schedules and appendices of the SUSDP to avoid overlaps between the schedules in the NSW Poisons List.

The Member proposed that the NDPSC review recent decisions which have resulted in an overlap between the Schedules and Appendix C of the SUSDP and consider amendments to the Schedule 6 entries for Basic Orange 31, methyl methacrylate, formaldehyde and paraformaldehyde.

With regard to ethylhexanediol, the Committee noted that the October 2006 NDPSC Meeting included this substance in Schedule 4 to harmonise with New Zealand and that the February 2007 NDPSC Meeting confirmed that the Schedule 4 entry was intended to capture animal therapeutic use only.

RESOLUTION 2008/53 - 64

The Committee decided to foreshadow for consideration at the October 2008 NDPSC Meeting, amendments to the Schedule 4 ethylhexanediol entry and to the Schedule 6 entries for Basic Orange 31, methyl methacrylate, formaldehyde and paraformaldehyde.

FORESHADOWED DECISION (for consideration at the October 2008 Meeting)

Schedule 4 – Amendment

ETHYLHEXANEDIOL – Amend entry to read:

† ETHYLHEXANEDIOL for animal therapeutic use only.

Schedule 6 – Amendments

BASIC ORANGE 31 – Amend entry to read:

† BASIC ORANGE 31 (2-[(4-aminophenyl)azo]-1,3-dimethyl-1H-imidazolium chloride) **except**:

(a) in preparations for skin colouration and dyeing of eyelashes or eyebrows; or

(b) in hair dye preparations containing 1 per cent or less of Basic Orange 31 when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN;

If in eyes wash out immediately with water; and

WARNING - This product contains ingredients which may cause skin irritation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye.

written in letters not less than 1.5 mm in height.

FORMALDEHYDE – Amend entry to read:

† FORMALDEHYDE (excluding its derivatives) **except**:

(a) for human therapeutic use;

(b) in oral hygiene preparations;

(c) in nail hardener cosmetic preparations containing 5 per cent or more of free formaldehyde;

(d) in nail hardener cosmetic preparations containing 0.2 per cent or less of free formaldehyde when labelled with the statement:

PROTECT CUTICLES WITH GREASE OR OIL;

(e) in other preparations containing 0.2 per cent or less of free formaldehyde when labelled with the warning statement:

CONTAINS FORMALDEHYDE; or

(f) in preparations containing 0.05 per cent or less of free formaldehyde.

METHYL METHACRYLATE – Amend entry to read:

† METHYL METHACRYLATE (excluding its derivatives) **except**:

(a) for cosmetic use; or

(b) in preparations containing 1 per cent or less of methyl methacrylate as residual monomer in a polymer.

PARAFORMALDEHYDE – Amend entry to read:

† PARAFORMALDEHYDE (excluding its derivatives) **except**:

(a) for human therapeutic use;

(b) in oral hygiene preparations;

(c) in nail hardener cosmetic preparations containing 5 per cent or more of free formaldehyde;

(d) in nail hardener cosmetic preparations containing 0.2 per cent or less of free formaldehyde when labelled with the statement:

PROTECT CUTICLES WITH GREASE OR OIL;

(e) in other preparations containing 0.2 per cent or less of free formaldehyde when labelled with the warning statement:

CONTAINS FORMALDEHYDE; or

(f) in preparations containing 0.05 per cent or less of free formaldehyde.

21.1.3 EPIDERMAL GROWTH FACTOR

PURPOSE

The Committee considered an editorial amendment to the Schedule 7 entry epidermal growth factor.

BACKGROUND

The November 1996 NDPSC meeting included "epidermal growth factor other than for human therapeutic use" in Schedule 7.

DISCUSSION - SUBMISSIONS

The NDPSC Secretariat requested that the Committee consider amending the schedule entry from "other than for" to "**except** for".

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee acknowledged that "**except** for" is the standard wording used in the SUSDP for exceptions in scheduling entries

The Committee agreed that the Schedule 7 entry for epidermal growth factor should be amended in line with this standard wording.

The Committee also agreed to further amend the entry to read "**except** in preparations for human therapeutic use.

RESOLUTION 2008/53 - 65

The Committee decided to editorially amend the Schedule 7 entry to read epidermal growth factor **except** in preparations for human therapeutic use.

Schedule 7 - Amendment

EPIDERMAL GROWTH FACTOR – Amend entry to read:

EPIDERMAL GROWTH FACTOR **except** in preparations for human therapeutic use.

21.1.4 APPENDIX F, PART 1, WARNING STATEMENT 102

PURPOSE

The Committee considered an editorial amendment to Warning Statement 102 in Appendix F, Part 1 of the SUSDP.

BACKGROUND

The Committee noted that the February 2005 NDPSC Meeting considered an extension to the timeframe to implement the revised label statements for non-prescription aspirin products and decided to:

(a) include *"In children 12-16 years of age with or recovering from chicken pox, influenza or fever"* in Warning Statement 102, for inclusion in SUSDP Amendment 20/2, effective 1 January 2006; and

(b) include, for clarity, *"(Please note that the statement in children 12-16 years of age with or recovering from chicken pox, influenza or fever will be incorporated into WS 102 effective from 1 January 2006.)* in the consolidated SUSDP 20, effective 1 June 2005.

DISCUSSION - SUBMISSIONS

The Committee noted that the amendment at (b) above was included in the SUSDP No.20 consolidation.

The Committee also noted that the amendment at (a) was **not** included in SUSDP No.20 Amendment No.2 and therefore was not included during consolidation of SUSDP No.21.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that, although Appendix F is only for dispensed medicines not captured by TGA's Required Advisory Statements for Medicine labels (RASML), the anomaly in Warning Statement 102 should be corrected.

RESOLUTION 2008/53 - 66

The Committee decided to editorially amend Warning Statement No.102 in Appendix F, Part 1 of the SUSDP, in line with the original intent of the decision of the February 2005 NDPSC Meeting.

Appendix F, Part 1 – Amendment

102. Amend entry to read:

102. Unless a doctor has told you to, don't use [*this product / name of the product*]:
For more than a few days at a time
With other medicines containing aspirin or other anti-inflammatory medicines
If you have asthma
In children under 12 years of age
In children 12-16 years of age with or recovering from chicken pox, influenza or fever
If you are pregnant.

21.1.5 MALDISON - MALATHION

PURPOSE

The Committee considered a nomenclature amendment to the Appendix E, Part 2 maldison entry.

BACKGROUND

The October 2006 NDPSC Meeting amended Schedule 3, changing maldison to malathion to harmonise with New Zealand.

The June 2007 NDPSC Meeting editorially amended Schedule 5 and Schedule 6, changing maldison to malathion to be consistent with the Schedule 3 amendment.

DISCUSSION - SUBMISSIONS

The Committee noted that the Appendix E Part 2 maldison entry was overlooked during editorial consideration at the June 2007 NDPSC Meeting.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the Appendix E Part 3 maldison entry be changed to malathion in line with the nomenclature amendments made at the October 2006 and June 2007 NDPSC Meetings.

RESOLUTION 2008/53 - 67

The Committee decided to editorially amend the Appendix E Part 2 maldison entry to read malathion.

Appendix E, Part 2 – Amendment

Maldison – Amend entry to read:

POISON	**STANDARD STATEMENTS**
Malathion at 20 per cent or less	A

21.1.6 METHOXAMINE

PURPOSE

The Committee considered an editorial amendment to the Schedule 2 methoxamine entry.

BACKGROUND

The October 2007 NDPSC Meeting amended the Schedule 2 methoxamine entry to read:

METHOXAMINE in preparations for external use **except** in preparations containing 1 per cent or less of methoxamine.

DISCUSSION - SUBMISSIONS

The Committee noted that the Secretariat had made a minor editorial amendment to the Schedule 2 methoxamine entry during publication of SUSDP No.22 Amendment No.3. The duplicate wording "in preparations" was deleted with the Schedule 2 entry amended to read:

METHOXAMINE for external use **except** in preparations containing 1 per cent or less of methoxamine.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the intent of the scheduling decision of October 2007 was to be methoxamine in preparations for external use.

The Committee agreed that the Schedule 2 methoxamine entry be amended to read METHOXAMINE in preparations for external use **except** containing 1 per cent or less of methoxamine.

RESOLUTION 2008/53 – 68

The Committee decided to editorially amend the Schedule 2 methoxamine entry.

Schedule 2 – Amendment

METHOXAMINE – Amend entry to read:

METHOXAMINE in preparations for external use **except** containing 1 per cent or less of methoxamine.

ACTION

– *Include in SUSDP No.23 Amendment No.1*

21.1.7 COLECALCIFEROL - CHOLECALCIFEROL

PURPOSE

The Committee considered a nomenclature amendment to the Appendix J cholecalciferol entry.

BACKGROUND

The August 1986 DPSSC Meeting included cholecalciferol in rodent baits in Schedule 6, noting its similarity to calciferol (Schedule 6 in rodent baits). The November 1987 DPSSC Meeting included cholecalciferol (and calciferol) in Appendix J. The August 1992 DPSSC Meeting rescheduled cholecalciferol for use as a rodenticide to Schedule 7.

The October 2006 NDPSC Meeting agreed to amend the Schedule 7 entry to read colecalciferol to harmonise with the nomenclature used for medicines in New Zealand. However, the corresponding Appendix J entry was overlooked.

The Schedule 7 and Appendix J entries specify a particular form of vitamin D (colecalciferol/cholecalciferol). The Schedule 4 vitamin D entry addresses all forms of vitamin D (including colecalciferol and ergocalciferol). This scheduling harmonises with New Zealand.

The February 2008 NDPSC Meeting considered a proposal to harmonise the use of colecalciferol and cholecalciferol:

- Medsafe New Zeland uses colecalciferol;
- Environmental Risk Management Authority (ERMA) New Zealand uses cholecalciferol;
- Schedule 7 and Appendix J are not part of medicines scheduling. As such, SUSDP could adopt the cholecalciferol spelling thereby harmonising with ERMA's spelling.

The Committee deferred consideration for the Secretariat to determine the reasons why colecalciferol was proposed by the TTHWP to the October 2006 NDPSC Meeting.

DISCUSSION – SUBMISSIONS

The Committee noted that the TTHWP's table for unharmonised medicines provided to the October 2006 NDPSC Meeting:

- asserted that colecalciferol was the TT Ingredient Name and INN name;
- recommended Australia consider cross-referencing colecalciferol and ergocalciferol to vitamin D;
- recommended Australia consider amending the nomenclature in Schedule 7 to colecalciferol for consistency;
- did not indicate whether the TTHWP was aware that ERMA used the cholecalciferol spelling.

The Committee noted that the TTHWP's recommendation had overlooked the Appendix J cholecalciferol entry.

The Committee noted that:

- colecalciferol is the INN;
- colecalciferol and cholecalciferol are both ANNs;
- colecalciferol is the BAN (British Approved Name);
- cholecalciferol is listed in the United States Pharmacopeia (USP) and the European Pharmacopoeia (PhEur).

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee confirmed that the INN should be used in the SUSDP.

The Committee agreed that, for clarity, a cross reference should be in included in the index between colecalciferol and cholecalciferol.

RESOLUTION 2008/53 - 69

The Committee decided to amend the Appendix J cholecalciferol entry to the include the INN spelling of colecalciferol. The Committee also decided to include a cross reference between cholecalciferol and colecalciferol in the SUSDP index.

Appendix J - Amendment

CHOLECALCIFEROL – Amend entry to read:

POISON **CONDITIONS**

Colecalciferol.....1

SUSDP Index - Amendment

CHOLECALCIFEROL – Amend entry to read:

CHOLECALCIFEROL
See COLECALCIFEROL

COLECALCIFEROL – Amend entry to read:

COLECALCIFEROL
See also VITAMIN D

21.1.8 FRUSEMIDE/ FUROSEMIDE

PURPOSE

The Committee considered a nomenclature issue for frusemide/ furosemide.

BACKGROUND

Frusemide/ furosemide is a potent loop diuretic with a rapid action. Like the other loop or high-ceiling diuretics it is used in the treatment of oedema associated with heart failure, including pulmonary oedema, and with renal and hepatic disorders and may be effective in patients unresponsive to thiazide diuretics. It is also used in high doses in the management of oliguria due to renal failure or insufficiency. Frusemide is also used in the treatment of hypertension, either alone or with other antihypertensives.

Frusemide is the current AAN for this substance, however the current INN is furosemide.

The Therapeutic Goods Committee (TGC), at its Meeting of 17 December 2003, recalled that the harmonisation of AANs and INNs had been of interest to it since 1998 when changes were made to the nomenclature used in the British Pharmacopeia for a number of substances. The TCG noted that the changes to INN from BAN had not been implemented for the substances adrenaline and noradrenaline due to concerns regarding potential medication errors. The TGC discussed a number of matters relating to the issues of conversion from AANs to INNs but confirmed its previous stance that INNs be adopted in Australia unless a specific exemption was made. Based on this, the TGC recommended that XXXXX develop an implementation plan for this process and report back to the TCG at its March 2004 Meeting.

XXXXX has made some progress on this project, however no changes have been implemented at this time. For new chemical entities, Australia now routinely adopts the INN.

Currently there are 48 products registered on the Australian Register of Therapeutic Goods (ARTG) with the ingredient frusemide and 1 with the ingredient furosemide which is labelled furosemide (frusemide).

DISCUSSION - SUBMISSIONS

At its 38th Meeting, the MCC noted that the INN (and BAN) for frusemide was furosemide and that confusion was occurring about this as some newer products were using the INN while older products were still using the previous BAN (frusemide). The MCC agreed that the schedule entry for frusemide be amended to reflect the current INN, furosemide. Further, the MCC recommended that the NDPSC harmonise on this matter.

Given the nature of this particular substance and its essential place and frequent use in emergency medicine, the Committee considered the inclusion of a cross reference in the index may be warranted.

DISCUSSION – RELEVANT MATTERS UNDER 52E

A Member stated that if furosemide was not also made the AAN, then this terminology would not appear on the labels of TGA approved products. The Committee agreed that this may be the case initially, but noted that there was currently one product available which used this terminology and that this was likely to increase.

RESOLUTION 2008/53 - 70

The Committee decided to editorially amend the Schedule 4 ‘frusemide’ entry to the alternate spelling ‘furosemide’. The Committee also decided to include a cross reference from ‘frusemide’ to ‘furosemide’ in the SUSDP index.

Schedule 4 - Amendment

FRUSEMIDE – Amend entry to read:

FUROSEMIDE (frusemide).

SUSDP Index - Amendment

FRUSEMIDE – Amend entry to read:

FRUSEMIDE
See FUROSEMIDE

21.1.9 LEVOMEPROMAZINE/ METHOTRIMEPRAZINE

PURPOSE

The Committee considered a nomenclature issue for methotrimeprazine/ levomepromazine.

BACKGROUND

Methotrimeprazine/ levomepromazine is a phenothiazine with pharmacological activity similar to that of both chlorpromazine and promethazine. It has antihistaminic actions as well as CNS effects resembling those of chlorpromazine. It is also reported to have analgesic activity. It is used in the treatment of various psychoses including schizophrenia, as an analgesic for moderate to severe pain usually in non-ambulatory patients, and for premedication. It is also used in palliative care for the control of symptoms such as restlessness, agitation, and as an adjunct to opioid analgesia, as well as being an effective broad-spectrum antiemetic in nausea and vomiting.

Methotrimeprazine is the current AAN for this substance, however the current INN is levomepromazine.

The Therapeutic Goods Committee (TGC), at its Meeting of 17 December 2003, recalled that the harmonisation of AANs and INNs had been of interest to it since 1998 when changes were made to the nomenclature used in the British Pharmacopeia for a number of substances. The TCG noted that the changes to INN from BAN had not been implemented for the substances adrenaline and noradrenaline due to concerns regarding potential medication errors. The TGC discussed a number of matters relating to the issues of conversion from AANs to INNs but confirmed its previous stance that INNs be adopted in Australia unless a specific exemption was made. Based on this, the TGC recommended that XXXXX develop an implementation plan for this process and report back to the TCG at its March 2004 Meeting.

XXXXX has made some progress on this project, however no changes have been implemented at this time. For new chemical entities, Australia now routinely adopts the INN.

DISCUSSION - SUBMISSIONS

At its 38th Meeting, the MCC noted that the INN (and BAN) for methotrimeprazine was actually levomepromazine and that there was one product in the Medsafe database which was registered using the current INN. The MCC agreed that the schedule entry for methotrimeprazine be amended to reflect the current INN, levomepromazine. Further, the MCC recommended that the NDPSC harmonise on this matter.

DISCUSSION – RELEVANT MATTERS UNDER 52E

A Member noted that, while there was no product registered in Australia, levomepromazine was used regularly in the palliative care setting via access through either the Special Access Scheme or the Authorised Prescriber program under TGA legislation. The Member further noted that all product imported into and used in Australia under these schemes was labelled levomepromazine.

RESOLUTION 2008/53 - 71

The Committee decided to editorially amend the Schedule 4 'methotrimeprazine' entry to the INN 'levomepromazine'. The Committee also decided to include a cross reference from 'methotrimeprazine' to 'levomepromazine' in the SUSDP index.

Schedule 4 - Amendment

METHOTRIMEPRAZINE – Amend entry to read:

LEVOMEPROMAZINE.

SUSDP Index - Amendment

METHOTRIMEPRAZINE – Amend entry to read:

METHOTRIMEPRAZINE
See LEVOMEPROMAZINE

21.1.10 TRANEXAMIC ACID

PURPOSE

The Committee considered an editorial amendment to the Appendix F, Part 3 tranexamic acid entry.

BACKGROUND

The February 2007 NDPSC Meeting deleted the Schedule 3 tranexamic acid entry to harmonise with New Zealand. The Appendix H tranexamic acid entry was also deleted.

DISCUSSION - SUBMISSIONS

The Committee noted that the Appendix F Part 3 tranexamic acid entry was overlooked for consideration at the February 2007 NDPSC Meeting.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that as tranexamic acid is no longer included in Schedule 3, the Appendix F Part 3 entry is not required.

RESOLUTION 2008/53 - 72

The Committee decided to delete the Appendix F Part 3 tranexamic acid entry.

Appendix F, Part 3 – Amendment

Tranexamic acid – delete entry.

21.1.11 HYDROCORTISONE

PURPOSE

The Committee considered an editorial amendment to the Appendix F Part 3 hydrocortisone entry.

BACKGROUND

The February 2007 NDPSC Meeting included hydrocortisone in combination with an anaesthetic for rectal use in Schedule 2.

DISCUSSION - SUBMISSIONS

The Committee noted that the Appendix F Part 3 hydrocortisone entry was overlooked at the February 2007 NDPSC Meeting.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the Appendix F Part 3 hydrocortisone entry be amended to reflect the scheduling decision of the February 2007 NDPSC Meeting to include hydrocortisone for topical rectal use in both Schedule 3 and Schedule 2.

RESOLUTION 2008/53 - 73

The Committee decided to amend the Appendix F Part 3 hydrocortisone entry to include Schedule 2 topical rectal use.

Appendix F, Part 3 – Amendment

Hydrocortisone – Amend entry to read:

POISON	**WARNING STATEMENTS**	**SAFETY DIRECTIONS**

Hydrocortisone

(a)	for dermal use when included in Schedule 2 or 3.	38,72,73,74,75
(b)	for topical rectal use when included in Schedule 2 or 3.	38,75

21.1.12 CHOLINE SALICYLATE / SALICYLIC ACID

PURPOSE

The Committee noted an editorial amendment to the index of the SUSDP No.23 cross-referencing choline salicylate and salicylic acid.

BACKGROUND

Choline salicylate is a derivative of salicylic acid used in the treatment of pain and fever, in the management of rheumatic disorders and as a local analgesic.

The June 2007 NDPSC Meeting considered a New Zealand Medicines Classification Committee recommendation to schedule choline salicylate. The meeting noted that as a derivative of salicylic acid, choline salicylate has not been considered for scheduling as it is captured by the parent entry for salicylic acid.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee noted that as a result of an enquiry concerning the scheduling of choline salicylate, the NDPSC Secretariat cross-referenced choline salicylate and salicylic acid in the index of SUSDP No.23.

The Committee agreed that the cross-reference would add clarity to the scheduling of these two substances and endorsed the action of the NDPSC Secretariat to amend the index of the SUSDP No.23.

RESOLUTION 2008/53 - 74

The Committee noted the editorial amendment to the index of SUSDP No.23 cross-referencing choline salicylate and salicylic acid.

21.1.13 SUSDP NO.23 CONSOLIDATION – PREFACE PAGE

PURPOSE

The Committee noted an editorial amendment to the Preface page of the SUSDP No.23.

BACKGROUND

The *Preface* on page v of the consolidated SUSDP No.22 reads:

The Standard for the Uniform Scheduling of Drugs and Poisons is the decisions of the National Drugs and Poisons Schedule Committee, regarding classification of drugs and poisons into Schedules for inclusion in the relevant legislation of the States and Territories. It also includes model provisions about containers and labels, and recommendations about other controls on drugs and poisons.

This document is presented with a view to promoting uniform scheduling of substances and uniform labelling and packaging requirements throughout Australia. It has no legal standing other than that given to it by relevant legislation.

DISCUSSION - SUBMISSIONS

The Committee acknowledged that the SUSDP is now required to be lodged on the Federal Register of Legislative Instruments (FRLI), a repository of Commonwealth legislative instruments, explanatory statements and compilations of legislative instruments in electronic form and an authoritative source for legislative instruments and compilations of legislative instruments.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the sentence "*It has no legal standing other than that given to it by relevant legislation"* in the Preface was no longer correct.

The Committee endorsed the action taken by the NDPSC Secretariat to have the Preface page amended during consolidation of the SUSDP No.23.

RESOLUTION 2008/53 - 75

The Committee noted the editorial amendment to the SUSDP No.23, being the deletion of the obsolete wording "*It has no legal standing other than that given to it by relevant legislation"* from the Preface page.

21.2 SUSDP AMENDMENT

The Committee considered proposed editorials to the draft SUSDP No.23 Amendment No.1.

BACKGROUND

The amendments arising from decisions made by the Committee at its February 2008 Meeting (except where separately specified) were consolidated in a draft SUSDP No.23 Amendment No.1 for review by the June 2008 NDPSC Meeting.

DISCUSSION - SUBMISSIONS

Comment was received from the Queensland jurisdictional member:

- Change the order of the exceptions in the Schedule 3 amendments for brompheniramine, chlorpheniramine, dexchlorpheniramine, diphenhydramine, doxylamine, pheniramine and triprolidine (February 2008 Resolution 2008/52 – 20):

  [SUBSTANCE] in oral preparations **except**:

  (a) ~~for the treatment of children under 2 years of age~~ when included in Schedule 2; or

  (b) ~~when included in Schedule 2~~ for the treatment of children under 2 years of age.

- Delete superfluous "or" at the end of (c) in the Schedule 4 amendment for paracetamol (February 2008 Resolution 2008/52 - 25.

  PARACETAMOL:

  (a) when combined with aspirin or salicylamide or any derivative of these substances **except** when separately specified in these Schedules;

  (b) in slow release tablets or capsules containing more than 665 mg of paracetamol;

  (c) in non-slow release tablets or capsules containing more than 500 mg of paracetamol; ~~or~~

  (d) in individually wrapped powders or sachets of granules each containing more than 1000 mg of paracetamol; or

  (e) for injection.

- Change semi-colon to colon before (i) and change semi-colon to a comma at end of (ii) in the Schedule 4 amendment for *Piper methysticum* (February 2008 Resolution 2008/52 – 21):

PIPER METHYSTICUM (kava) in preparations for human use **except** when included on the Australian Register of Therapeutic Goods in preparations:

(a) for oral use when present in tablet, capsule or teabag form that is labelled with a recommended maximum daily dose of 250 mg or less of kavalactones, and~~;~~ :

(i) the tablet or capsule form contains 125 mg or less of kavalactones per tablet or capsule; or

(ii) the amount of dried whole or peeled rhizome in the teabag does not exceed 3 g~~;~~ ,

and, where containing more than 25 mg of kavalactones per dose, compliant with the requirements of the *Required Advisory Statements for Medicine Labels*;

(b) in topical preparations for use on the rectum, vagina or throat containing dried whole or peeled rhizome or containing aqueous dispersions or aqueous extracts of whole of peeled rhizome; or

(c) in dermal preparations.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed with the editorial change to the Schedule 3 sedating antihistamines entries and the Schedule 4 paracetamol and *Piper methysticum* entries.

RESOLUTION 2008/53 - 76

The Committee noted the draft SUSDP No.23 Amendment No.1 and decided to editorially amend:

- the order of the exceptions in the Schedule 3 sedating antihistamine entries for brompheniramine, chlorpheniramine, dexchlorpheniramine, diphenhydramine, doxylamine, pheniramine and triprolidine.
- the Schedule 4 paracetamol entry by deleting the superfluous “or” at the end of (c); and
- the Schedule 4 *Piper methysticum* entry by changing “and;” to “and:” at (a) and changing “3 g;” to “3 g,” at (ii)

The Committee also noted that editorial amendments agreed to at Items 21.1 would be included in SUSDP No.23 Amendment No.1.

Schedule 3 – Amendments

BROMPHENIRAMINE, CHLORPHENIRAMINE, DEXCHLORPHENIRAMINE, DIPHENHYDRAMINE, DOXYLAMINE, PHENIRAMINE AND TRIPROLIDINE – Amend entries to read:

[SUBSTANCE] in oral preparations **except**:

(a) when included in Schedule 2; or

(b) for the treatment of children under 2 years of age.

Schedule 4 - Amendments

PARACETAMOL – Amend entry to read:

PARACETAMOL:

(a) when combined with aspirin or salicylamide or any derivative of these substances **except** when separately specified in these Schedules;

(b) in slow release tablets or capsules containing more than 665 mg of paracetamol;

(c) in non-slow release tablets or capsules containing more than 500 mg of paracetamol;

(d) in individually wrapped powders or sachets of granules each containing more than 1000 mg of paracetamol; or

(e) for injection.

PIPER METHYSTICUM – Amend entry to read:

PIPER METHYSTICUM (kava) in preparations for human use **except** when included on the Australian Register of Therapeutic Goods in preparations:

(a) for oral use when present in tablet, capsule or teabag form that is labelled with a recommended maximum daily dose of 250 mg or less of kavalactones, and:

(i) the tablet or capsule form contains 125 mg or less of kavalactones per tablet or capsule; or

(ii) the amount of dried whole or peeled rhizome in the teabag does not exceed 3 g,

and, where containing more than 25 mg of kavalactones per dose, compliant with the requirements of the *Required Advisory Statements for Medicine Labels*;

(b) in topical preparations for use on the rectum, vagina or throat containing dried whole or peeled rhizome or containing aqueous dispersions or aqueous extracts of whole of peeled rhizome; or

(c) in dermal preparations.