Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

National Drugs and Poisons Schedule Committee

Record of Reasons

40th Meeting
24-26 February 2004

Section 52D(2) of the *Therapeutic Goods Act 1989* (the Act) provides the power for the NDPSC to amend the Poisons Standard or prepare a new Standard. The NDPSC takes into account relevant matters mentioned in Section 52E of the Act when making a scheduling decision. The *Record of the Reasons* contains the basis of scheduling decisions and other outcomes arising from the meeting. Please note that the *Record of the Reasons* includes extracts from the NDPSC minutes which have been edited to remove confidential information.

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GLOSSARY

ABBREVIATION	*NAME*
AAN	Australian Approved Name
AC	Active Constituent
ACSPA	Australian Consumer and Specialty Products Association
ADEC	Australian Drug Evaluation Committee
ADI	Acceptable Daily Intake
ADRAC	Adverse Drug Reactions Advisory Committee
AGRD	Australian Guidelines for the Registration of Drugs
AHMAC	Australian Health Ministers' Advisory Council
APMF	Australian Paint Manufacturers Federation
APVMA	Australian Pesticides and Veterinary Medicines Authority
AQIS	Australian Quarantine and Inspection Service
ARfD	Acute Reference Dose
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
FDA	Food and Drug Administration (US)
FOI	Freedom of Information
FSANZ	Food Standards Australia New Zealand
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% of a population of experimental organisms. Usually expressed as mg per litre (mg/L) as a concentration in air.
LD_{50}	The concentration of a substance that produces death in 50% of a population of experimental organisms. Usually expressed as milligrams per kilogram (mg/kg) of body weight
MCC	Medicines Classification Committee
MEC	Medicines Evaluation Committee
MOH	Ministry of Health (NZ)
NCCTG	National Coordinating Committee of Therapeutic Goods
NDPSC	National Drugs and Poisons Schedule Committee
NHMRC	National Health and Medical Research Council
NICNAS	National Industrial Chemicals Notification & Assessment Scheme
NOEL	No Observable Effect Level
NOHSC	National Occupational Health & Safety Commission
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
RFI	Restricted Flow Insert
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
SVT	First aid for the solvent prevails
TCM	Traditional Chinese Medicine
TGA	Therapeutic Goods Administration
TGC	Therapeutic Goods Committee
TGO	Therapeutic Goods Order
TTHWP	Trans-Tasman Harmonisation Working Party
TTMRA	Trans-Tasman Mutual Recognition Agreement
UK	United Kingdom
USA	United States of America
WHO	World Health Organization
WP	Working Party
WS	Warning statement

1.8 NDPSC WORKING PARTIES

1.8.1 TRANS-TASMAN HARMONISATION WORKING PARTY

1.8.1.2 MATTERS ARISING FROM NDPSC (39TH MEETING) CONSIDERATION OF TTHWP ITEMS

1.8.1.2.1 FLUORIDES

PURPOSE

The Committee considered the foreshadowed decision to replace the term 'dentifrice' with 'pastes, powders and gels' from the Schedule entries for fluoride in order to harmonise with New Zealand.

BACKGROUND

The Schedule entries for fluorides for therapeutic use in the SUSDP include the term "dentifrice" but no definition was ever included in SUSDP Part 1. The fluoride entries in the NZ medicine classification categories refer specifically to pastes, powders or gels for the cleaning of teeth.

The 9th TTHWP Meeting (June 2003) agreed to recommend to the NDPSC (Recommendation 9/1) that the Schedule 2, 3 and 4 entries for fluorides be amended to remove the term "dentifrice" to specify "pastes, powders or gels for the cleaning of teeth" to harmonise with NZ. The cut-offs for fluorides in Schedule 4 and 2 were already harmonised.

At 39th NDPSC (Oct 2003) Meeting a Member advised that the term "dentifrice", as used in NZ incorporates a whole range of oral hygiene products including toothpastes and mouthwashes, and is only used as part of the definition for "related products" in NZ legislation. If the term "dentifrice" was adopted, a whole range of dental hygiene products already on the market in NZ would be adversely affected irrespective of whether such products were appropriately labelled.

The Member also sought advice with regard to the regulatory status of mouthwashes in Australia following implementation of the new devices legislation. If fluoride mouthwashes were covered by the new devices legislation, Pharmacy Only (Schedule 2) products in NZ may be available as unrestricted products in Australia irrespective of the harmonised scheduling entries.

At 39th (Oct 2003) meeting the Committee agreed to replace the term "dentifrice" in the SUSDP with "pastes, powders or gels for the cleaning of teeth" to harmonise with NZ and foreshadowed consideration of this decision at the February 2004 meeting.

The Committee at its October 2003 meeting sought advice on the regulatory status of mouthwashes in Australia following the implementation of the new devices legislation.

DISCUSSION

The Committee noted the advice from the Office of Devices, Blood and Tissues (ODBT) that, in accordance with the *Drug & Devices Distinctions* document of February 1998, medicated mouthwashes are regulated as medicines. Toothpastes that are scheduled or contain other chemicals for which therapeutic claims beyond permitted oral hygiene claims are made, are also regulated as medicines.

The XXXXXXXXX submission and an email from XXXXXXXXX advised that there were a number of errors in the gazetted foreshadowed amendments. The Committee noted the errors and agreed that these should be corrected.

The Committee also noted XXXXXXXXX argued that the schedule entries for fluoride were confusing and inconsistent. The XXXXXXXXX also encouraged the Committee to simplify the schedules and provide greater consistency of cut off limits.

Use of the term 'dentifrice'

Members considered the submission from XXXXXXXXX which argued for the retention of the term "dentifrice" in the SUSDP, as in its opinion, "dentifrice" does not refer to specific product presentations, and simply defines a product used for cleaning the teeth. They state that the inclusion of particular product types in the proposed definition ie. "pastes, powders and gels for the cleaning of teeth," has the potential to inhibit innovation of future product delivery forms for cleaning teeth. XXXXXXXXX argued that new product technology innovations, such as fluoride foams, would fall outside the proposed amendment.

The Committee noted XXXXXXXXX's comment that replacing the term 'dentifrice' with 'powders pastes and gels' would reclassify gel products with greater than 1000mg/kg and less than 2.5% fluoride ion, from Schedule 2 to Schedule 3. XXXXXXXXX argued that it was inconsistent that two of its topical products which were "effectively the same formulation, with the same fluoride concentration, the same registered indications of use, and the same labelling layout and patient usage directions' should be included in different schedules. The Committee noted that this view was based on XXXXXXXXX's interpretation of the Schedules.

The Committee considered that replacing the term 'dentifrice' with 'pastes powders and gels' would enable harmonisation with New Zealand and that if a sponsor developed a novel product formulation for cleaning the teeth it would be open to them to apply to the NDPSC at that time to consider the scheduling of that product formulation.

Proposal for consistency in the schedule entries for topical fluorides

XXXXXXXXX also requested the Committee to consider simplifying and improving the consistency of the fluoride schedule entries, by harmonising the schedule entries for topical fluorides. XXXXXXXXX agued that on safety grounds there was no rational for

the differentiating between the scheduling of topical fluoride products used for dental hygiene purposes and topical fluoride dentifrices. The Committee noted that XXXXXXXXX did not submit any supporting data.

Members noted that currently, topical fluoride products that are dental hygiene products (such as mouth rinses and mouthwashes) are exempt from scheduling when supplied with fluoride concentrations of 100mg/kg or below. However, topical fluoride products that are dentifrices are exempt from scheduling when supplied with fluoride concentrations of 1000mg/kg or below.

The Committee noted that, if accepted, the XXXXXXXXX proposal would exempt from scheduling all topical fluoride products that contain 1000mg/kg or less of fluoride ion (>0.1% > 2.5%).

XXXXXXXXX also proposed that all topical fluoride products within the fluoride range (>0.1% > 2.5%) be included in Schedule 2. XXXXXXXXX argued that "the scheduling of dentifrices that contain over 1000mg/kg fluoride in Schedule 3 seems anachronistic, when all other forms of topical fluoride have always been included in Schedule 2."

The Committee noted that the NHMRC have raised issues about the possibility of adverse effects from excessive chronic fluoride ingestion (resulting from dental fluorosis) and that this may occur primarily from excessive levels of fluorides in infant formulae and toothpaste. The Committee also noted that the Review of Water Fluoridation and Fluoride Intake from Discretionary Fluoride Supplements, 1999 (NHMRC Fluoridation Report) had recommended a number of ways to reduce excessive fluoride intake.

Members noted information from the Poisons Information Centres of children consuming large amounts of toothpaste, but few reports of mouthwashes being consumed by children. Members thought that this may well be because of the much greater availability of toothpastes. Members also noted that the bioavailability of fluoride from other dental hygiene products such as mouthwashes was likely to be much greater than from toothpastes. (The level of fluoride in mouthwashes is also discussed under Agenda Item 14.1.1). The Committee noted that XXXXXXXXX had not provided any data to support an increase in the level of fluoride in dental hygiene products exempted from scheduling.

Reports from overseas were also discussed by the Committee. Members agreed that it is important to consider total consumption of fluoride when assessing the safe levels, especially in relation to chronic consumption and the possibility of fluorosis. Information from the USA or other countries would need to be assessed against such factors as the level of fluoridation of water supplies compared to Australia. The Committee agreed that more data were necessary before such a change could be considered.

DECISION 2004/40 - 1

The Committee agreed to amend the schedule entries for fluorides to remove the term 'dentrifice' and replace it with 'pastes, powders or gels for the cleaning of teeth.' The

Committee noted that this would harmonise the scheduling of flouorides with New Zealand.

The Committee did not agree that the cut off level for other dental hygiene products should be the same as that for with 'pastes, powders or gels for the cleaning of teeth' or to delete the Schedule 3 entry for fluoride. The Committee noted that the exemption level for 'other dental hygiene products' was also addressed under Agenda Item 14.1.1.

The Committee's reason for its decision was that replacing the term ' dentifrice' with 'pastes, powders or gels for the cleaning of teeth' would bring greater clarity to the scheduling.

The scheduling amendments can be found under Item 14.1.1.

1.8.1.2.2 PROMETHAZINE

PURPOSE

The Committee considered the decision foreshadowed at the October 2003 meeting to exempt promethazine in packs containing 12 or less such tablets or capsules for prevention or treatment of motion sickness from scheduling.

BACKGROUND

The October 2002 meeting of the TTHWP recommended that the NDPSC consider exempting small packs of preparations of promethazine labelled for the prevention or treatment of motion sickness from scheduling. The TTHWP advised that small packs of travel sickness preparations containing promethazine were allowed to be sold in New Zealand as general sales medicines in specified outlets such as transport terminals or aboard a ship or plane.

The Committee at the 39th (0ctober 2003) meeting agreed to consider harmonisation of the scheduling outcome with New Zealand by foreshadowing a decision to exempt from scheduling small packs of preparations containing promethazine for prevention or treatment of motion sickness.

DISCUSSION

The Committee noted that a number of public submissions had been received. The submissions from the XXXXXXXXX, the XXXXXXXXX, the XXXXXXXXX, XXXXXXXXX and the XXXXXXXXX all expressed concern that allowing this medicine into general sale would increase the level of abuse of these products. The XXXXXXXXX also commented that the lack of harmonisation with New Zealand occurred because of legislative differences and not lack of harmonisation of scheduling. Several submissions also commented on the risks associated with the potential side effects of sedating antihistamines.

Submissions from XXXXXXXXX, the XXXXXXXXX, XXXXXXXXX and XXXXXXXXX questioned the equity of exempting travel sickness preparations containing sedating antihistamines from scheduling but not exempting other preparations for motion sickness.

The XXXXXXXXX submissions also raised several issues related to the remaining Schedule 2 entries for sedating antihistamines. These were considered under Agenda Item 1.8.1.2.5.

Concerns over abuse

The Committee discussed the risk of abuse of sedating antihistamines and noted that some antihistamines were more likely to be abused than others. The Committee noted reports of abuse of dimenhydrinate and information from the Internet providing advice for those intending to use antihistamines as recreational drugs. However, the Committee were not aware of specific abuse problems with promethazine. One Member highlighted the point made by the XXXXXXXXX that to support the foreshadowed amendment would "provide unrestricted and unsupervised supply of a central nervous depressant that has marked sedative properties." The Committee also noted the comment that free availability may lead to advertising which would encourage consumption.

Concern over the sedating effects of antihistamines

A number of the submissions raised the risks associated with the use of promethazine and other sedating antihistamines, namely that this may impair a person's motor skills. Members noted this concern. Members also noted the required warnings for sedating antihistamines in Appendix F of the SUSDP.

Comparing Australian and New Zealand legislative restrictions.

The Committee noted the restriction on access which was included in the New Zealand legislation which limited access to motion sickness preparations containing sedating antihistamines to transport terminals, boats and planes. Members were aware that there are provisions in a number of Australian jurisdictions which would enable special licences to be issued to supply scheduled travel sickness medication where circumstances

warranted it. Several Members advised that they had a mechanism to allow boats (eg. boats on the Great Barrier or Bass Strait) to carry travel sickness medication. Members noted that while the Commonwealth controlled airports, States generally would be able to issue licences to suitable outlets if a genuine need was clearly demonstrated by the proposed seller.

Claims that travel sickness mainly affects children

The Committee noted the claims by the XXXXXXXXX that car sickness mainly affected children and that other forms of travel may induce motion sickness in people of any age until the person becomes fully adapted to the typed of motion. While the Committee agreed with the XXXXXXXXX claims, it did not support the XXXXXXXXX's view that open access to motion sickness medications in an uncontrolled environment appeared illogical from a pathophysiological perspective.

Effect of the foreshadowed change

One Member raised a concern that the effect of supporting the foreshadowed amendment would be to make small packs of travel sickness medication containing promethazine or other sedating antihistamines freely available and that this would move beyond the provisions in the New Zealand legislation. A Member also raised the point that the foreshadowed amendment would enable any pack size of antihistamines for travel sickness to be sold as a Schedule 2 product.

OUTCOME

The Committee agreed that the current scheduling of promethazine for travel sickness remained appropriate. It was also agreed that promethazine should be added to the unharmonised list of entries for review after two years. The reasons for the Committee's decision were that:

- it is within the jurisdiction of most States and Territories to authorise the supply of promethazine in travel sickness products from selected outlets where a genuine need can be clearly demonstrated;

- concerns over making products which may be abused more widely available;

- concerns about public health and safety issues over rode the advantages of harmonising with New Zealand.

1.8.1.2.3 MECLOZINE

PURPOSE

The Committee considered the TTHWP recommendation to exempt meclozine in packs containing 12 or less such tablets or capsules for prevention or treatment of motion sickness from scheduling requirements.

BACKGROUND

The October 2002 meeting of the TTHWP recommended that the NDPSC consider exempting small packs of preparations of meclozine labelled for the prevention or treatment of motion sickness from scheduling. The TTHWP advised that small packs of travel sickness preparations containing meclozine were allowed to be sold in New Zealand as general sales medicines in specified outlets such as transport terminals or aboard a ship or plane.

The Committee agreed at its 39th (October 2003) meeting to consider harmonisation of the scheduling outcome with New Zealand for prevention or treatment of motion sickness. Additionally, the Committee noted that at present there were no products containing meclozine listed on the ARTG for supply in Australia.

DISCUSSION

The Committee noted that a number of submissions had been received. The submissions from the XXXXXXXXX, the XXXXXXXXX, XXXXXXXXX and the XXXXXXXXX all expressed concern that this would increase the level of abuse of these products. The XXXXXXXXX also commented that the lack of harmonisation with New Zealand occurred because of legislative differences and not lack of harmonisation of scheduling.

The industry submissions also raised several issues related to the remaining Schedule 2 entries for sedating antihistamines. These were considered under Agenda Item 1.8.1.2.5.

Details of the Committee's discussion on a number of matters common to travel sickness products containing sedating antihistamines are set out in the discussion of promethazine at Agenda Item 1.8.1.2.2.

Concerns about teratogenicity

The October 2003 meeting noted that meclozine was included in Schedule 4 and that this classification was possibly due to potential teratogenicity associated with the use of meclozine.

Members were advised that the last time the issue of teratogenicity of meclozine was discussed by ADEC was in 1969 when the ADEC noted that there was no evidence of

teratogenicity. At that time ADEC also considered that small packages containing meclozine for travel sickness did not present a concern.

New Zealand position

Members noted that meclozine was Pharmacy Only (S2) medicine in New Zealand with the exception for travel sickness packs as outlined above. Members noted that all other sedating antihistamines were in Schedule 3 in Australia except in small packs for the prevention and treatment of motion sickness. Members also noted that there was one product in the market in New Zealand but none in Australia. Members agreed that, as there was no product on the market in Australia and that any product coming on to the Australian market would need to be fully evaluated before it could be marketed here, there appeared to be no public health and safety issues which would preclude meclozine being re-scheduled from S4 to S2 for the treatment of travel sickness.

The Committee agreed that the proposal to re-schedule meclozine to Schedule 2 should be foreshadowed for the next meeting of the NDPSC. Members asked that the Secretariat seek advice from ADEC before the meeting on the teratogenicity of meclozine.

OUTCOME

The Committee agreed to foreshadowed a decision to reschedule meclozine from Schedule 4 to Schedule 2 for the treatment or prevention of motion sickness. The reasons for this decision were that:

- there appeared to be no public health and safety issues which would preclude meclozine being re-scheduled from S4 to S2 for motion sickness; and

- any product coming on to the Australian market would need to be fully evaluated before it could be marketed.

Decision foreshadowed for consideration at NDPSC Meeting 41 (June 2004).

Schedule 2 – New Entry

MECLOZINE in primary packs containing 12 or less tablets or capsules of meclozine for the prevention or treatment of motion sickness, **except** in preparations for the treatment of children under two years of age.

Schedule 4 - Amendment

MECLOZINE – amend entry to read:

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

1.8.1.2.4 DIMENHYDRINATE

PURPOSE

The Committee considered the decision foreshadowed at the 39th (October 2003) meeting to exempt preparations of dimenhydrinate in packs containing 12 or less such tablets or capsules for prevention or treatment of motion sickness from scheduling.

BACKGROUND

The October 2002 meeting of the TTHWP recommended that the NDPSC consider exempting small packs of dimenhydrinate labelled for the prevention or treatment of motion sickness from Schedule 2 of the SUSDP. The TTHWP advised that small packs of travel sickness preparations containing dimenhydrinate were allowed to be sold in New Zealand as general sales medicines in specified outlets such as transport terminals or aboard a ship or plane.

The Committee agreed at the October 2003 meeting to consider harmonisation of the scheduling outcome with New Zealand by foreshadowing a decision to exempt from scheduling small packs of dimenhydrinate for prevention or treatment of motion sickness.

DISCUSSION

The Committee noted that a number of submissions had been received. The submissions from the XXXXXXXXX, the XXXXXXXXX, the XXXXXXXXX, XXXXXXXXX and the XXXXXXXXX all expressed concern that allowing this medicine into general sale would increase the level of abuse of these products. The XXXXXXXXX also commented that the lack of harmonisation with New Zealand occurred because of legislative differences and not lack of harmonisation of scheduling.

Submissions from XXXXXXXXX, the XXXXXXXXX and XXXXXXXXX questioned the equity of exempting travel sickness preparations containing sedating antihistamines from scheduling but not exempting other preparations for motion sickness. XXXXXXXXX supported inclusion of oral liquid dimenhydrinate preparations in Schedule 2.

The industry submissions also raised several issues which related to the remaining Schedule 2 entries for sedating antihistamines are set out in the discussion of promethazine in Agenda Item 1.8.1.2.5.

Details of the Committee's discussion on a number of matters common to travel sickness products containing sedating antihistamines are set out in Agenda Item 1.8.1.2.2.

The Committee noted that there were reports of abuse which specifically mentioned dimenhydrinate and also material from the internet giving details, not only of the risk and

side effects but also, of the nature of the high and the duration of the effects for those wishing to abuse dimenhydrinate.

One Member noted that the fatal dose of dimenhydrinate in children has been reported as low as 600 mg which is equivalent to one 12 x 50 mg tablet pack.

Members agreed that part (b) of foreshadowed amendment was not considered appropriate for dimenhydrinate (unlike the other sedating antihistamines) as this substance is not used as part of cough/cold combination preparations.

OUTCOME

The Committee agreed that the current scheduling of dimenhydrinate for travel sickness remained appropriate It was also agreed that dimenhydrinate should be added to the list of unharmonised entries for review after two years. The reasons for the Committees decision were that:

- it is within the jurisdiction of most states and territories to authorise the supply of dimenhydrinate in travel sickness products where a need can be demonstrated;
- concerns over making a substance which may be abused more widely available;
- concerns about public health and safety issues over rode the advantages of harmonising with New Zealand.

1.8.1.2.5 SEDATING ANTIHISTAMINES/CODEINE

PURPOSE

The Committee considered the decision foreshadowed at the October 2003 meeting to amend the scheduling of combined antihistamine preparations containing other active ingredients including paracetamol, codeine and pseudoephedrine.

BACKGROUND

The 8th meeting of the Trans-Tasman Harmonisation Working Party (TTHWP) recommended that New Zealand harmonise the scheduling of combined antihistamine preparations containing other active ingredients including codeine, paracetamol and pseudoephedrine with Australia. The June 2003 NDPSC discussed concerns about the inappropriate use of sedating antihistamines especially single active preparations, particularly for sedation of infants and children. These preparations remained in Schedule 3. The meeting endorsed TTHWP Decision 8/8 which recommended a number of amendments to the New Zealand Classification of Medicines and referred this

decision to NZ for consideration. The TTHWP agreed on the following broad principles for harmonisation of antihistamines:

- Antihistamines and preparations with the potential for serious abuse be included in S4/Part 1;
- Single-active preparations of sedating antihistamines be included in S3/Part II; and
- Single-active preparations of non-sedating antihistamines and specified combination preparations of antihistamines be included in S2/Part III.

The 39th (Oct 2003) NDPSC meeting noted that the amendments relating to TTHWP Decision 8/8 would reclassify a significant number of existing oral sedating antihistamine products in combination with analgesics such as paracetamol in NZ as well as Australia. The Committee agreed to foreshadow amendments to the SUSDP which would align scheduling with the registration status of products while maintaining consistency with the recommendations of TTHWP Decision 8/8:

DISCUSSION

The Committee noted that a number of submissions had been received. The submissions from the XXXXXXXXX, the XXXXXXXXX, the XXXXXXXXX and the XXXXXXXXX all expressed concerns about the proposed scheduling change.

Submissions from XXXXXXXXX and XXXXXXXXX supported the proposed change while XXXXXXXXX raised concern as to whether the changes would result in any change for the S2 scheduling of products containing codeine. XXXXXXXXX raised some issues about apparently contradictory statements and the definition of "night time dose".

The committee noted that some stakeholders, including XXXXXXXXX seemed to be confused about exactly what the effect of the foreshadowed amendment would be. The Committee felt that the record of reasons from the October 2003 meeting was reasonably clear. However, the Committee agreed that in light of the apparent confusion it may be wise to clarify the position.

Concerns about the sedating effect of antihistamines

The Committee discussed the concerns expressed about the sedating effects of antihistamines and noted the comments from the XXXXXXXXX that the half-life and duration of action of some sedating antihistamines may have effects on the following day even if the dose is only taken at night. In particular, several submissions raised the risks to those driving or operating machinery. Members noted the comments from the XXXXXXXXX and the XXXXXXXXX which pointed out the difference in the potency and duration of different sedating antihistamines. The Committee considered that the required label warning statements specified for antihistamines in Appendix F of the

SUSDP adequately addressed these risks.

Concerns about abuse

Several submissions raised the issue that moving these combination sedating antihistamine preparations to Schedule 2 would enable them to be advertised thereby leading to increased use and abuse. Members noted that while there may be increased usage, the restrictions requiring the sedating antihistamine to be combined with another therapeutically active substance should minimise the risk of abuse. The Committee also noted that, because of different interpretations of the Schedule 2 entry relating to combination products for treating the symptoms of coughs, cold and influenza, combination products containing sedating antihistamines had been on the market as S2 products for some time in Australia and New Zealand without any evidence of abuse.

Concern that each sedating antihistamine need to be considered separately

The XXXXXXXXX and the XXXXXXXXX both raised the issue of differences in the potency and sedating effects of different antihistamines. The Committee noted these concerns but considered that these issues would be addressed by the registration process. The Committee also noted that the rescheduling to Schedule 2 only applied to products where the antihistamine dose was labelled for use at night time (or bedtime). Further the Committee agreed that this concern was adequately addressed by the required label warning statements.

Confusion arising from the wording of the proposed entries

The Committee noted the confusion created by the proposed wording and considered a range of alternative wording to clarify the entry. In particular, Members noted the confusion over what combination products would be covered by the amendment and the meaning of "night time dose". Members agreed that the proposed wording should be clarified.

Members agreed that it was important to stress that the amendment only applied to preparations intended for use in relieving the symptoms of coughs, colds and influenza and where the sedating antihistamine was either combined with one or more therapeutically active substances or was included in a product which combined daytime and night-time preparations in the same pack – a day-night pack. The Committee also agreed that it may be less confusing to use 'bed-time' rather than night-time.

DECISION 2004/40 - 2

The Committee agreed that the Schedule 2 entry for sedating antihistamines and codeine should be amended as foreshadowed, except that the sedating antihistamine entry should be amended to clarify the Committee's intent. The reasons for the Committee's decision were:

- to maintain the status quo of existing day-night cough and cold preparations containing sedating antihistamines labelled for night time doses and labelled S2;

- to remove the specificity from existing sedating antihistamine entries in the SUSDP to allow for inclusion of a wider range of substances in combination antihistamine preparations, where considered appropriate at registration;

- that the risks associated with the sedating effects of the antihistamines in these products were adequately addressed by (i) the requirements that the antihistamine be combined with at least one other therapeutically active substance in preparations for oral use and at least one of the other therapeutically active substances is a sympathomimetic decongestant or, when in a primary pack containing night time doses, the doses containing only the antihistamine are labelled for bed-time use only; and (ii) the label warning statements which the product was required to carry;

- that there had been no evidence of abuse or harm resulting from inappropriate use of these combination products despite the fact that, because of the varying interpretations of the Schedule 2 entries, a number of these products have been on the market for some time as Pharmacy Medicine;

- the products met the characteristics for inclusion in Schedule 2.

Schedule 2 - Amendments

BROMPHENIRAMINE – amend entry to read:

BROMPHENIRAMINE when combined with one or more other therapeutically active substances in oral preparations for the treatment of symptoms of coughs, colds or influenza when:

(a) at least one of the other therapeutically active substances is a sympathomimetic decongestant; or

(b) in a day-night pack containing brompheniramine in the bed-time dose,

except in preparations for the treatment of children two years of age or less.

CHLORPHENIRAMINE – amend entry to read:

CHLORPHENIRAMINE when combined with one or more other therapeutically active substances in oral preparations for the treatment of symptoms of coughs, colds or influenza when:

(a) at least one of the other therapeutically active substances is a sympathomimetic decongestant; or

(b) in a day-night pack containing chlorpheniramine in the bed-time dose,

except in preparations for the treatment of children two years of age or less.

CODEINE – amend entry to read:

CODEINE when:

(a) compounded:

(i) with a single non-opiate analgesic substance in tablets or capsules each containing 10 mg or less of codeine when:

(A) packed in blister or strip packaging or in a container with a child-resistant closure; and

(B) in a primary package containing 25 or less dosage units; or

(ii) with a single non-opiate analgesic substance in individually wrapped powders containing 10 mg or less of codeine when in a primary pack containing 25 or less dosage units; or

(iii) with one or more other therapeutically active substances:

(A) in divided preparations each containing 10 mg or less of codeine; or

(B) in undivided preparations containing 0.25 per cent or less of codeine; and

(b) labelled with a recommended daily dose not exceeding 60 mg of codeine.

DEXCHLORPHENIRAMINE – amend entry to read:

DEXCHLORPHENIRAMINE when combined with one or more other therapeutically active substances in oral preparations for the treatment of symptoms of coughs, colds or influenza when:

(a) at least one of the other therapeutically active substances is a sympathomimetic decongestant; or

(b) in a day-night pack containing dexchlorpheniramine in the bed-time dose,

except in preparations for the treatment of children two years of age or less.

DIPHENHYDRAMINE – amend entry to read:

DIPHENHYDRAMINE:

(a) in primary packs of 10 doses or less, for the prevention or treatment of motion sickness; or

(b) when combined with one or more other therapeutically active substances in oral preparations for the treatment of symptoms of coughs, colds or influenza when:

(i) at least one of the other therapeutically active substances is a sympathomimetic decongestant; or

(ii) in a day-night pack containing diphenhydramine in the bed-time dose,

except in preparations for the treatment of children two years of age or less.

DIPHENYLPYRALINE – amend entry to read:

DIPHENYLPYRALINE when combined with one or more other therapeutically active substances in oral preparations for the treatment of symptoms of coughs, colds or influenza when:

(a) at least one of the other therapeutically active substances is a sympathomimetic decongestant; or

(b) in a day-night pack containing diphenylpyraline in the bed-time dose,

except in preparations for the treatment of children two years of age or less.

DOXYLAMINE – amend entry to read:

DOXYLAMINE when combined with one or more other therapeutically active substances in oral preparations for the treatment of symptoms of coughs, colds or influenza when:

(a) at least one of the other therapeutically active substances is a sympathomimetic decongestant; or

(b) in a day-night pack containing doxylamine in the bed-time dose,

except in preparations for the treatment of children two years of age or less.

PHENIRAMINE – amend entry to read:

PHENIRAMINE:

(a) in eye drops; or

(b) when combined with one or more other therapeutically active substances in oral preparations for the treatment of symptoms of coughs, colds or influenza when:

(i) at least one of the other therapeutically active substances is a sympathomimetic decongestant; or

(ii) in a day-night pack containing pheniramine in the bed-time dose,

except in preparations for the treatment of children two years of age or less.

PROMETHAZINE – amend entry to read:

PROMETHAZINE:

(a) in primary packs of 10 doses or less, for the prevention or treatment of morion sickness; or

(b) when combined with one or more other therapeutically active substances in oral preparations for the treatment of symptoms of coughs, colds or influenza when:

(i) at least one of the other therapeutically active substances is a sympathomimetic decongestant; or

(ii) in a day-night pack containing promethazine in the bed-time dose,

except in preparations for the treatment of children two years of age or less.

THENYLDIAMINE – amend entry to read:

THENYLDIAMINE:

(a) in nasal preparations for topical use; or

(b) when combined with one or more other therapeutically active substances in oral preparations for the treatment of symptoms of coughs, colds or influenza when:

(i) at least one of the other therapeutically active substances is a sympathomimetic decongestant; or

(ii) in a day-night pack containing thenyldiamine in the bed-time dose,

except in preparations for the treatment of children two years of age or less.

TRIMEPRAZINE – amend entry to read:

TRIMEPRAZINE when combined with one or more other therapeutically active substances in oral preparations for the treatment of symptoms of coughs, colds or influenza when:

(a) at least one of the other therapeutically active substances is a sympathomimetic decongestant; or

(b) in a day-night pack containing trimeprazine in the bed-time dose,

except in preparations for the treatment of children two years of age or less

TRIPROLIDINE – amend entry to read:

TRIPROLIDINE when combined with one or more other therapeutically active substances in oral preparations for the treatment of symptoms of coughs, colds or influenza when:

(a) at least one of the other therapeutically active substances is a sympathomimetic decongestant; or

(b) in a day-night pack containing triprolidine in the bed-time dose,

except in preparations for the treatment of children two years of age or less.

1.8.1.2.6 AMPHOTERICIN

PURPOSE

The Committee considered the foreshadowed inclusion in Schedule 3 of topical preparations containing amphotericin for the treatment of oral candidiasis.

BACKGROUND

The 8th meeting of the Trans Tasman Harmonisation Working Party (TTHWP) recommended that topical preparations containing amphotericin for the treatment of oral candidiasis be included in Schedule 3 of the SUSDP (Recommendation 8.11). This would harmonise the scheduling with New Zealand.

This item was considered at the 39th (Oct 2003) NDPSC meeting at which a pre-meeting submission from XXXXXXXXX submitted that amphotericin should not be rescheduled to Schedule 3 based on potential side effects and that it is the treatment of choice for most serious systemic fungal infections. It was noted that the Martindale 31st edition states, 'Amphotericin is used in the treatment of serious disseminated fungal infections when it is given by intravenous infusion, but serious adverse effects are common'.

Members agreed to defer further consideration of the matter to the February 2004 meeting to allow advice to be sought from the ADEC on the potential for resistance to develop with topical use of amphotericin.

DISCUSSION

Members noted that Minutes for the last meeting of ADEC were not yet available. However, advice from the ADEC secretariat indicated that ADEC considered that the matter should be referred to EAGAR.

The Committee noted that consideration of a substance for the treatment of a fungal infection probably fell outside the terms of reference for EAGAR. However, the Committee considered that EAGAR had the expertise to provide the necessary advice to NDPSC and agreed that, if the matter was considered to be outside its terms of reference, EAGAR should be asked to convene a special advisory panel to provide advice on this matter.

Members agreed that the Secretariat should ask EAGAR to consider the NDPSC request and be asked to provide advice in time for the June 2004 meeting.

OUTCOME

The Committee agreed to defer a decision on endorsing recommendation 8/11 of the TTHWP until the June 2004 meeting to enable advice to be sought from EAGAR.

1.9 PROPOSED ROUTINE CHANGES TO THE SUSDP

There were no items considered.

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

There were no items considered.

2.2 SUSDP, PART 2

There were no items considered.

2.3 SUSDP, PART 3

There were no items considered.

2.4 SUSDP, PART 5

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 PACKAGING OF S8 PRODUCTS

PURPOSE

The Committee considered correspondence from XXXXXXXXX on the decision of NDPSC Meeting 39 (October 2003) to include container requirements for Schedule 8 products in Part 2 of the SUSDP.

BACKGROUND

The 39th NDPSC Meeting considered the proposal to include new container requirements for Schedule 8 poisons under Part 3 of the SUSDP, foreshadowed at NDPSC Meeting 38 (June 2003). Members agreed that it was appropriate to include packaging provisions of Schedule 8 poisons in Part 2 of the SUSDP for safety reasons and to ensure Australian harmonisation (Decision No. 2003/39-6).

DISCUSSION

The Committee noted that XXXXXXXXX had asked that the decision 'tamper-evident packing requirement' be reconsidered as it would impose additional steps in the manufacturing process, some of which may be contrary to the intent of the packaging requirement, ie greater security risks. The company submitted that diversion is more likely to occur post-dispensing.

A Member pointed out that the "Guideline for the Tamper-Evident Packaging of Medicines, Complementary Healthcare products and Medical Devices" had been superseded by the "Code of Practice for the Tamper-Evident Packaging (TEP) of Therapeutic Goods".

This Member was of the view that the company had misunderstood the intent of the recommended Schedule 8 container provisions.

The Committee was informed that the Schedule 8 container requirements had been in force in NSW for some time. The provision required Schedule 8 products to be sealed in such a way to allow visible detection of entry for possible diversion rather than deliberate tampering for adulteration.

The XXXXXXXXX Member indicated that sealed or glued down packaging would be acceptable. The XXXXXXXXX Member advised the meeting that discussions had been held with the company and that it had requested a delay in implementation of the Schedule 8 container requirements.

Other Members agreed that XXXXXXXXX had misinterpreted the decision of the 39th NDPSC Meeting concerning tamper-evident packaging. The purpose of the Schedule 8 proposal was for auditing purposes such that the package is so sealed that evidence of tampering with primary packaging is clear. The Committee favoured having a seal for auditing purpose on Schedule 8 products packaged in such a way that it is clear that they have been opened.

DECISION 2004/40 – 3 – Variation to Amendment (DECISION 2003/39 – 6)

The Committee agreed that it was appropriate to include packaging provisions of Schedule 8 poisons in Part 2 of the SUSDP for diversion reasons and to ensure Australian harmonisation. The Committee, however, further agreed to vary Decision 2003/39-6 by amending the implementation date to 1 May 2005.

Part 2 –LABELS AND CONTAINERS

CONTAINERS - New Entry

Schedule 8 poisons

25A. (1) A person who supplies any Schedule 8 poison must ensure that the Schedule 8 poison is packaged in such a way that its primary pack is so sealed that, when the seal is broken, it is readily distinguishable from other sealed primary packs.

(2) This paragraph does not apply to the supply of a Schedule 8 poison by a:

(a) medical practitioner, dentist or veterinary surgeon in the practice of his or her profession;

(b) pharmacist on the prescription of a medical practitioner, dentist or veterinary surgeon;

(c) pharmacist employed at a hospital, on the written requisition of a medical practitioner, a dentist or the nurse in charge of the ward in which the Schedule 8 poison is to be used or stored; or

(d) nurse on the direction in writing of a medical practitioner or dentist.

4. OTHER OUTSTANDING MATTERS FROM PREVIOUS MEETINGS

4.1 CHILD RESISTANT PACKAGING DEFINITION

PURPOSE

The Committee considered a foreshadowed amendment to the SUSDP - Part 1 – Interpretation, Sub- paragraph 1(1) the definitions for "Child-resistant closure" and "Child-resistant packaging".

BACKGROUND

Child-resistant packaging (CRP) and child-resistant closure (CRC) are defined in the SUSDP as those that conform to Australian Standard AS1928-2001. AS1928-2001 specifies the requirements for reclosable and non-reclosable packages which are defined as:

- Reclosable package – containers with closures that, once open, can be reclosed to its original form.
- Non-reclosable package – a package in which a unit of use is individually protected until time of release (eg. blister packs, strip, pouch and sachet).

As a consequence of the consideration of the scheduling of ivermectin at the October 2003 NDPSC meeting, the Committee decided that the definition of child-resistant closure/packaging in the SUSDP was too narrow for the purposes of poisons regulation. Specifically, the current definitions do not account for packaging and closures which are sufficient to render their contents inaccessible to children but would fail to meet the strict definition of CRP or CRC according to AS1928-2001. The Committee agreed to adopt the definition for child-resistant packaging from the Draft Therapeutic Good Order 65 (TGO 65).

DISCUSSION

The Committee recalled that the amendment foreshadowed at the October 2003 meeting would allow for consistency between the definitions of child-resistant packaging in the SUSDP and Draft TGO 65.

The Committee noted that public submissions were received form XXXXXXXXX, XXXXXXXXX, the XXXXXXXXX, the XXXXXXXXX, XXXXXXXXX, and XXXXXXXXX.

XXXXXXXXX supported the foreshadowed amendment. He advised that he believed that the foreshadowed changes would be welcome in the packaging industry and would not deleteriously affect the integrity of child resistant closures and other devices in Australia. However, he made the following recommendations:

- That the Committee consider further amending the SUSDP to require that child resistant closures/devices comply with the current version of AS1928 or other listed standard; and
- In the absence of a version update to the listed standard, closures should be field tested on a regular basis (every three to five years).

XXXXXXXXX advised that the first paragraph of the foreshadowed amendment which includes the definition for "Child-Resistant Packaging" is inconsistent with the definition used in the *Therapeutic Goods Act* and Regulations. Furthermore, the company indicated that the proposed wording is clumsy, ambiguous and very loose and that terms such as "reasonable time" and "young child" are very much open to interpretation. It also considered that the meaning of last part of the definition was not clear, "…..but does not mean packaging which all such children cannot open, or obtain the content of, within reasonable time."

XXXXXXXXX advised that it was extremely concerned at the proposal to combine two separate interpretations (for child-resistant closure and child-resistant packaging) into one interpretation for child-resistant packaging. XXXXXXXXX was of the view that the inclusion of "non-access packaging" in the proposed amendment may lead to confusion amongst sponsors as to which types of closure are acceptable for both medicines for human use and for agricultural and veterinary use. XXXXXXXXX urged the Committee to reconsider the foreshadowed proposal and strongly suggested that the entry for "child-resistant packaging" be consistent with TGO 65 when gazetted, without the inclusion of Part (5) referring to "non-access packages". Non-access packages should be included as a separate interpretation.

The APVMA advised that they supported the foreshadowed amendment to the definition of child-resistant closures and packages. Furthermore, the APVMA supported the amendment to the Schedule 5 entry for ivermectin allowing approval of packaging by the relevant registration authority.

The Non-Prescriptions Medicines Branch of the TGA supported the foreshadowed amendment. The NPMB believed that the amendment is consistent with other TGA regulatory requirements and its adoption in the SUSDP would facilitate the implementation of the Mandatory Advisory Statements for Medicine Labels (MASML).

XXXXXXXXX advised that the Standard Committee considered the issue of "non-access packaging" under AS4710-2001 as being separate from the standard for "child-resistant packaging" as covered under AS1928-2001. AS4710-2001 was not intended to cover child resistance and that the foreshadowed amendment may allow product marketers to support claims of child-resistance in packaging systems which are not compliant with AS1928-2001.

In a further submission and in response to XXXXXXXXX comments above, XXXXXXXXX made the following observations:

- AS4710 was modelled and derived from AS1928. Due to the fact that the majority of products which are "non access" are single use products (eg cockroach baits, toilet bowl disinfectant cages, etc) and are therefore discarded once the intended consumer product has been used. Hence, it is not possible to use AS1928 which requires two child panel tests and one adult panel test. AS4710 provides the identical test procedure as that of AS1928 in the first (before demonstration) child panel test - i.e. a minimum of 40 and up to 200 children between the ages of 42 and 51 months are given up to 5 minutes to open the package and gain access to the intended consumer product.
- An implied definition of child resistance is a delay of approximately five minutes before a child can possibly open a package. He drew the implied definition from the various standards (eg BS 8404:2001, ISO 8317:1993, AS 1928-2001, etc) which all use a time of five minutes to assess if a child can open a package. In this instance therefore AS4710-2001 is consistent with the implied definition of "child resistance".
- In relation to AS1928-2001 and AS4710-2001 the terms "non access" and "child resistance" are in effect synonymous terms. AS1928-2001 states "Packages shall comply with the Standard if not more than 30 children (15 percent) in the complete panel of 200 children gained access ....."(emphasis added AS1928-2001 2.3.2.1 p7). Whereas AS4710-2001 states (2.2.2a) p6) "Packages shall comply with this Standard if not more than 20 children (10% in the complete panel of 200 children gained access ....". (emphasis added) Therefore the test of child resistance is if a child can or cannot gain access in a five minute time period.
- One interpretation of XXXXXXXXX statement " marketers will use the definition to support claims for child resistance which are not compliant with AS1928." is that AS1928 should be the only acceptable Standard which should be included in the SUSDP. This was the very issue debated in the NDPS Committee's last meeting, which lead to a broadening of the definition by including a number of international standards.

The Committee noted that a Member submitted the following comments for the discussion:

- Child tests done in the UK and USA have shown that conventional non-reclosable blister packaging used for pharmaceuticals is not child-resistant. Jurisdictions including the USA, UK and Canada have Poison Prevention Packaging Regulations and Standards for non-reclosable child-resistant packages for non-pharmaceutical products that include child testing. It would be desirable to specify that non-reclosable packaging comply with a Standard or Testing Procedure that requires child testing when it is used for products that are required to be in child-resistant packaging.
- There is no definition of a blister or strip package in the suggested amendment, or elsewhere in the SUSDP. The suggested amendment does not exclude the use of any particular material for blister and strip packaging and there is no requirement for testing for seal strength and integrity as required under AS 1928-2001 *Child-resistant packages*. It would be appropriate to continue to require that the packaging comply

with Section 3 (Requirements for Non-Reclosable Packages) of AS 1928-2001 as the Standard defines blister and strip packaging, ensures that packaging is tested for seal strength and integrity and has requirements in relation to packaging materials, if there is no child testing for non-reclosable packaging when it is used for products that are required to be in child-resistant packaging. The suggested Amendment 1. Paragraph (4) would potentially result in any type of non-reclosable packaging being accepted even though no child, or other testing would be required.

- It is unclear what is meant by non-access access packaging in paragraph (5) of the suggested amendment. It is appropriate that non-access and non-contact packaging that meets the requirements of AS 4710–2001 *Packages for chemicals not intended for access or contact with their contents by humans* (AS 4710–2001) be deemed child-resistant.
- AS 4710-2001 *Packages for chemicals not intended for access or contact with their contents by humans* covers non-access/non-contact packaging such as cockroach baits and rodent baits. It is inappropriate to test access packaging to this Standard as there is only a 5-minute child test, with no demonstration of how to access the package. While AS 1928–2001 covers non-reclosable packaging it does not require child testing for non-reclosable packaging. This deficiency has prompted some sponsors who want to demonstrate that their non-reclosable packaging is child-resistant to have the packaging tested according to the child test requirements of AS 4710–2001 even though such packaging does not meet the definition of a non-access or non-contact package. Options in relation to non-reclosable access packaging would be to:
  - Have a separate Standard, which includes child and adult testing, for non-reclosable packaging for drugs and chemicals that are required to be in child-resistant packaging as in the Canadian Standard; or
  - Include child-testing for non-reclosable packaging in AS 1928-2001; or
  - Change the title, definition and child test procedure in AS4710-2001 to include non-reclosable access packaging. An adult test would also need to be included for non-reclosable access packaging.
- If the entry for "child-resistant closure" and "child-resistant packaging" is amended as suggested, the wording of Part 2 Labels and Containers subparagraph 25. (2) may also need amendment. The current wording indicates that child-resistant closures must retain their child-resistant properties for the expected life of the poison. The applicability of this requirement to non-reclosable access packaging needs to be considered. The reference to child-resistant closures in subparagraph 25. (2) should be changed to child-resistant packaging.
- Suggested options in relation to SUSDP Part 1 – Interpretation –1.(1) child-resistant packaging:
  - Include a requirement for blister and strip (non-reclosable) packaging to meet the requirements of a Standard that includes child testing, e.g. the US, Canadian and UK Standards.

- If the above requirement is not included, blister or strip packaging needs to be defined in the SUSDP. This could be achieved by requiring that blister or strip packaging meet the requirements of Section 3 of AS 1928-2001, i.e. change paragraph (4) of the preposed amendment to "is in the form of blister and strip packaging that complies with Section 3 (Requirements for Non-Reclosable Packages) of Australian Standard AS 1928-2001 *Child Resistant Packages*.
- Change (5) of the proposed amendment to "non-access/non-contact packaging that complies with the requirements of Australian Standard AS 4710–2001 entitled *Packages for chemicals not intended for access or contact with their contents by humans*".

The Committee noted that the TGA exercised control over the type of CRC/CRP fitted to a product in accordance to TGO 65 by refusing or withdrawing product registration if the closure chosen by the applicant complies with an inappropriate standard. If the Committee were to decide to remove the current definitions for CRC and CRP from the SUSDP and replace them with the foreshadowed proposal, the capacity of the NDPSC to stipulate the standard to which a closure must comply may be removed. Accordingly, the Committee was advised that it may wish to consider retaining the CRC definition.

A Member expressed the opinion that it was inappropriate to include AS 4710-2001 in the definition of child-resistant packaging on the grounds that the Standard tests for packaging that is designed not to be opened. Furthermore, a number of Members expressed concern regarding the removal of the definition for child-resistant closure from the SUSDP.

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The Committee agreed to retain and broaden the current definition of child-resistant closure and to include a separate definition for non-access packaging in the SUSDP. Furthermore, the Committee agreed to amend the foreshadowed definition of child-resistant packaging to incorporate the comments received.

Part 1 – Interpretation - Amendment

Sub-paragraph 1.(1)

"Child-resistant closure" – amend entry to read:

"Child-resistant closure" means:

(a) a closure that complies with the requirements for a child-resistant closure in at least one of the following standards as specified or amended from time to time:

(i) the Australian Standard AS1928-2001 entitled *Child-resistant packages*;

(ii) the International Organization for Standardization Standard ISO 8317:1989 *entitled Child-resistant packaging-requirements and testing procedures for reclosable packages*;

(iii) the British Standards Institution Standard BS EN 28317:1993 entitled *Child-resistant packaging- requirements and testing procedures for reclosable packages*;

(iv) the Canadian Standards Association Standard CSA Z76.1-99 entitled *Reclosable child –resistant packages*;

(v) the United States Code of Federal Regulations, Title 16, Section 1700.15, entitled *Poison prevention packaging standards* and Section 1700.20, entitled *Testing procedure for special packaging*;

(b) a closure approved by any order made under section 10(3) of the Commonwealth *Therapeutic Goods Act 1989*; or

(c) in the case of a can fitted with a press-on lid, a lid of the design known as "double tight" or "triple tight".

"Child-resistant packaging" – amend entry to read:

"Child-resistant packaging": means packaging that:

(a) complies with the requirements of the Australian Standard AS1928-2001 entitled *Child-Resistant Packages* as specified or amended from time to time; or

(b) is reclosable and complies with the requirements of at least one of the following standards as specified or amended from time to time.

(i) the International Organization for Standardization Standard ISO 8317:1989 *entitled Child-resistant packaging-requirements and testing procedures for reclosable packages*;

(ii) the British Standards Institution Standard BS EN 28317:1993 entitled *Child-resistant packaging- requirements and testing procedures for reclosable packages*;

(iii) the Canadian Standards Association Standard CSA Z76.1-99 entitled *Reclosable child –resistant packages*;

(iv) the United States Code of Federal Regulations, Title 16, Section 1700.15, entitled *Poison prevention packaging standards* and Section 1700.20, entitled *Testing procedure for special packaging*;

(c) is approved as child-resistant by any order made under section 10(3) of the Commonwealth *Therapeutic Goods Act 1989*; or

(d) is in the form of a blister and strip packaging in which a unit of use is individually protected until the time of release and that complies with Section 3 (Requirements for non-Reclosable Packages) of Australian Standard AS 1928-2001 *Child-resistant packages*.

Part 1 – Interpretation – New Entry

Sub-paragraph 1.(1)

"Non-access packaging" is packaging that complies with the requirements of Australian Standard AS4710-2001 entitled *Packages for chemicals not intended for access or contact with their contents by humans*, in relation to products that are not intended for human therapeutic use.

4.2 NAPHTHALENE

PURPOSE

The Committee considered an additional Appendix F warning statement for naphthalene.

BACKGROUND

The October 2003 meeting considered an application from XXXXXXXXX to vary the label of an existing registered product, XXXXXXXXX, consisting of 990 g/kg of naphthalene. The product is to be used as a moth repellent in wardrobes, clothes drawers and for the protection of books and other paper or cloth based material in storage.

The Committee considered the Office of Chemical Safety (OCS) evaluation report and noted that, based on the available data, the recommendation that the existing poison scheduling for naphthalene remained appropriate. The Committee was also asked to consider adding the following warning statement to Appendix F of the SUSDP:

- Do not use on the clothing of infants or in the bedrooms of young children.

The Committee raised the issue of whether an appropriate definition for young children was available and agreed to request that the evaluator present more information on the exposure studies referred to in the evaluation, including the ages of children involved, the study location and publication date. The Committee agreed to defer their consideration of this matter to the February 2004 Meeting.

DISCUSSION

The Committee noted the evaluator's response which raised the following points for consideration:

- Case reports have come from India, the USA, Canada, Greece and Australia. A large proportion of the cases reported were in Negroes from the USA, which may reflect socio-economic factors as much as the relatively mild G6PD deficiency in this population. The USA has a substantial population with mediteranean ancestry where G6PD deficiency is more pronounced yet they do not appear in the literature from the USA.
- Although most case reports of naphthalene poisoning are relatively old, the lack of recent case reports is likely to reflect firstly the lack of novelty of such cases, and therefore the lack of incentive to publish such reports, and possibly also the availability of a wide range of other pesticide products which compete with naphthalene in the market.
- Although most cases of infants poisoned by naphthalene clothing or bedding occurs neonatally this does not necessarily indicate that slightly older infants are not also susceptible, although probably to a lesser extent. Factors influencing the relative susceptibility of infants include:
  - Neonates in general have lower erythrocyte levels of cytochrome b5 reductase, glutathione peroxidase, glutathione synthetase and catalase which makes these cells inherently more susceptible to oxidative damage.
  - New born children are more likely to encounter clothing treated with naphthalene immediately on moving from the hospital to the home, as at this point clothing stored from previous children or gifted from other families will first be removed for use. Levels of naphthalene in the clothing will also be higher at this point as it is likely to have had a considerable time to take up naphthalene fumes, perhaps years.
  - Neonates are relatively immobile resulting in greater inhalation exposure to naphthalene given off by their clothing.
  - Infants have a high surface area to body mass ratio (increasing dermal absorption on a mg/kg bw basis) and potentially higher dermal flux rates.
- Individuals with a congenital deficiency of G6PD reductase will clearly be especially sensitive neonatally but remain at risk beyond the neonatal period. The report of young Greek army recruits developing haemolytic anemia, with one death, from exposure to naphthalene treated bedding reinforces the need for caution in over interpreting the significance of the ages of the patients in the case reports cited above. Clearly, susceptible individuals, ie G6PD deficiency common in Negroes (approximately 10% of normal erythrocyte G6PD levels) and some Mediterranean peoples (as low as < 1% of normal erythrocyte G6PD levels), are at potential risk from inhaled and dermally absorbed naphthalene even into adulthood.
- As haemolytic anaemia in G6PD deficient subjects can occur as a result of exposure to a number of drugs and chemicals, naphthalene as a causative agent in this group is likely to be readily overlooked, particularly where exposure is via the skin or inhalation rather than ingestion.

- Inhalation and dermal absorption are not the only issues with children. The product initiating the original CPAS (OCS) report is a naphthalene flake to be sprinkled in clothes drawers, and therefore readily accessible to young children. The data clearly indicates that young children, say 12 to 36 months, can occasionally find naphthalene attractive and need only eat a small proportion of a mothball to experience significant toxicity requiring hospitalization and blood transfusion.
- The original recommendations made by OCS to not use on the clothing of infants (who are largely immobile and appear to be more sensitive to naphthalene toxicity) or in the bedrooms of young children (where they are likely to remain in a closed room for 8 to 10 hours and are likely to have greater accessibility to locations where naphthalene balls or flakes are used) recognizes both the extended exposure periods of these groups and the apparent higher sensitivity of infants. The recommendation also recognizes the potential for children to suffer significant morbidity from ingestion of small amounts of naphthalene which some find attractive.

The Committee noted a table detailing the type of naphthalene exposure, the subjects age and the outcome of the exposure is presented was also submitted (Attachment 1 at Item 24).

The Committee was informed that a public submission was received from the XXXXXXXXX The XXXXXXXXX advised that as an interested party and stakeholder with regard to this substance, it wished to be informed of the outcome and provided with an opportunity to comment on the decision. Furthermore, should additional labelling requirements be recommended by the Committee, XXXXXXXXX requested that the manufactures be allowed sufficient time (eg. two years) to implement such changes.

Members agreed that, based on the additional data provided by the evaluator, an appropriate definition for children is three years of age or less. Furthermore, the Committee thought it appropriate that the warning statement should also preclude the use of naphthalene on children's bedding and that "young " was unnecessary and should be removed.

The Committee, upon consideration of the submission made by XXXXXXXXX, agreed to delay the implementation date for Warning Statement 105 until 1 May 2005.

The XXXXXXXXX Member informed the Committee that there is currently a significant problem in XXXXXXXXX regarding the importation and sale of inappropriately packaged and labelled naphthalene balls (mothballs). It was reported that these products are being imported from Asia, predominantly Vietnam, and sold through discount retails stores and Asian food stores. The Committee was advised that as relatively small quantities of naphthalene are being brought into Australia by business or individuals not traditionally involved in the chemicals industry, the importation and sale of these product is difficult to control. The XXXXXXXXX Member advised that XXXXXXXXX is currently experiencing a similar problem. Members expressed concern that products containing naphthalene were being sold without appropriate warning statements and safety directions.

The XXXXXXXXX Member informed the Committee that NICNAS is about to introduce legislation into the Commonwealth Parliament which would require all introducers of chemicals to be registered and that this would provide a mechanism through which the inappropriate importation of chemicals could be controlled. The XXXXXXXXX Member agreed to bring the issues raised by XXXXXXXXX and XXXXXXXXX to the attention of NICNAS.

The Committee asked that the remaining States and Territories report to the next meeting any similar problems regarding the importation and sale of inappropriately packaged and labelled naphthalene balls (mothballs).

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The Committee agreed that the Schedule 6 entry for all users for naphthalene remained appropriate. Furthermore, the Committee supported the addition of the following warning statement to Appendix F to alert users of the potential hazard naphthalene products present to young children - those being three years of age or less.

APPENDIX F Part 1 – New Entry

105. Do not use on the bedding or clothing of infants or in the bedrooms of children three years of age or less.

APPENDIX F Part 3 – Amendment

Naphthalene – amend entry to read:

POISON	**WARNING STATEMENTS**	**SAFETY DIRECTIONS**
Naphthalene (permitted until 30 April 2005)		
(a) in block, ball, disc or pellet form, enclosed in a device which, in normal use, prevents removal or ingestion of its contents;	9	
(b) in other forms.	9	1
Naphthalene (mandatory from 1 May 2005)		
(c) in block, ball, disc or pellet form, enclosed in a device which, in normal use, prevents removal or ingestion of its contents;	9, 105	

(d) in other forms. 9, 105 1

4.3 HOME GARDEN PRODUCTS - CONSIDERATION OF PACK SIZES

PURPOSE

The Committee considered a proposal to include a pack size limit for home garden pesticides in the SUSDP.

BACKGROUND

The Committee at the October 2003 meeting considered a proposal to limit pack sizes of home garden products to 1 kg/L through an amendment to Part 3 of the SUSDP.

The APVMA had obtained advice suggesting that the upper size limit of their labelling code (1 kg/L) may not be enforceable. There was a concern that larger pack sizes in and around the home could increase the potential of an accidental poisoning, through opened and unused chemical product being stored in the home for longer periods of time. As a consequence, the labelling code may not provide adequate protection to the public should an applicant wish to market products in quantities above 1 kg or L to home garden chemical users.

The Committee was advised that the proposal to restrict home garden product pack sizes through an amendment to Part 3 may not be successful as not all jurisdictions adopt this part of the SUSDP into their own poisons legislation.

The Committee proposed that the jurisdictions consult with the areas with in their respective Governments responsible for administering agricultural and veterinary chemical use legislation to determine whether home garden pack sizes could be limited through State and Territory legislation. In addition, the Committee agreed that the APVMA should determine whether the trend toward larger home garden pack sizes was significant enough an issue to warrant the inclusion of restrictions in the SUSDP.

DISCUSSION

The Committee noted the following advice from the jurisdictions and the APVMA:

- The XXXXXXXXX Member advised that there is no facility in any legislation administered by the Departments of Human Services or Primary Industries to place a pack size limit on products intended for home garden use. Both Departments considered that if a size limit was required it could be controlled through the registration process. However, doubts exist as to its effectiveness given the difficulty of controlling the sale of larger pack sizes through agricultural chemical outlets to the home garden use market. Both Departments would like to see the supply of S7

products restricted to agricultural producers only, but once again are not able to determine where the line could be drawn.

- The XXXXXXXXX Member advised that there is nothing specific in either the XXXXXXXXX Poisons Act/Regulations or veterinary or agricultural legislation that specifies pack sizes for home garden use products. However, Part 2 of the SUSDP for containers and labels is adopted through Poisons Regulations 1965 by XXXXXXXXX.
- The XXXXXXXXX Member advised that a Ministerial order could be made under Section 20 of XXXXXXXXX 's *Agricultural and Veterinary Chemicals (Control of Use) Act 1995* to regulate the capacity of pack sizes that may be sold. However, it was unlikely that this provision would be used in such a manner. The National Registration Scheme for Agricultural and Veterinary Chemicals is based on a split of responsibilities between the States and the Commonwealth. The States being responsible for controlling the use of chemical products and the Commonwealth through the APVMA being responsible for regulating manufacture and supply up to the point of retail sale. The issue of pack sizes would seem to be a matter that should properly be regulated through the *Agricultural and Veterinary Chemicals Code Act 1994* administered by the APVMA. Accordingly, the matter should be pursued further with the APVMA. While the APVMA' s labelling code may not be enforceable, there may be some other means within the legislation they administer to apply such restrictions - maybe through the conditions of registration or approval of labels under section 23 of the Code.
- The XXXXXXXXX Member advised that the soon to be enacted *Agricultural and Veterinary Products (Control Of Use) Act 2002* regulates the "user" (eg training requirements to handle restricted products, etc) not the "purchaser" and does not operate at point of sale. Furthermore, the APVMA legislation would be a more appropriate way of addressing pack size limits for pesticides.
- The XXXXXXXXX Member advised that the Act by which XXXXXXXXX implements its obligations under the national registration scheme for agricultural and veterinary chemicals (*Pesticides Act 1999*), does not provide power for XXXXXXXXX to control pack sizes of pesticides.
- The Committee noted that no reports were supplied by XXXXXXXXX, the XXXXXXXXX or the XXXXXXXXX.
- The APVMA advised that there are currently 182 registered Schedule 5 and 6 home garden products with pack sizes in excess of 1 kg/L. The APVMA does not support a change to the SUSDP to limit home garden pack sizes for scheduled products to a maximum of 1 L or 1 kg. Whilst APVMA appreciates the concerns of the Committee, it considers that enhanced controls would be better achieved through changes to the APVMA Ag Requirements Series and/or the Ag Labelling Code. This would allow a more flexible risk-based approach.

The Committee was informed that public submissions were received from XXXXXXXXX, the XXXXXXXXX and XXXXXXXXX.

XXXXXXXXX advised that they market several home garden products in pack sizes in excess of 1 kg/L (2 and 4 L bottles and 12.5 kg bags). These product are sold in dilute formulations so that when used according to label directions these products do not pose any significant health effects to home gardeners. Accordingly, home gardeners should be able to continue to purchase these products.

The XXXXXXXXX advised that a number of member companies manufacture/market home garden product in pack sizes greater than 1 kg/L. The XXXXXXXXX was of the view that the determination of an appropriate pack size for home garden products should remain on a case-by-case with the APVMA in the context of a full registration. Should concerns be raised about a substance/product then it could be referred to the NDPSC for consideration. If the Committee were to impose a pack size limit, the XXXXXXXXX believes that manufactures and marketers of home garden products would be either forced to seek exemptions through the States and Territories or manufacture concentrates rather than ready-to-use products of sale to the home garden market.

XXXXXXXXX advised that, as a marketer of a home garden product (2 L), the appropriate pack size for a pesticide product should be determined by the APVMA on a case-by-case basis at the time of registration. A "blanket" restriction on pack size through the SUSDP could result in the consumer being forced to purchase multiple packs which would not necessarily reduce the potential for storage of part-used product. Industry may also opt to market concentrates or choose to seek exemptions for their products from the States and Territories which could be a difficult, lengthy and onerous process.

A Member advised that it was preferable that home garden products be available in ready-to-use packs even if pack sizes are greater than 1 kg/L rather than as concentrates in volumes of 1 kg/L or less.

The XXXXXXXXX Member assured the Committee that the home garden product pack sizes could be controlled, where appropriate, through changes to the APVMA Ag Requirements Series.

OUTCOME

The Committee agreed that the appropriate mechanism to control home garden product pack sizes should be through the APVMA registration process.

4.5 METHYLCYCLOPENTADIENYL MANGANESE TRICARBONYL

PURPOSE

The Committee considered the foreshadowed Schedule 7 entry for methylcyclopentadienyl manganese tricarbonyl (MMT).

BACKGROUND

The NDPSC considered the scheduling of MMT at its October 2003 meeting where the Committee agreed to foreshadow its inclusion in Schedule 7 with a cut-off to Schedule 6 for fuel additive preparations containing 10% or less of MMT when fitted with a child-resistant closure. The Committee based its decision on the acute toxicological profile of MMT and that the use pattern of consumer products fitted with a child-resistant closure would limit the exposure direct to the public.

MMT is an anti-valve seat recession additive in automotive lead replacement petrol. MMT is also an octane enhancer. It is either pre-blended at the refinery or added to unleaded petrol by the vehicle owner and acts as a lubricating agent to prevent excessive valve seat wear and recession of the valve seat into the automotive cylinder head.

The Committee noted that the companies producing these products and who had provided information to NICNAS for their assessment had not taken the opportunity to make a submission to the NDPSC with regard to the scheduling of MMT. The Committee agreed foreshadow the proposed scheduling of MMT to allow interested parties to comment prior to a decision being made.

DISCUSSION

The Committee was informed that a number of public submissions were received from companies and industry groups involved in the importation, reformulation and manufacture of MMT or products containing the substance.

Members noted that the consensus of opinion regarding the foreshadowed scheduling proposal was that industry had not had sufficient time to fully assess the regulatory and commercial impact of the Committee's decision. Consequently, XXXXXXXXX requested that the Committee defer the matter to allow for an adequate assessment of the implications resulting from the scheduling decision to be completed.

The Committee was informed that by deferring consideration of this matter MMT would remain unscheduled for another several months. A Member questioned the appropriateness of such a decision given that the Committee had identified that the availability of MMT in consumer products warranted control through scheduling on the basis of its acute toxicity profile.

The Committee was advised that NICNAS considered that exposure to MMT resulting from the use of consumer products was likely to pose a greater risk to human health than its use in industrial settings during the formulation and distribution of lead replacement fuels.

A Member advised the Committee that it is likely that the availability of many consumer products currently marketed containing MMT would be controlled as a consequence of these formulations containing other scheduled substances.

OUTCOME

The Committee agreed to defer consideration of this matter to the June 2004 meeting to allow XXXXXXXXX more time to make their submissions.

4.6 METHYLCYCLOPROPENE

PURPOSE

The Committee considered correspondence regarding the scheduling of 1-methylcyclopropene (1-MCP).

BACKGROUND

1-MCP was exempt from the requirements of scheduling based on its low toxicity profile at the June 2003 meeting. The product, XXXXXXXXX, is a powder that, when mixed with water in a proprietary generating system, releases the volatile ingredient 1-MCP as a gas from the 1-MCP XXXXXXXXX. 1-MCP is an irreversible inhibitor of ethylene action at the preclimacteric or ripening stages in fruit.

[paragraph deleted]

Whilst the Committee agreed that the toxicological profile of 1- MCP gas when used as a plant growth regulator may be appropriate for a scheduling exemption, the following issues were raised:

- A lack of technical information on the nature of the ingredients contained in the product including the 1-MCP XXXXXXXXX, and that the absence of this information did not allow the Committee to determine whether scheduling was warranted or that it was appropriate to list such ingredients separately in Appendix B of the SUSDP; and
- No data was provided to support the applicant's claim that 1-MCP gas was kept within the 1-MCP XXXXXXXXX via a physical mechanism, ie. XXXXXXXXX, and that the structure of the XXXXXXXXX falls apart upon contact with water thereby releasing the 1-MCP gas.

The Committee agreed to seek further information regarding the issues described above so that consideration of scheduling of other substances contained with in the product, including the 1-MCP XXXXXXXXX, could be undertaken if appropriate.

DISCUSSION

The Committee noted a submission from the applicant, XXXXXXXXX, in which the following comments were made in response to the issues raised by the Committee at the June 2003 meeting:

[paragraphs deleted]

Members were of the opinion that sufficient information had been submitted by the applicant to clarify the data deficiencies identified at the June 2003 meeting regarding technical information on the ingredients contained in the product and the nature of the interaction between 1-MCP and XXXXXXXXX.

OUTCOME

The Committee agreed that the current Appendix B entry for 1-MCP remained appropriate.

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

5.1 SUSDP, PART 4

5.1.1 STAR ANISE OIL AND ANISE OIL

PURPOSE

The Committee considered the scheduling of star anise oil and anise oil.

BACKGROUND

The scheduling of anise oil was considered at the February 2000 meeting where it was included in Schedule 5. The decision was taken on the basis of the potential of anise oil to result in human toxicity, as its LD50 value corresponded with the Schedule 5 criterion for oral toxicity. Exemptions from scheduling for small volumes (subject to certain packaging requirements) and preparations containing concentrations less than 50% were also included and were based on the reduced risk associated with such presentations.

Anise oil is a carminative, mildly expectorant and a common ingredient of cough preparations. It is also a used a flavouring. Anise oil is extracted from the seeds of *Pimpinella anisum* L. while star anise oil is derived from the seeds of *Illicium verum* Hooker f.

In response to an enquiry regarding the scheduling of anise oil and star anise oil, it was brought to the attention of the Secretariat that there was an inconsistency in the scheduling of these two essential oils. Anise oil and star anise oil both contained the same

active ingredient, *trans*-anethole, as the principle constituent (at levels of greater than 80%). While anise oil was included in Schedule 5, star anise oil was not listed in the SUSDP.

DISCUSSION

The Committee noted that an Essential Oils Working Party (EOWP) monograph on Anise oil showed that the oils derived from *Pimpinella anisum* L. (aniseed) and *Illicium verum* Hooker f. (star anise) differ little in composition despite being derived from different botanical sources.

The Committee was informed that public submission were received from XXXXXXXXX, the XXXXXXXXX, the XXXXXXXXX and XXXXXXXXX.

The XXXXXXXXX stated that two entirely different oils have been classified as one oil in the current scheduling. In addition, the XXXXXXXXX highlighted that the chief constituent is anethole which has not been scheduled. The company was of the opinion that neither anise, aniseed (star anise) oil or anethole should be scheduled. The XXXXXXXXX claimed that the oils have been used extensively in the flavour and pharmaceutical industry and both have been granted a generally regarded as safe (GRAS) status by FEMA and are approved by FDA for food use (GRAS). Furthermore, both materials have also been issued with Council of Europe Numbers.

The XXXXXXXXX reiterated its previous submission made to the EOWP. The minutes of the May 2000 meeting noted that the XXXXXXXXX opposed the Schedule 5 entry for anise oil on the basis of its long history of use in the food and flavouring industries, the absence of human evidence of safety problems and the basis for the scheduling being the acute oral toxicity in the rat.

The XXXXXXXXX and XXXXXXXXX submissions sought to reserved the right to make post meeting comment.

The Committee noted advice from XXXXXXXXX, the Committee's XXXXXXXXX expert Member and the XXXXXXXXX regarding the scheduling of star anise oil. XXXXXXXXX advised that, in relation to the constituents present in the oils derived from *Pimpinella anisum* L. (aniseed) and *Illicium verum* Hooker f. (star anise), *trans*-anethole was present in both oils at levels between 80 and 90% and that the remaining essential oil components were below levels likely to influence the hazard potential. Although, anise oil and star anise oil are derived from different plants and have differences in their minor constituents, they exhibit similar toxicity for the rat and similar *trans*-anethole content. Since the potential toxicity for both oils is due to the *trans*-anethole content (oral LD50 for the rat of 2.09 g/kg), it was XXXXXXXXX opinion that the same scheduling status would apply to both oils.

A Member advised that during the consideration of anise oil by the EOWP, *Pimpinella anisum* L. (aniseed) and *Illicium verum* Hooker f. (star anise) were both considered to be

sources of this essential oil on the basis that their extracts both contained *trans*-anethole as the major constituent. On that basis, it would not be unreasonable to include a separate entry for star anise oil in Schedule 5. The Committee was also informed that the British Pharmacopoeia monograph on star anise oil considers that both plants are sources of the essential oil.

The Committee noted that if an entry for star anise oil were to be included in Schedule 5 with the exemptions currently afforded to anise oil, the regulatory impact was expected to be low as the majority of uses would be exempt, such as, when present in foods (through Appendix A) and when in small aromatherapy packs. Food additives would only be affected if the volume is large or the concentration of the oil is greater than 50%.

DECISION 2004/40 - 6

The Committee agreed that as anise oil and star anise oil were derived from different botanical sources, a separate Schedule 5 entry for star anise oil was warranted on the basis of the toxicity exhibit by its *trans*-anethole content. An exemption from scheduling for star anise oil products when meeting certain specific requirements was also supported for consistency with the Schedule 5 entry for anise oil.

Schedule 5 – New Entry

STAR ANISE OIL **except**:

(a) when packed in containers having a nominal capacity of 50 mL or less fitted with a restricted flow insert, and labelled with the warning:

KEEP OUT OF REACH OF CHILDREN; or

(b) in preparations containing 50 per cent or less of star anise oil.

5.1.2 CREOSOTE AND RELATED COMPOUNDS AND FRACTIONS

PURPOSE

The Committee considered the scheduling of creosotes and related compounds or fractions.

BACKGROUND

The June 2003 meeting agreed to ask the Office of Chemical Safety (OCS) to review the safety of coal tar creosote. This request was based upon concerns being raised about the carcinogenic potential of creosote and safety for use as a wood preservative.

At the June 2003 meeting, the Committee considered an overview of the draft CICAD on coal tar creosote prepared by the OCS. The Committee was asked to consider:

- the creation of a specific SUSDP entry for coal tar creosote, with entries if and as necessary for other coal tar derived mixtures, and wood creosote.
- whether the marketing of coal-tar creosote as a wood preservative should be limited to industrial use and to licensed applicators.
- whether all marketed coal tar creosote preparations should be required to contain limits on specific toxic and carcinogenic contaminants of concern (eg. less than 0.005% by weight of benzo[*a*]pyrene and water-extractable phenols at less than 3% by weight).
- the appropriateness of coal tar preparations being available for the treatment of psoriasis (and for any other cosmetic uses that may exist).
- the appropriateness of creosote being available in oral pharmaceutical preparations.

The Committee asked that advice be sought from the APVMA, MEC and CMEC regarding the potential impact on existing products should creosote and related substances be scheduled.

DISCUSSION

The Committee was informed that there are currently 10 products containing creosote registered by the APVMA. The majority (7) are for the treatment of timber and timber products, but there are also a farm disinfectant product, a liniment product and an anti-fouling paint registered containing creosote with concentrations ranging between 43 g/L to 1044 g/L. In addition to these products, there are another 11 products containing coal tar or tar acids. These products are registered for use as dog and cat washes, equine grooming aids, ointments, disinfectants and blowfly strike treatments with concentrations ranging between 3 g/L to 419 g/L.

The Committee noted that the Medicines Evaluation Committee (MEC) supplied the following for consideration:

- The ARTG includes products containing ‘creosote’, coal tar, ‘tar’ (pine tar) and cade oil (juniper tar).
- None of the products containing ‘creosote’ have been evaluated by the TGA; most are listed and most appear to be indicated for use as expectorants/decongestants for coughs;
- If described correctly, products containing ‘creosote’ should contain ‘wood creosote’ (as defined by the AAN);

- All the Australian products containing coal tar are registered, with most of the evaluated products indicated for itchy skin and/or scalp conditions (eg. psoriasis, seborrhoeic dermatitis, seborrhoea, dandruff, eczema, dermatitis) – ie. conditions consistent with those accepted by the ARGOM policy guideline on 'Coal tar preparations';
- At least two of the 'grandfathered' products containing coal tar are indicated for nappy rash – ie. these products do not comply with the ARGOM guideline;
- Most of the evaluated registered products containing pine tar are indicated for use on itchy and/or inflamed skin (eg. dermatitis, eczema, dry skin, nappy rash, psoriasis);
- Most of the products containing cade oil are 'grandfathered' – all the registered products are intended for inflamed skin/scalp conditions; and
- A number of the products contain more than one tar.

The Committee noted advice from the Office of Complementary Medicines (OCM) indicating that, as creosote is regulated as an over-the-counter registrable, they are unable to provide comment.

Members noted a public submission from the XXXXXXXXX advising of their interest in creosote and sought the right to make post-meeting comment.

The Committee was informed that the Office of Chemical Safety (OCS) was currently undertaking a review of the public health issues surrounding coal tar creosote use in products registered by the APVMA, expected to be completed in 2005.

A Member expressed concern that there appeared to be no uniformity in the use of the terms "creosote", "wood creosote", "coal tar creosote" and "coal tar BP". Similarly, the type of the creosote present in the registered and listed medicines identified by the MEC and the products registered by the APVMA were also poorly defined.

The Committee asked that the nature and percentage of the creosote present in the registered and listed medicines and agricultural and veterinary products be determined in consultation with the TGA and the APVMA. Furthermore, the Committee asked that "coal tar creosote" be clearly defined.

OUTCOME

The Committee agreed to defer this agenda item to the June 2004 meeting to allow further information and advice to be obtained.

5.1.3 DIETHYLENE GLYCOL BUTYL ETHER

PURPOSE

The Committee considered the scheduling of diethylene glycol butyl ether (DEGBE).

BACKGROUND

XXXXXXXXX and XXXXXXXXX submitted a joint application seeking an exemption from scheduling for DEGBE from the Schedule 6 entry for ethylene glycol monoalkyl ethers and their acetates. The applicants advised that DEGBE products intended for consumer uses are typically cleaning products containing concentrations of the chemical of 1% to 13%. DEGBE may also be used in household paints, the majority of which would be restricted to industrial products. Approved agricultural products contain DEGBE in concentrations ranging from 1% to 98%.

At the November 1984 meeting, the Committee included ethylene glycol monoalkyl ethers and their acetates in Schedule 6 of the SUSDP. This scheduling was reaffirmed at the May 1992 meeting of the Committee. At its June 2003 meeting the Committee confirmed that DEGBE was included in Schedule 6 by virtue of the provisions of Part 1, paragraph 2(c) of the SUSDP.

DISCUSSION

The Committee noted the NICNAS evaluation report submitted which relied principally on the EU report for DEGBE and some original papers on the chemical provided by the applicant. The report raised the following points for consideration:

- The chemical is not considered to be acutely toxic by the oral route in rats (LD50 (fasted and fed) = 7292 and 9623 mg/kg bw, respectively) and mice (LD50 (fasted and fed) = 2406 and 5526 mg/kg bw, respectively), nor via the dermal route (LD50 = 2764 mg/kg bw) in rabbits. No toxic effects were seen following exposure of rats to the maximum attainable vapour concentration for 7 hours. However, the EU report notes that the data did not allow a definite conclusion to be drawn on the acute toxicity of the chemical by inhalation due to the low concentration (≈120 mg/m^3) that was achieved. It should be noted that some of the consumer cleaning products are in aerosol form and others are in spray packs, which would liberate droplets into the atmosphere.
- The results of an acute dermal irritation study indicating that the chemical is not a skin irritant based on occupational health criteria. In a 13-week dermal study in Sprague-Dawley rats (10 animals/sex), at 200, 600 and 2000 mg/kg bw/day, however, the chemical was shown to be a mild irritant even at the lowest dose tested. Erythema was observed at the application site at all doses tested. In the high dose group necrosis and eschar formation were observed in some animals. A NOAEL for local effects of < 200 mg/kg body weight/d was identified. No conclusions can be drawn on acute inhalation toxicity.
- The EU report concludes that DEGBE should be classified as irritant to the eyes. For scheduling purposes, however, the degree of irritation is important. The paper of Ballantyne (1984) is discussed in the EU report and deemed acceptable despite not having been undertaken to OECD Test Guidelines. Using the undiluted chemical,

moderate to severe chemosis is seen within 1 hour following instillation, mild keratitis is also found immediately, and after one day iritis is present. Symptoms do not resolve completely until day 10 and the author states that the cornea appeared normal after 10 days but this abnormality seems to be related to keratitis. Irritant symptoms for solutions of 50%, 25% and 10% DEGBE resolved within 7 days. The EU report concludes the chemical is not corrosive to the skin, eyes or respiratory tract. DEGBE is not mutagenic following a series of tests. There are no carcinogenicity studies in animals.

- There is no evidence of dermal sensitisation.
- The acute oral toxicity profile and dermal irritation potential is not consistent with either a Schedule 5 or Schedule 6 entry. The acute dermal toxicity in rabbits and eye irritation potential is consistent with a Schedule 5 entry.
- There is a low hazard from repeated use consistent with a Schedule 5 entry.
- The risk to consumers arises from dermal absorption and inhalation of aerosol particles from oven cleaners and spray painting. No data is presented on concentrations of DEGBE in paints, however, oven cleaners and spray paints would likely be used in confined spaces and consumers could face repeated exposure in using these products. No information is given on the other components of the cleaning products.
- No indication is given that the cleaning products are fitted with child-resistant closures. Whilst it would be difficult for a child to open a paint tin without tools, they could access open or partially opened cans in the home. Furthermore, tins of thinners are usually fitted with a screw cap and could be easily opened.
- On the basis of the above considerations, XXXXXXXXX recommended that DEGBE be included in Schedule 5 of the SUSDP on the basis that its toxic properties are consistent with a Schedule 5 listing. The evaluator also indicated that there are insufficient data on the toxicity of the products into which DEGBE will be incorporated to determine a scheduling cut-off.

The Committee was informed that public submissions were received from XXXXXXXXX and XXXXXXXXX.

XXXXXXXXX advised that they have an interest in DEGBE and sought the right to make a post-meeting comment.

XXXXXXXXX advised that they supported the proposal to down-schedule DEGBE.

The XXXXXXXXX evaluator advised the Committee that there were data gaps with regard to the inhalation toxicity exhibited by DEGBE. The Committee agreed that exempting all preparations of DEGBE from the requirements of scheduling would be inappropriate in the absence of data on inhalation toxicity given that the substance would be used in domestic cleaning products such as oven cleaners which are often applied as aerosols and used in confined spaces.

A Member informed the Committee that given its current scheduling status under the Schedule 6 class entry for ethylene glycol monoalkyl ethers and their acetates, preparations containing 10 per cent or less of DEGBE are currently exempt from the requirements of scheduling. Therefore given this and its long history of use, an entry in Schedule 5 for DEGBE with an exemption for preparations containing 10 per cent or less would appear to be supported by the available data. Members agreed that the 10 percent exemption cut-off was also consistent with the eye irritation data supplied by the applicant.

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The Committee agreed to include DEGBE in Schedule 5 with an exemption from the requirements of scheduling for preparations containing 10 per cent or less. The Committee also agreed to include the CAS name of DEGBE in the index of the SUSDP.

Schedule 5 – New Entry:

DIETHYLENE GLYCOL MONOBUTYL ETHER **except** in preparations containing 10 per cent or less of diethylene glycol monobutyl ether.

Index – New Entry:

2-(2-BUTOXYETHOXY)ETHANOL

See DIETHYLENE GLYCOL MONOBUTYL ETHER

5.1.4 10,10'-OXYDIPHENOXARSINE

PURPOSE

The Committee considered the scheduling of 10,10′-oxydiphenoxarsine (OBPA).

BACKGROUND

XXXXXXXXX submitted an application requesting:

- The down-scheduling of preparations containing 5.25% w/w or less of OBPA from Schedule 7 to Schedule 6. As these preparations are to be used to blend with other polymer raw materials during the extrusion and moulding of polymer articles, the applicant's proposition was based on the argument that these OBPA preparations will not be supplied to the public and will only be used by trained industrial polymer/plastic processors; and

- That OBPA be exempt from the SUSDP when contained in polymer/plastic articles containing a maximum concentration of OBPA of 525 ppm (or expressed as arsenic content, 156 mg/kg of polymer).

The intended use for OBPA is as a microbiocide in polymer articles. Polymers containing OBPA at the proportions describe above will be used to make bath mats, shower curtains, swimming pool liners, vinyl upholstery in boats, wall coverings, tarpaulins, awnings, ditch linings, shoe soles and other similar applications. It is unclear from the application as to the exact nature of the other similar applications. The maximum concentration of OBPA proposed to be used in the end-use articles is 525 ppm (525 mg/kg) OBPA, or expressed as arsenic content, a maximum concentration of 156 ppm (156 mg/kg) of arsenic.

The company's product, XXXXXXXXX, is a range of preparations (liquid or sold forms) containing XXXXXXXXX or less of OBPA or expressed as arsenic content XXXXXXXXX or less of arsenic in a variety of carriers/solvents such as 'XXXXXXXXX, XXXXXXXXX XXXXXXXXX and similar XXXXXXXXX.

DISCUSSION

The Committee noted the NICNAS evaluation report which raised the following points for consideration:

- OBPA has very high oral toxicity, which can cause death or severe injury at low exposure – with an acute oral LD50 (rat) of 15-40mg/kg bw and the ability to cause severe and prolonged eye irritation. A Schedule 7 classification for the active ingredient (OBPA) is appropriate. The current exception of OBPA in Schedule 7 relates specifically to the consumer use of OBPA in silicone rubber mastic containing 120 mg/kg or less of arsenic.
- The XXXXXXXXX range of preparations are intended solely for industrial use and will be subject to relevant State and Territory occupational, health and safety legislation. Acute toxicity data was provided for one preparation only, XXXXXXXXX (4.75% OBPA). The acute toxicology of XXXXXXXXX is consistent with moderate acute oral and dermal toxicity, and high dermal and eye irritancy. No chronic toxicity data was available for XXXXXXXXX.
- No toxicity data was provided for any of the other XXXXXXXXX preparations. However, it is considered unlikely that there would be a significant increase in the LD50 of a 5.25% preparation of OBPA compared to a 4.75% OBPA preparation given a decrease in the concentration of OBPA from 100% to 4.75% results in a (98%) increase in the value of the LD50 of OBPA from 15 mg/kg to 770 mg/kg. It is unclear from the application as to the exact nature of the OBPA preparations that will be imported into Australia.
- The lowest NOEL in studies submitted on OBPA pertains to foetal toxicity following dermal application of 0.3 mg/kg bw. An equivalent oral dose study was not available.

- The applicant proposes an exemption from the schedules for domestic articles such as bath mats, shower curtains swimming pool liners, vinyl upholstery in boats, wall coverings, tarpaulins, awnings, ditch linings, shoe soles and other similar applications containing up to 525 ppm OBPA.
- The main risks associated with the use of OBPA relates to the potential leaching or dislodgment of OBPA from polyvinyl chloride (PVC) and polyurethane (PU) articles.
- Possible exposure scenarios include swimmer whole body exposure and possible incidental ingestion of pool water containing OBPA leached from a pool liner; dermal absorption for an adult and child wearing treated shoes without socks or clothing; and dermal absorption by a young child crawling naked on vinyl floor coverings. The applications are for household use on a potentially daily basis and as such any risks will be ongoing.
- The lowest margins of exposure (MOE) were noted for PVC swimming pool liners and water beds, mattresses and (upholstery) leather.
- The present application does not indicate OBPA-treated plastics will be used for contact with food, clothing, children's wear or domestic water hoses.
- It is not known why the applicant proposed an OBPA treat rate of 525 ppm OBPA compared to the 500 ppm treat dose investigated in the submitted study.
- The dislodgement rate from the article is assumed to be at a level of 50% of the analytical Level of Detection (LOD). If it is assumed that the dislodgment rate is 100% of the LOD, then MOEs will be half the estimated values stated in the table Summary of OBPA Human Health Risk Assessment.
- Based on the exposure scenarios described above, it is appropriate to exclude OBPA treated PVC and PU bath mats, shower curtains swimming pool liners, vinyl upholstery in boats, wall coverings, tarpaulins, awnings, ditch linings, shoe soles containing not more than 525 ppm OBPA from scheduling.
- On the basis of the above considerations, XXXXXXXXX has recommended that:
  - The Schedule 6 entry for arsenic be amended to include OBPA preparations containing 5.25% or less of 10,10'-oxydiphenoxarsine and include a warning statement that OBPA industrial preparations are intended exclusively for industrial use; and
  - The Schedule 7 entry for arsenic be amended such that polyvinyl chloride and polyurethane extruded and moulded articles containing no more than 156 mg/kg of arsenic as OBPA be exempt from the Scheduling.

The Committee was informed that the scheduling consideration of OBPA was included in the pre-February 2004 meeting gazette and no public submissions were received.

The Committee was advised that limiting the supply of OBPA to industrial users by amending the Schedule 6 entry for arsenic to include the warning statements

"WARNING - For industrial use only" and "WARNING - Not to be supplied for domestic use" may not be enforceable by the States and Territories.

A Member expressed concern that exposure may result if plastic products containing OBPA are recycled at the end of their useful lives. The Committee was advised that OBPA is present in plastic articles at low levels and that leaching studies have shown that migration of the compound from the polymer matrix is extremely low. Furthermore, the leachate will contain arsenic as OBPA which has a much different toxicity profile to that exhibited by elemental arsenic. The Members agreed that OBPA should not be included in articles in contact with foodstuffs, packaging or potable water.

A Member expressed concern that the applicant's argument for inclusion of OBPA in Schedule 6 was flawed on the basis that limiting its supply to only "trained industrial polymer/plastic processors" was more consistent with the current SUSDP definition of a Schedule 7 poison. The Member was reminded that the inclusion of a substance in Schedule 7, whilst restricting availability does, by virtue of State and Territory legislation, impose further restrictions on supply and use beyond those required by the SUSDP. It was suggested that the motivation for seeking a down-scheduling may be prompted by a desire to remove the additional controls applied by the States and Territories. The Committee was advised that some jurisdictions have the capacity to provide industrial users with exemptions from these additional controls on supply and use of Schedule 7 substances.

A Member also expressed concern that the inclusion of OBPA in Schedule 6 on the condition that the substance was not used domestically had a high potential for non-compliance.

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The Committee agreed that, as a Schedule 6 poison, it would be difficult to limit the availability OBPA to industrial users and did not support the inclusion of OBPA preparations in Schedule 6. The Committee did, however, agree that OBPA polyvinyl chloride and polyurethane extruded and moulded articles did not pose a unreasonable risk to human health where OBPA particles from these articles did not come into contact with food, drinking water, peoples skin or animal feeds. The Committee agreed that such polymer/plastic articles containing a maximum of 525 mg/kg OBPA (equivalent to 160 mg/kg arsenic) could be exempt from the requirements of scheduling. The Schedule 7 entry for arsenic was amended accordingly.

Schedule 7 - Amendment

ARSENIC **–** amend entry to read:

ARSENIC **except**:

(a) when separately specified in this Schedule;

(b) when included in Schedule 4 or 6;

(c) as selenium arsenide in photocopier drums;

(d) as 10,10'-oxydiphenoxarsine in silicone rubber mastic containing 120 mg/kg or less of arsenic;

(e) as 10,10′-oxydiphenoxarsine contained in polyvinyl chloride and polyurethane extruded and moulded articles containing 160 mg/kg or less of arsenic other than when included in articles:

(i) in contact with food stuffs, animal feeds or potable water;

(ii) of clothing and footwear in contact with the skin;

(iii) used as infant wear; or

(iv) intended for use as packaging materials;

(f) in animal feeds containing 75 g/tonne or less of arsenic; or

(g) in paints containing 0.1 per cent or less of arsenic calculated on the non-volatile content of the paint.

5.1.5 ISOHEXADECANE AND ISODODECANE

PURPOSE

The Committee considered the scheduling of isohexadecane and isododecane.

BACKGROUND

XXXXXXXXX submitted an application for exemption from scheduling for their XXXXXXXXX products containing isohexadecane and isododecane on the grounds that the packaging and the viscosity of the products minimises the risk of aspiration into the lungs.

The XXXXXXXXX are XXXXXXXXX consisting of two sealed compartments, XXXXXXXXX. These two compartments fit into XXXXXXXXX. The larger, XXXXXXXXX, compartment is made of XXXXXXXXX and contains XXXXXXXXX white mineral oil, exempt from scheduling, as the burning fuel. The smaller, XXXXXXXXX, compartment is made from XXXXXXXXX and contains the liquid fragrance. When depleted containers are disposed of a refill can be purchased. There are

two variants of the fragrance containing between 12 and 15% isododecane and 48 and 60% isohexadecane.

DISCUSSION

The Committee noted the company's submission that argued for an exemption from Schedule 5 on the basis that:

- the contents of the bottles are securely sealed and only controlled release is possible through the wick;
- it is not readily possible for a person to swallow any significant quantities of the liquid hydrocarbons inside the bottles;
- based on the European Dangerous Preparations Directive classification criteria for R65 (Harmful: may cause lung damage if swallowed), which is based on the viscosity of the liquid hydrocarbons, the product (i.e. fragrance) has a measured viscosity which is above the criteria and R65 classification is not required; and
- overall given the sealed packaging and the viscosity considerations, the risk of aspiration into the lungs of the product will be minimal.

The Committee also noted the NICNAS evaluation report which raised the following points for consideration:

- From the toxicity data in the MSDS:
  - Isohexadecane was reported to have an acute oral LD50 value of 36600 mg/kg and isododecane has a value > 2000 mg/kg, however, it cannot be excluded that the value is < 5000 mg/kg.
  - No acute dermal toxicity data was reported for either hydrocarbon.
  - An acute inhalation 4-hour LC50 value of > 1850 mg/L was reported for isododecane.
  - Both hydrocarbons can defat the skin and lead to irritation and/or dermatitis.
  - Isododecane may cause eye irritation.
  - Both hydrocarbons are an aspiration hazard.
- There is no further toxicity data available. Overall, the MSDS for the liquid hydrocarbons do not provide sufficient data to allow a critical evaluation of acute health effects. More detailed toxicity data would need to be submitted by the company for a complete and robust evaluation of the toxicity profile to be undertaken. Similarly, only limited toxicity data are provided in the submitted MSDS for the products. Consequently, it cannot be determined precisely whether health effects such as defating and/or eye irritation reported for the liquid hydrocarbons would be seen with the products, but it could be assumed considering the relatively high concentrations of liquid hydrocarbons present (i.e. > 60 %).

- The contents of the bottle are not securely sealed as exposure can occur via the wick, if the wick is pulled out, and leakage from the bottle may occur if the burner is not kept in an upright position.
- From the very limited information provided in MSDS the acute toxicity profiles of isohexadecane and isododecane are considered consistent with a Schedule 5 entry: low potential for causing harm. These liquid hydrocarbons are considered to have significant toxicity, as they are an aspiration hazard and have skin and/or eye irritation potential.
- The designated liquid hydrocarbons are present in the XXXXXXXXX products at a concentration greater than 25 %.
- On the basis of the above considerations, XXXXXXXXX recommended that the scheduling of isohexadecane and isododecane remained appropriate and that the application for exemption from scheduling be rejected.

Members were advised that consideration of the scheduling of isohexadecane and isododecane was included in the pre-February 2004 meeting gazette notice and no public submissions were received.

The Committee was of the opinion that the contents of the fragrance burner were likely to be accessible and that, as a consequence, an exemption from the requirements of scheduling was not appropriate.

OUTCOME

The Committee agreed that the current scheduling of isohexadecane and isododecane under the Schedule 5 entry for liquid hydrocarbons remained appropriate.

5.1.6 SODIUM DICHLOROISOCYANURATE

PURPOSE

The Committee considered the warning statements and safety directions for sodium dichloroisocyanurate.

BACKGROUND

XXXXXXXXX submitted an application seeking an exemption from labelling requirements for their XXXXXXXXX. Specifically, the applicant claimed that a number of the warning statements and safety directions required for their product containing dichloroisocyanurates were unnecessary on the grounds that the packaging is purpose built and designed to minimise exposure of the chemicals to the consumer. No change to the scheduling of dichloroisocyanurates was requested.

The XXXXXXXXX consists of a XXXXXXXXX cage which sits inside the rim of the toilet bowl. The cage contains two separate and sealed compartments, the first with a

capacity of XXXXXXXXX and containing liquid ingredients such as surfactants and fragrance. The second compartment consists of a cartridge containing a 7 g compressed block consisting of 50% sodium dichloroisocyanurate, equating to 27% available chlorine (summary in the submission states 20% chlorine). A small quantity of the contents of the compartments is released each time the toilet is flushed.

A review of chlorinating compounds was considered at the August 1999 NDPSC meeting. Subsequent NDPSC meetings have considered stakeholder comment culminating in the decision at the October 2002 meeting to implement scheduling changes to chlorinating compounds on the basis that the acute toxicological profile associated with this class of compounds was appropriately included in Schedule 6. With regard to dichloroisocyanurates, its schedule 5 entry was deleted and replaced with entries for dichloroisocyanuranic acid in Schedule 6 with a cut off to Schedule 5 for preparations containing 40 per cent or less available chlorine.

DISCUSSION

The Committee noted the applicant's submission in which the following arguments in support of their exemption proposal were tendered:

- Warning Statements 10. and 18. - *May produce severe burns* and *Product will irritate the eyes, nose, throat and skin.* Sealed cartridge does not allow direct skin or eye contact. Dust and vapours released are minimal.
- Warning Statements 22. And 23. - *Highly reactive oxidizing chlorine compound* and *May cause fire or explosions*. Quantity of sodium dichloroisocyanaurate in product is small (3.5g).
- Safety Direction 8. - *Avoid breathing dust vapour or spray mist*. Minimal release of dust, vapour, spray mist.
- Safety Direction 13. - *Do not allow product to come into contact with combustible materials such as paper, fabric, sawdust or kerosene*. Sealed cartridge will avoid any contact with combustible material. Kerosene is generally not used to clean toilets.
- Safety Direction 14. - *Do not allow to get damp*. Product is designed to come in contact with water.
- Safety Direction 15. - *Store under cover in a dry, clean, well ventilated place away from direct sunlight*. Product is used in indoors.
- Safety Direction 16. - *Store and transport in an upright container*. Product is designed to be transported in any orientation.
- Safety Direction 17. - *Do not mix with other chemicals*. Packaging dose will avoid easy mixing with other chemicals apart from those in second compartment.
- Safety Direction 18. - *Do not mix with different types of chlorinating chemicals*. Packaging will avoid easy mixing with other chemicals.

- Safety Direction 19. - *Use clean containers for dispensing*. No other container is required for dispensing.
- Safety Directions 20. and 21. - *Mix with water only* and *Do not add water to product - add product to water, but in case of fire drench with water*. No mixing is required by the user.
- Safety Direction 22. - *In case of spillage flush with large quantities of water*. Packaging prevents spillage.
- Safety Direction 26. - *Avoid contact with clothing*. Packaging will avoid contact with clothing.

Members were informed that, as a consequence of the inconsistencies highlighted above, the applicant requested that only the following warning statement and safety directions in addition to the signal word and first aid directions be required on the label:

- Warning Statement - 5. *Irritant*
- Safety Directions - 1. *Avoid contact with eyes*, 4. *Avoid contact with skin*, 12. *Do not allow product to come into contact with other chemicals, especially acids* and 7. *Wash hands after handling*.

The Committee noted the NICNAS evaluation report which raised the following points for consideration:

- Sodium dichloroisocyanurate exhibits the following toxicities: acute oral LD50 of 1420 mg/kg (rat), acute dermal LD50 of >5000 mg/kg (rat) and >2000 mg/kg (rabbit), moderate skin irritation to rabbits (500 mg) and nil to humans (0.5% aqueous solution), severe eye irritation to rabbits (100 mg) and nil skin sensitization in guinea pig studies. No data on a acute inhalation LC50 is available.
- Based on above information, the chemical has low oral and dermal toxicity. Sodium dichloroisocyanurate is a moderate skin irritant with the skin irritancy being dose dependent. Data submitted previously to the NDPSC for another product containing sodium dichloroisocyanurate indicated that 30% and 12% are corrosive to the skin and at 6% and 3% the chemical is a skin irritant. The chemical is a severe eye irritant and a product containing the chemical up to 30% is a slight eye irritant. The presence of any dust or loose material would cause severe eye irritation and moderate skin and respiratory irritation.
- On the claim for exemption from warning statement labelling requirements, the XXXXXXXXX evaluator made the following comments:
  - The company claims that since the cartridge is sealed, skin or eye contact is not possible. However the product is designed to release a small quantity of the chemical when the toilet is flushed which indicates that it is not completely sealed. If any dust or loose particles of the chemical are formed in the cartridge during transport or handling they could escape through the "openings" and cause skin or eye damage during installation into the toilet bowl. Skin and eye exposure

could also occur if the dispenser is damaged during transport or storage and the damaged product is handled by consumers. In addition, the product is placed within reach of children (toilet bowl rim) and exposure from inadvertent handling is possible. Information obtained in the past by the NDPSC from Poisons Information Centres, for products with similar use, had noted that ingestion can occur by sucking of the product or finger licks, without opening the suspending cage.

- The company seeks exemption from labelling as a highly reactive oxidizing compound that may cause fire or explosions on the basis that the quantity of sodium dichloroisocyanurate in the cartridge is small (XXXXXXXXX). It is suggested that the company obtain formal opinion on the oxidizing and explosive potential from the panel of Competent Authorities controlling the Australian Dangerous Goods (ADG) Code.

- On the claim for exemption from safety direction labelling requirements, the XXXXXXXXX evaluator made the following points:
  - The following safety directions - 13. *Do not allow product to come into contact with combustible materials such as paper, fabric, sawdust or kerosene*, 14. *Do not allow to get damp*, 15. *Store under cover in a dry, clean, well-ventilated place away from direct sunlight*, 21. *Do not add water to product - add product to water, but in case of fire drench with water* are relevant for storage purposes and are appropriate on the label. The company has not provided information on how the chlorination reaction is controlled when exposed to sunlight during storage.
  - With regard to exemption from the safety directions -17. *Do not mix with other chemicals* and 18. *Do not mix with different types of chlorinating chemicals*, no data has been submitted to show that the product would not create a hazard or potentiate the hazards of other chemicals when mixed with them.
  - Exemption from safety direction 19. *Use clean containers for dispensing* appears reasonable as the product is to be fitted into the toilet bowl rim and no other container is required for dispensing.

- On the basis of the above considerations, XXXXXXXXX recommended that the warning statements and safety directions as they appear in the entry for Sodium dichloroisocyanurate in SUSDP Vol 18, amendment 1 Parts (g) and (h) page 20, with the exception of safety direction 19, are appropriate. The evaluator further recommended that the application by XXXXXXXXX be rejected and that the wording of Safety Direction 14 (*do not allow to get damp*) may be inappropriate for a product which is to be placed in toilet bowl. The addition of the words "*during storage*" may overcome the problem.

The Committee noted that XXXXXXXXX, the XXXXXXXXX and XXXXXXXXX submitted public comment. Each advised that they have an interest in the Committee's consideration of sodium dichloroisocyanurate and sought the right to make post-meeting comment.

The Committee noted that the Appendix F, Part 3 entry for sodium dichloroisocyanurate in (Paragraph (g) SUSDP Vol 18, Amendment 1) includes an exemption from the labelling requirements for warning statements and safety directions for compressed blocks or tablets containing 21 g or less of sodium dichloroisocyanurate for use in toilet cisterns only when in preparations contain 10 per cent or more of available chlorine.

DECISION 2004/40 - 9

The Committee agreed to amend the current Appendix F, Part 3 entry for dichloroisocyanurate to specify appropriate warning statements and safety directions that are relevant for products containing dichloroisocyanurates used only in toilet bowls. The Committee further agreed to differentiate between the warning statements and safety directions required during use and storage of the product.

Appendix F, Part 3 – Amendment.

Dichloroisocyanurates – insert paragraphs (i) and (j) as follows:

(i) in other compressed blocks or tablets containing 10 per cent or more of available chlorine in preparations containing 5 g or less of sodium dichloroisocyanurate for use in toilet bowls only.

(a) during storage

Warning statement……..22,23,10
Safety Directions……12,13,14,15,17,18,21

(b) during use

Warning statements…….5
Safety Directions…….1,4,7,12

(j) in other compressed blocks or tablets containing 10 per cent or more of available chlorine certified by a relevant State or Territory authority as not being a Dangerous Good of Class 5.1 (oxidising substances) in preparations containing 5 g or less of sodium dichloroisocyanurate for use in toilet bowls only.

(a) during storage

Warning statement……..22,10
Safety Directions……12,13,14,15,17,18,21

(b) during use

Warning statements…….5

Safety Directions…….1,4,7,12

5.1.7 ALKALINE SALTS

PURPOSE

The Committee considered the outcomes of a XXXXXXXXX review into current scheduling of alkaline salts.

BACKGROUND

Alkaline salts were included in Schedule 5 at the May 1978 meeting. In 1985 the label requirement "BURNS SKIN AND THROAT" was introduced for automatic dishwasher detergents. The August 1993 DPSSC meeting considered a review of the scheduling of alkaline salts prepared by XXXXXXXXX following a company proposal at the February 1993 DPSSC meeting that all automatic dishwashing detergents be classified as Schedule 5, irrespective of their pH. This suggestion had been made as it was felt by a segment of industry that such products were capable of the same type of severe injury caused by those products with a pH of 11.5 and greater. The Committee noted the report and decided to seek further information on the relationship of physicochemical measurements such as alkalinity, Titratable Alkaline Reserve (TAR) and pH to tissue damage. Information submitted by various stakeholders was considered at subsequent NDPSC meetings. At the February 1996 meeting the Committee agreed that laundry products should be separated from dishwasher powders in the schedule entry as a first step. And when a suitable pH/TAR test method had been standardised, it was recommended that the Committee examine the technical implications of the new method for laundry powders in the light of exposure patterns, to ascertain if a more refined entry for this type of product was warranted. The Committee also agreed to work with industry representatives to initiate discussions on further developing the pH/TAR test and its implications with laundry powders. This appears to be the last consideration of this review.

DISCUSSION

The Committee noted the XXXXXXXXX report which raised the following points for consideration:

- The last review of scheduling of alkaline salts in 1993-1996 resulted in the current entry in the SUSDP. The review addressed issues relating to alkaline salts, including the cut-off pH for scheduling, total alkalinity, the concentration at which the pH of a product should be measured, and the greater accessibility of automatic dishwasher detergents compared with laundry detergents in the home.
- Currently, several automatic dishwasher detergents and most laundry detergents are unscheduled as they have a pH of ≤11.5 at the specified concentration in the entry for

alkaline salts in the SUSDP. The available literature indicates products with a pH of ≥11.5 are likely to cause corrosive effects. The pH of a product is not the only determinant of the extent of injury that may be associated with an exposure. Products with a pH of ≥11 and <11.5 are likely to be irritant. There may be variations in the extent of injury associated with products that have the same pH, but different formulations. This is particularly the case if products have high total alkalinity. While the unscheduled laundry detergents and automatic dishwasher detergents are unlikely to be corrosive, they are likely to be irritant and there are risks associated with exposures.

- Based on data on calls to the XXXXXXXXX Poisons Information Centre, there are a large number of exposures to laundry detergents and automatic dishwasher detergents each year. There are more calls about exposures to laundry detergents than automatic dishwasher detergents. There are a significant number of presentations to hospitals for assessment of exposures to laundry detergents and automatic dishwasher detergents.
- Examination of the labelling of some commonly available automatic dishwasher detergents and laundry detergents showed first aid information and warning statements are inconsistent, and in some cases inadequate in terms of alerting consumers to the irritant nature of the products and the appropriate action to take if there is an inappropriate exposure. This is particularly the case for laundry detergents. Variability in labelling may be confusing for consumers who want to choose lower toxicity products. If there is no signal heading alerting consumers to the potential toxicity of a product, they may be less aware of the need to store the product safely. Scheduling, or a requirement for warning and first aid statements, based on the irritant properties of the products, could minimise the likelihood of adverse effects occurring if there is an exposure.
- The US, Canada and the European Union have corrosive and irritant categories for hazardous products; there are labelling requirements for irritant products. Canada takes the alkali reserve of a product into account, as well as pH, in determining whether a product is classified as corrosive or irritant. The US, New Zealand and Canada include consideration of performance criteria such as skin and eye irritation in assessing whether hazardous products are classified as corrosive or irritant.
- The criteria for scheduling of alkaline salts need review to ensure that products that contain alkaline salts and are irritant, are considered; and that labelling of irritant products is adequate to protect consumers from the risk associated with exposures. In this context, it would be appropriate to review the cut-off pH for alkaline salts, total alkalinity and performance criteria for products as formulated, and the specified concentration at which the pH is measured, in relation to the entry for alkaline salts in the SUSDP.
- The review proposed the following options with regard to the scheduling of alkaline salts:
  - Change the cut-off pH for inclusion in Schedule 5 to “more than 11.0”;

- Take the alkali reserve into account, as well as the pH, in determining whether a product is scheduled;
- Specify performance criteria when considering the scheduling of products containing alkaline salts, eg. results of Draize test, OECD test methods 404 (skin irritation), 405 (eye irritation);
- Have a subcategory in Schedule 5 for irritant products;
- Change the concentration at which the pH is measured for scheduling purposes to 50% for laundry detergent (if the pH of a 50% solution can be accurately measured, otherwise measure the pH of a 25% solution).

The Committee noted that public submissions were received from XXXXXXXXX, the XXXXXXXXX, XXXXXXXXX, XXXXXXXXX and XXXXXXXXX.

XXXXXXXXX, the XXXXXXXXX, XXXXXXXXX and XXXXXXXXX all advised that they have an interest in alkaline salts and sought the right to make post-meeting comment.

XXXXXXXXX advised that they have no objection to alkaline salts being in Schedule 5. However, the company highlighted concerns regarding what it viewed as inconsistencies in the first aid statements for such products. XXXXXXXXX was of the opinion that the first aid statements for a product containing alkaline salts are unnecessary stronger than those imposed on a product containing sodium hydroxide, a more corrosive substance. XXXXXXXXX proposed an alignment between the first aid statements for alkaline salts and sodium hydroxide in Schedule 5. Accordingly, they suggested that the entry for alkaline salts in Appendix E Part 2 be revised with the following first aid statements – A, G3, E2 and S1.

Members were of the view that there was insufficient information to consider amending the Schedule 5 entry for alkaline salts in accordance with the options presented by the XXXXXXXXX report. Similarly, there was insufficient information to support a change to the first aid instructions. Accordingly, the Committee asked that more information be obtained on the control of similar substances in the US, Canada, NZ and Europe and in particular the way the issue of irritancy is addressed.

OUTCOME

The Committee agreed to defer consideration of this matter to a later meeting so as to allow additional information to be obtained.

5.2 SUSDP, PART 5

There were no items considered.

5.2.1 WARNING STATEMENTS AND GENERAL SAFETY DIRECTIONS ESTABLISHED BY OFFICE OF CHEMICAL SAFETY FOR AGRICULTURAL AND VETERINARY CHEMICALS (STANDING AGENDA ITEM)

There were no items considered.

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

6.1 ETHOXYSULFURON

PURPOSE

The Committee considered the scheduling of ethoxysulfuron.

BACKGROUND

XXXXXXXXX applied for the registration of the new product XXXXXXXXX, containing ethoxysulfuron at 600 g/L, for the control of nutgrass and certain broadleaf weeds in sugarcane. Ethoxysulfuron is a sulfonylurea that acts by inhibiting acetolactate synthase and blocking the biosynthesis of branched amino acids.

DISCUSSION

The Committee noted the following points raised in the OCS evaluation report for consideration:

[paragraphs deleted]

Based on the acute oral toxicity of ethoxysulfuron and the product, the XXXXXXXXX recommended that an entry in Schedule 5 was appropriate.

The Committee noted that the toxicity observed for ethoxysulfuron in the laboratory studies was observed at high doses.

DECISION 2004/40 - 10

The Committee agreed that, based on the compound's low acute toxicity profile, a Schedule 5 entry was warranted.

Schedule 5 – New Entry

ETHOXYSULFURON.

6.2 IMIDACLOPRID AND MOXIDECTIN

PURPOSE

The Committee considered the scheduling of imidacloprid and moxidectin.

BACKGROUND

Imidacloprid is an ectoparasiticide belonging to the chloronicotinyl group of compounds and moxidectin is a macrocyclic lactone. The XXXXXXXXX range of products contains 10% imidacloprid and either 2.5% moxidectin (for dogs) or 1% moxidectin (for cats) and is administered topically. XXXXXXXXX is marketed for the prevention and control of flea infestations, the prophylaxis of heartworm infection and the control of major gastrointestinal worm infections in cats and dogs.

The scheduling of XXXXXXXXX XXXXXXXXX range of spot-on products was considered at the October 2002 meeting. During an extensive discussion of the original application, the Committee identified two major issues.

- **Acute Toxicity of Product**:

The Committee noted that ingestion of a 4 mL tube of the product by a 10 kg child would result in a dose (approximately 400 mg/kg of product) which lay between the no observable effect level (200 mg/kg) and the first dose producing deaths (1000 mg/kg) according to acute oral toxicity study in rats. Conversely, accidental ingestion of the contents of an entire 4mL tube provided a margin of safety of 2.5 against a potentially lethal dose of product for a 10kg child. Members were broadly agreed that this provided an inadequate margin of safety, which required the product to be clearly labelled POISON.

- **Risk of Neurotoxicity Following exposure to Recently Treated Dogs**:

The consensus of opinion supported the view that the potential maximum dose ingested following direct contact as calculated by XXXXXXXXX (1.54 mg/kg) for a 10 kg child provided no margin of safety in comparison with the NOEL for neurotoxicity (1 mg/kg). Accordingly it was felt that the Schedule 6 signal heading POISON was more likely to alert parents to the dangers of post-treatment contact than CAUTION for Schedule 5.

The Committee agreed that on the basis of the acute toxicity of the product and the potential for acute neurotoxicity following post treatment exposure with larger dogs, the product be included in Schedule 6. This decision came into effect, by virtue of State and Territory legislation, on 1 January 2004.

At the June 2003 meeting the Committee considered a proposal to reschedule a pour-on preparation containing 0.5 % or less of moxidectin to be applied externally on the back of cattle or deer to Schedule 5 of the SUSDP. It was recognised that there may be grounds for inclusion in Schedule 5 for external use preparations containing 2% or less of

moxidectin for the treatment of animals such as cattle, sheep or deer. However, the Committee did not support the same approach with preparation for use on companion animals or pets such as cats and dogs on the grounds that there was a high potential for toxicity from physical contact with animals treated with moxidectin, particularly children.

XXXXXXXXX applied to have XXXXXXXXX spot-on products with a single dose volume of 1 mL or less rescheduled to Schedule 5.

DISCUSSION

The Committee noted the following points raised in the OCS evaluation report for consideration:

[paragraphs deleted]

- The applicant argued that the margins of safety for the ingestion of a 1 mL tube or less of XXXXXXXXX for dogs or cats, and for the hand to mouth transfer of moxidectin from a pet recently treated with the same products, are sufficient to justify the inclusion of these products in Schedule 5 of the SUSDP.
- On the basis of these calculations, and taking into account the child resistant packaging of the product, the Committee may consider preparations containing 2.5 per cent or less of moxidectin when packed in single dose tubes of 1 mL or less for the treatment of cats and dogs, for inclusion in Schedule 5 of the SUSDP.
- The Committee noted that the current Schedule 5 entry for imidacloprid was consistent with the scheduling recommendation made for this product by the OCS.

The Committee agreed that there was a clear margin of safety and that the neurological hazard posed by the product was likely to be minimal for a tube limited to a volume of 1 mL or less.

DECISION 2004/40 - 11

The Committee agreed to include moxidectin in Schedule 5 when packed in single dose tubes with a volume of 1 mL or less on the basis that exposure to the product as a consequence of its packaging would not be a toxicological concern.

Schedule 5 - Amendment

MOXIDECTIN - amend entry to read:

MOXIDECTIN:

(a) in preparations for external use for the treatment of animals other than cats and dogs, containing 0.5 per cent or less of moxidectin;

(b) in preparations for external use for the treatment of cats and dogs, containing 2.5 per cent or less of moxidectin packed in single dose tubes with a volume of 1 mL or less; or

(c) for internal use for the treatment of animals:

(i) in divided preparations for dogs, containing 250 micrograms or less of moxidectin per dosage unit in a pack containing 6 or less dosage units; or

(ii) in other preparations containing 2 per cent or less of moxidectin.

Schedule 6 – Amendment

MOXIDECTIN - amend entry to read:

MOXIDECTIN for external use:

(a) in preparations containing 2.5 per cent or less of moxidectin when packed in single dose tubes for the treatment of cat and dogs **except** when included in Schedule 5; or

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

6.3 ETHYL FORMATE

PURPOSE

The Committee considered the scheduling of ethyl formate.

BACKGROUND

XXXXXXXXX applied for registration of XXXXXXXXX for control of stored product and related pests in produce and quarantine treatments. It is proposed as an alternative to methyl bromide and phosphine. XXXXXXXXX is a non-flammable mixture of ethyl formate (16.7% w/w) in liquid XXXXXXXXX. XXXXXXXXX was included in the XXXXXXXXX formulation for the purposes of eliminating flammability, improving efficacy, and for its potential to reduce sorption of ethyl formate on the treated commodities.

DISCUSSION

The Committee noted the following points raised in the OCS evaluation report for consideration:

- The oral toxicity of ethyl formate is low, with LD50 values of 1850 mg/kg (lowest reported in rats), 2075 mg/kg (rabbits) and 1110 mg/kg (guinea pigs). It has low dermal toxicity in rabbits (LD50>20 mL/kg, approximately equivalent to >18,400 mg/kg). There is no LC50 value available for exposure to ethyl formate by inhalation. Five out of 6 rats died following a 4-hour exposure at 24,000 mg/m^3.
- Ethyl formate is a severe eye irritant. It is a slight skin irritant, a respiratory irritant, and at high doses, a central nervous system depressant. Animal studies have shown that exposure to high concentrations of ethyl formate by inhalation may produce narcosis followed by death due to respiratory or cardiovascular arrest. Humans exposed to ethyl formate vapour at ~1000 mg/m^3 experienced irritation of the eyes and upper respiratory tract.
- There are no adequate studies to establish the long-term effects of ethyl formate exposure, and reproduction and developmental studies are lacking. Ethyl formate was not mutagenic in bacteria and yeast.
- Ethyl formate entering the body is expected to be rapidly hydrolysed to ethanol and formic acid. Given the marked species differences in the rate at which formic acid is oxidised to CO_2, humans are expected to be more sensitive to the systemic effects resulting from ethyl formate exposure than laboratory animals, excluding non-human primates.
- Due to rapid hydrolysis, systemic exposure to ethyl formate itself is likely to be limited, and the effects of a possible elevation of systemic formate levels need to be considered. According to in vitro studies in rodents, formic acid or formate may produce developmental effects, but at high concentrations that are predicted to be maternotoxic. As elevated systemic formic acid levels are implicated in various pathologic effects arising from methanol intoxication in humans, it is possible that exposure to high levels of ethyl formate will produce similar outcomes.
- On the basis of the above considerations, and the limited toxicological database, the OCS recommended that ethyl formate be placed in Schedule 6 of the SUSDP.

A Member advised that the principle concern was the rapid hydrolysis of ethyl formate and the potential toxicity resulting from the corresponding hydrolysis products. Accordingly, it was agreed that a Schedule 6 entry was appropriate.

Some Members expressed concern that if the product were to be included in Schedule 6, its sale could not be limited to professional users. The Committee noted that the product would be marketed in large gas cylinders (XXXXXXXXX) and as such it would be unlikely that the product would be used domestically.

The Committee noted with concern that very little data on inhalation toxicity of ethyl formate had been submitted despite this being the most likely mode of exposure for a fumigant. Members were advised that the APVMA has the power to review products and that this deficiency would be dealt with through appropriate label warnings during the registration process.

DECISION 2004/40 - 12

The Committee agreed to include ethyl formate in Schedule 6 when packaged and labelled as an agricultural fumigant on the basis of expected rapid hydrolysis *in vivo* and the limited toxicological database.

Schedule 6 - New Entry

ETHYL FORMATE when packed and labelled for use as a fumigant.

6.4 PYRIDALYL

PURPOSE

The Committee considered the scheduling of pyridalyl.

BACKGROUND

XXXXXXXXX applied for the registration of the new product XXXXXXXXX containing 500 g/L pyridalyl. Pyridalyl represents a new class of insecticide with an unknown mode of insecticidal action. XXXXXXXXX is an emulsifiable concentrate and will be used to control *Heliothis punctigera* (native budworm) and *H. armigera* (cotton bollworm) in cotton.

DISCUSSION

The Committee noted the following points raised in the OCS evaluation report for consideration:

[paragraphs deleted]

- The OCS suggested that the moderate to strong skin sensitisation potential of pyridalyl would warrant its inclusion in Schedule 6. However, safety directions on products containing pyridalyl may provide an appropriate warning of the sensitisation potential such that scheduling may not be required.

A Member expressed concern that pyridalyl may influence steroid metabolism and that it exhibits characteristics common of substances that are long-lasting in biological systems and persistent in the environment. The Committee noted that there is likely to be

significant contact by farm workers with plants to which XXXXXXXXX has been applied. Consequently, an exemption from scheduling would be inappropriate.

The Committee was advised that the Department of the Environment and Heritage is currently assessing the impact of pyridalyl use on the environment and that the APVMA would act on any recommendations regarding its use resulting from that assessment.

Whilst the Committee expressed concern regarding the persistence and endocrine disrupting potential of pyridalyl, Members agreed that its skin sensitisation potential alone warranted its inclusion in Schedule 6.

DECISION 2004/40 - 13

The Committee agreed to include pyridalyl in Schedule 6 on the basis of its strong skin sensitisation potential.

Schedule 6 - New Entry

PYRIDALYL.

6.5 PROCYMIDONE

PURPOSE

The Committee considered the scheduling of procymidone.

BACKGROUND

XXXXXXXXX submitted an application for the extension of use of XXXXXXXXX and XXXXXXXXX to treat grey mould in lentils. Both XXXXXXXXX and XXXXXXXXX are suspension concentrate (SC) formulations containing XXXXXXXXX procymidone as the active constituent and are currently used to control fungal diseases in a variety of food crops and turf. Procymidone is a member of the dicarboximide group of fungicides and is currently in Appendix B of the SUSDP. It was exempted from scheduling on the basis of its low acute toxicity in 1981.

DISCUSSION

The Committee noted the following points raised in the OCS evaluation report for consideration:

[paragraphs deleted]

- There are 13 other procymidone-based products currently registered in Australia. All products are SC formulations with similar uses to that of the XXXXXXXXX. The toxicology of the additional products has not been evaluated in this report.

- A published study reviewed in this report demonstrated feminisation of the male rat pups from dams treated orally with procymidone during gestation at 25 mg/kg bw/d and above and the effects reported were consistent with those observed with the closely related compound vinclozolin. No maternal toxicity was noted. There was no NOEL for foetal effects in this study. At the highest dose of 200 mg/kg bw/d most of the males had hypospadia, vaginal pouch and permanent nipples. These feminising effects on male pups were irreversible.
- In summary, procymidone, as with vinclozolin, is a teratogen that may potentially cause irreversible damage to the male foetus. It is an anti-androgen with a well-defined mechanism of action, and has demonstrated toxicity to the reproductive system in two different species (rats and mice). Procymidone can bind with the human AR, and there is potential for exposure of humans to procymidone in an occupational setting and from the ingestion of treated food commodities, some of which are consumed without processing. The toxicology and exposure profiles of procymidone are therefore incompatible with its current Appendix B (exempt) status and it is recommended that procymidone be placed in Schedule 7 of the SUSDP.
- Procymidone and vinclozolin are closely related chemically and toxicologically with similar hazard profiles. Consequently, in considering the scheduling of procymidone the Committee may also wish to foreshadow a reconsideration of the scheduling of vinclozolin, currently in Schedule 6, in the event that procymidone is included in Schedule 7 of the SUSDP.

The Committee noted that consideration of further procymidone studies at subsequent meetings in the late 1980's and early 1990's raised no concerns and, as such, an Appendix B exemption remained appropriate. No teratogenic effects were reported in rat and rabbit developmental studies evaluated at the time.

A Member expressed concern that procymidone may influence steroid metabolism and act as an endocrine disruptor. On those grounds an entry in Schedule 7 was justified.

The Committee was advised that the use these substances is currently being reviewed in Europe. The Committee also noted that the Organisation for Economic Co-operation and Development (OECD) had just recently validated the Hershberger Assay, a Test Guideline designed to screen potential endocrine disruptors in which procymidone and vinclozolin are used as positive controls.

The APVMA Member advised the Committee that there are currently no registered products in Australia containing vinclozolin. The Members noted that the substance was currently included in Schedule 6. The Committee agreed that the Secretariat would review the previous considerations of vinclozolin to determine whether the teratogenicity and endocrine disrupting potential was adequately addressed and report to the next meeting.

The Committee noted with some concern that additional toxicological data for procymidone was only made available after the applicant was advised of the

recommendations in the OCS evaluation report. The Committee agreed that this matter should be referred to the APVMA.

DECISION 2004/40 - 14

The Committee agreed that there was sufficient information regarding the teratogenic potential of procymidone to warrant inclusion in Schedule 7.

Schedule 7 – New Entry

PROCYMIDONE.

Appendix B – Amendment

PROCYMIDONE - delete entry

6.6 HELICOVERPA ARMIGERA

PURPOSE

The Committee considered the scheduling of nuclear polyhedrosis virus (NPV) of *Helicoverpa armigera* (HaNPV) occlusion bodies.

BACKGROUND

XXXXXXXXX submitted an application for the registration of XXXXXXXXX containing a new active constituent, HaNPV occlusion bodies. The product also contains a second virus, NPV of *Helicoverpa zea* (HzNPV) which may comprise up to 50% of the total occlusion bodies content. XXXXXXXXX is a liquid concentrate containing up to 2×10^9 occlusion bodies/mL of HaNPV and up to 1×10^9 occlusion bodies/mL of HzNPV. The recommended use rate for the control of *Helicoverpa spp*. (*H. armigera* and *H. punctigera*) in chickpeas, sorghum, sweetcorn, lettuce and cotton is 375-750 mL/ha.

Both HzNPV and HaNPV are naturally occurring members of the family *Baculoviridae*, which are widespread in the lepidopteran population and are reported to be specific for arthropod hosts.

HzNPV was first marketed in Australia in the 1970's and early 1980's under the trademark Elcar, as a wettable powder formulation. The registration for this product has since lapsed. The NDPSC considered the *Heliothis* nuclear polyhedrosis virus (Elcar) in November 1979, August 1980 and May 1981, and exempted it from scheduling on the basis of low toxicity.

DISCUSSION

The Committee noted the following points raised in the OCS evaluation report for consideration:

- HzNPV is in Appendix B of the SUSDP, having been exempted from poisons scheduling due to low toxicity. Due to the fact that different nomenclature was used to define the identity of the virus when it was previously considered, there is an Appendix B entry for 'Heliothis nuclear polyhedrosis virus', and a second entry for 'Polyhedrosis virus of *Helicoverpa zea* occlusion bodies'.
- Baculoviruses are generally regarded as safe to humans. Several toxicity studies have revealed that these viruses (including HzNPV) have low toxicity to animals and humans. DNA sequence studies revealed that HaNPV and HzNPV viruses have similar nucleotide sequences, and the viruses are likely to be variants of the same virus species. Although toxicity studies for the new active constituent (HaNPV) have not been provided by the sponsor, a review by Burges *et al.* (1980) cites a personal communication regarding tests conducted in mice and rats with HaNPV showing no adverse effects although details of the tests were not provided. Based on available information, the overall weight of evidence indicates that HaNPV is unlikely to cause significant toxicity in humans.
- As with Nuclear Polyhedrosis Virus of *Helicoverpa zea* occlusion bodies, toxicity of Nuclear Polyhedrosis Virus of *Helicoverpa armigera* occlusion bodies is likely to be low.
- The OCS has recommended that the NDPSC may wish to exempt HaNPV occlusion bodies from scheduling. Furthermore, the Committee may also wish to consider rationalising the current Appendix B entries for HzNPV.
- The Committee noted that the nuclear polyhedrosis virus is specific to lepidoptera and a Member advised that this class of virus is known to be stable. Another Member advised that viruses from this family have been marketed as biocides for several years without significant problems arising from their use.

DECISION 2004/40 - 15

The Committee agreed to exempt Nuclear Polyhedrosis Virus of *Helicoverpa armigera* occlusion bodies for agricultural use as a biological control agent from the requirements of scheduling on the basis of low toxicity. Furthermore, the Committee agreed to remove the reference to *Heliothis* nuclear polyhedrosis virus from Appendix B as it is redundant.

Appendix B – New Entry

SUBSTANCE	DATE OF ENTRY	REASON FOR LISTING	AREA OF USE
NUCLEAR POLYHEDROSIS VIRUS OF *HELICOVERPA ARMIGERA* OCCLUSION BODIES	February 2004	a	1.2

Appendix B – Amendment

HELIOTHIS NUCLEAR POLYHEDROSIS VIRUS – delete entry

6.7 PINE OIL

PURPOSE

The Committee considered the scheduling of pine oil.

BACKGROUND

XXXXXXXXX applied for an extension of use for their home garden product, XXXXXXXXX (containing 680 g/L pine oil) to allow commercial broadacre use. Pine oil is refined from the XXXXXXXXX of the XXXXXXXXX extract of *Pinus radiata*. Once applied to target plants, XXXXXXXXX removes the waxes from the outer skin of the foliage and promotes dehydration and plant death.

Historically, both pine oils and pinene have been exempt from the requirements of scheduling through inclusion in Appendix B. Although there was some literature about the intoxication of humans with pine oil derivatives, these substances have had widespread use over a long time and in the past the Committee had not considered there to be a significant problem. However, these entries where removed from Appendix B at the May 1985 NDPSC meeting due to no data being received by the Committee during its review of essential oils to indicate safety in human use.

DISCUSSION

The Committee noted the following points raised in the OCS evaluation report for consideration:

XXXXXXXXX is currently registered as a home garden product and is now proposed for broad acre application.

[paragraphs deleted]

- On the basis of its moderate skin irritation and severe eye irritation hazard, a Schedule 6 entry for pine oil for agricultural use is appropriate. Based on the guidelines for pesticides used by householders, the irritancy potential of domestic pesticide formulations should be low, and the product would appear to be unsuitable for home garden use.

The Office of Complimentary Medicines (OCM) advised that there are 171 products using oil, essential oil, liquid extract, dried extract, resin or dried resin from *Pinus sp*. The OCM further advised that there have been 3 reports of adverse reaction to a registered medicine for topical application containing XXXXXXXXX and that these had been judged to be of no significance.

The Committee was informed that public submissions were received from the XXXXXXXXX, the XXXXXXXXX, XXXXXXXXX, XXXXXXXXX and the XXXXXXXXX.

XXXXXXXXX, XXXXXXXXX and XXXXXXXXX each advised that they had an interest in pine oil and sought the right to make post-meeting comment.

XXXXXXXXX advised that pine oil is a generic name and is also rather ambiguous. Consequently, the use of this name in the SUSDP would capture all number of products into the Schedule unintentionally. Within pine oil there are a large number of different botanical species with different constituents. XXXXXXXXX further advised the α-Pinene is found in many different essential oils and, if scheduled, many products would be included that the Council originally accepted as not to be scheduled. *Pinus sylvestris* oil was considered for scheduling in detail a couple of years ago and the decision taken at the time was not to schedule. It was the view of XXXXXXXXX that if this decision were to be reversed it would create unnecessary costs for the industry that had made the investment on a prior ruling.

The XXXXXXXXX reiterated its previous submission made to the Essential Oils Working Party (EOWP). XXXXXXXXX advised that pine oil has uses in aromatherapy and should be subject to the same exemptions currently existing for other aromatic oils when packed in containers of 15 mL or less, fitted with flow control inserts and labelled with the warning NOT TO BE TAKEN and KEEP OUT OF THE REACH OF CHILDREN.

A Member sought clarification on whether the OCS evaluation report recommendation was targeted at pine oil in general or only to the oils extracted from *Pinus radiata*. The evaluator advised the Committee that the data evaluated was specific to the applicants product which contains oil derived from *Pinus radiata* and that any entry in the SUSDP should specifically refer to this source of pine oil. The Member advised that the inclusion of pine oil in Schedule 6 is warranted on the basis of its irritancy.

The Committee was informed that the scheduling of pine oil had previously been considered by the EOWP. At the time, the EOWP limited its consideration of pine oil to

uses involving small volumes such as in aromatherapy. The limited data available on the human toxicity prompted the NDPSC, on the recommendation of the EOWP, to remove pine oil from Appendix B and leave it unscheduled pending the submission of additional data. In contrast, the current proposal involves the large-scale agricultural use of products containing high concentrations of pine oil. Furthermore, the proposed use is likely to result in the pine oil product being mixed with surfactants and other ingredients that accentuate its irritant characteristics in order to achieve the required biological effect on plant material. On this basis, the Committee agreed that controlling the availability of pine oil when used as a herbicide through scheduling was warranted.

DECISION 2004/40 - 16

The Committee agreed to include pine oil derived from *Pinus radiata* in Schedule 6 when packaged and labelled for use as a herbicide on the basis that it is a moderate skin irritant and a severe eye irritant.

Schedule 6 – New Entry

PINE OILS (derived from *Pinus radiata*) when packed and labelled for use as a herbicide.

7. MATTERS REFERRED BY THE OFFICE OF CHEMICAL SAFETY

There were no items were considered.

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

BACKGROUND

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

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

The Commonwealth Government’s response to the JETACAR Report accepted “the concept that all antibiotics for use in humans and animals (including fish) be classified as S4 (prescription only)”. However, the Government’s acceptance was qualified by highlighting that “… certain antibiotic products might be exempted from this scheduling

class where the Australian Pesticides and Veterinary Medicines Authority (APVMA), the Therapeutic Goods Administration (TGA) and the NDPSC assess the antibiotic products as having a low and acceptable risk of promoting antibiotic resistance".

The Committee agreed at the June 2002 Meeting that the scheduling of antibiotics currently registered with the APVMA, but not separately listed in the SUSDP would be reviewed. This intention was included in the post - October 2002 meeting notice published in the Commonwealth of Australia Gazette No GN 49, 11 December 2002.

The Committee agreed to consider each substance gazetted for consideration at the February 2004 meeting individually. These were tiamulin (8.2), diaveridien (8.3), neomycin (8.4) and roxarsone (8.5). Additionally, the Committee also agreed to consider the following substances considered initially at the October 2003 meeting; virginiamycin (8.1) and penethamate (8.6); and correspondence received concerning tylosin (8.7).

8.1 VIRGINIAMYCIN

PURPOSE

The Committee considered a request seeking the reinstatement of virginiamycin for use in feed additives for horses in Schedule 5.

BACKGROUND

The scheduling of virginiamycin was considered at the February 2003 meeting where it was included in Schedule 4 for all uses based on advice received from the Expert Advisory Group on Antimicrobial Resistance (EAGAR). EAGAR advised that continued unrestricted use of virginiamycin posed an unacceptable risk to human health from the development and transfer of organisms resistant to this class of antibiotics in food animals. The scheduling decision was consistent with Recommendation 6 of the Government response to the Joint Expert Advisory Committee on Antibiotic Resistance (JETACAR) and came into effect on 1 September 2003.

XXXXXXXXX markets a feed additive, XXXXXXXXX, which contains 10 g/kg virginiamycin. It is used in conjunction with high grain diets to maintain low blood D-lactate (of gut origin) and to reduce the risk of laminitis. The company sought continued inclusion of virginiamycin for the treatment of horses in Schedule 5 on the basis that treatment of non-food producing animals did not pose a threat to humans through the development of resistant bacterial strains.

DISCUSSION

The Committee was informed that a submission received from XXXXXXXXX was referred to EAGAR for assessment. No public submissions were received in response to the pre-meeting gazette notice. XXXXXXXXX argued for the continued inclusion of their virginiamycin containing product in Schedule 5 on the grounds that:

- Recent usage data indicated that the amount of virginiamycin sold for use in horses was approximately XXXXXXXXX of total virginiamycin usage in Australia, before the substance was moved to Schedule 4 for all species.
- The use of the virginiamycin in horses is discontinuous as a result of grain diets being fed to athletic horses during a performance build up period. Peak periods of usage occur in Spring and Autumn.
- Given the limited usage in horses, it was considered that there is no risk to human health by reinstating virginiamycin in Schedule 5.
- Laminitis results in permanent damage to the horses hoof and that the removal of virginiamycin from Schedule 5 will make access by horse owners more difficult and may lead to animal welfare issues.

Members noted advice received from EAGAR which recommended the inclusion of virginiamycin in Schedule 5 only in relation its use in horses and no other species. Furthermore, EAGAR advised that the pack size should be no greater than 5 kg and that all other packaging greater than 5 kg should remain Schedule 4. Should it not be possible to restrict its use to horses and pack sizes to 5 kg or less, EAGAR recommended that virginiamycin remain in Schedule 4 for all uses.

The Committee also noted advice received from the APVMA which stated that virginiamycin should remain in Schedule 4 for all uses including use in non-food producing animals.

A Member expressed concern over the possibility of misuse through the incorporation of virginiamycin in bulk stock feeds prepared for food producing species if it were made available in Schedule 5. The APVMA Member advised that diversion of virginiamycin into these off-label uses would be unlikely on the basis that the cost of purchasing large quantities of the antibiotic in small packs would be prohibitive.

The Committee acknowledged the usefulness of virginiamycin in the prevention of laminitis in horses and agreed that its inclusion in Schedule 5 would facilitate its availability to horse owners that may have difficulty in accessing a veterinarian.

DECISION 2004/40 - 17

The Committee agreed to include virginiamycin for the prevention of laminitis in horses in packs of 5 kg or less in Schedule 5 of the SUSDP. The Committee further agreed that all other uses were to remain Schedule 4.

Schedule 4 – Amendment

VIRGINIAMYCIN – amend entry to read:

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

Schedule 5 – New Entry

VIRGINIAMYCIN in animal feed additives containing 1 per cent or less of virginiamycin for the prevention of laminitis in horses when in a pack of 5 kg or less.

8.2 TIAMULIN

PURPOSE

The Committee considered the scheduling of tiamulin.

BACKGROUND

Tiamulin is used for the control of swine dysentery associated with *Serpulina hyodysenteriae*, the treatment of swine bacterial enteritis caused by *Escherichia coli* and *Salmonella choleraesuis* and the treatment of bacterial pneumonia caused by *Pasteurella multocida*.

Tiamulin was included in Schedule 4 with an exemption in animal feeds containing 25% or less of antibiotics substances in 1983. Use in animal feed premixes (≥ 25%) and soluble concentrates (≥ 45%) were included in Schedule 5 in 1998.

DISCUSSION

The Committee was informed that XXXXXXXXX had made a public submission in which it advised that it holds the registration for six products containing tiamulin of which only one is currently being marketed. The company further stated that it had no objection to the rescheduling of tiamulin to Schedule 4 for all uses. The Committee was advised that the submission from XXXXXXXXX was referred to EAGAR for assessment.

The Committee noted that no further public submissions were received in response to the pre-meeting gazette notice.

Members noted interim advice from EAGAR stating that tiamulin is a valuable therapeutic agent in pigs and poultry and recommended that it should be classified as Schedule 4.

The Committee noted advice from the APVMA recommending that the continued use of tiamulin should be under veterinary prescription only (Schedule 4).

DECISION 2004/40 - 18

The Committee agreed to include tiamulin in Schedule 4 for all uses on the basis of advice from the EAGAR and the APVMA.

Schedule 4 – New Entry

TIAMULIN.

Schedule 5 - Amendment

TIAMULIN – delete entry

8.3 DIAVERIDINE

PURPOSE

The Committee considered the scheduling of diaveridine.

BACKGROUND

Diaveridine is an antiprotozoal used in veterinary practice for the control of coccidiosis in poultry.

Diaveridine was first considered by the Committee in 1969 and was exempted from scheduling on the basis that it exhibited low toxicity. At the February 2003 meeting diaveridine was reinstated in Appendix B of the SUSDP on the grounds that it was only used in the poultry industry.

DISCUSSION

The Committee noted that the scheduling consideration of diaveridine was included in the pre-February 2004 meeting gazette notice and that no public submissions were received.

The Committee was informed that EAGAR advised that the continued use of diaveridine for current veterinary indications remained appropriate. However, the continued use of an equivalent human agent, trimethoprim and the potential and realisation of resistance to agents in the same class as diaveridine and to the development of cross resistance to other antibiotics led EAGAR to recommend that diaveridine be included in Schedule 4. This advice is consistent with the JETACAR recommendations. The Committee noted EAGAR's recommendation that the scheduling status of other agents used in combination diaveridine, most notably the sulfonamides, also be reviewed. Members were advised that trimethoprim is currently listed as a Schedule 4 medicine only, while the sulfonamides outside of Schedule 4, sulfacetamide, sulfadiazine, sulfadimidine, sulfamerazine, sulfaquinoxaline and sulfathiazole are listed for review at the June 2004 meeting.

The Committee noted advice from the APVMA recommending that the continued use of diaveridine should be under veterinary prescription only (Schedule 4).

DECISION 2004/40 - 19

The Committee agreed to include diaveridine in Schedule 4 for all uses on the basis that there is potential for, and realisation of, resistance to agents in the same class as diaveridine and to the development of cross resistance to other antibiotics.

Schedule 4 – New Entry

DIAVERIDINE.

Appendix B - Amendment

DIAVERIDINE – delete entry

8.4 NEOMYCIN

PURPOSE

The Committee considered the scheduling of neomycin.

BACKGROUND

Neomycin is an aminoglycoside antibiotic used topically in the treatment of human infections of the skin, ear, and eye due to susceptible staphylococci and other organisms. In veterinary medicine products containing neomycin are used for the treatment of diarrhoea in food producing and companion animals, bovine mastitis and skin infections.

The scheduling of neomycin was first considered in 1971 and included in Schedule 6 for ocular use for veterinary purposes. At the May 1978 meeting, neomycin was also included in Schedule 4 with an exemption to Schedule 6 in place of the blanket Schedule 4 entry for antibiotics.

DISCUSSION

The Committee was informed that the scheduling consideration of neomycin was included in the pre-February 2004 meeting gazette notice and that no public submissions were received.

The Committee noted EAGAR's advice that, due to the potential for selection of cross resistance to other aminoglycosides with the resulting loss of agents of medium/high importance in the treatment of human infections and co-selection of resistance in other classes of antibiotics, neomycin should remain in Schedule 4 for all dosage levels and formulations except vaccines which do not require scheduling.

The Committee noted advice from the APVMA recommending that the continued use of neomycin should be under veterinary prescription only (Schedule 4).

The Committee was informed that there are 41 registered products containing neomycin, however, all but 5 are currently in Schedule 4. The remaining products containing neomycin are vaccines and, as such, are exempt from scheduling. The Members noted that the regulatory impact of including neomycin in Schedule 4 for all uses was expected to be low.

DECISION 2004/40 - 20

The Committee agreed to include neomycin in Schedule 4 for all uses on the basis of the potential for selection of cross resistance to other aminoglycosides and co-selection of resistance in other classes of antibiotics.

Schedule 4 – Amendment

NEOMYCIN – amend entry to read

NEOMYCIN.

Schedule 6 – Amendment

NEOMYCIN – delete entry

8.5 ROXARSONE

PURPOSE

The Committee considered the scheduling of roxarsone.

BACKGROUND

Roxarsone is an organic arsenic-containing compound used as a growth promotor in animal feeds.

Roxarsone is not specifically mentioned in the SUSDP but is covered under the Schedule 7 entry for arsenic.

According to the APVMA's PUBCRIS database, all three registered products containing (at 1000 g/kg) were currently labelled as Schedule 7 substances.

DISCUSSION

The Committee was informed that the scheduling consideration of roxarsone was included in the pre-February 2004 meeting gazette notice and that no public submissions were received.

Members noted advice from EAGAR which stated that as result of there being limited implications for antibiotic resistance, the current scheduling of roxarsone remained appropriate.

The Committee noted advice from the APVMA recommending that the continued use of roxarsone should be under veterinary prescription only (Schedule 4).

OUTCOME

The Committee agreed that the current Schedule 7 status of roxarsone remained appropriate.

8.6 PENETHAMATE

PURPOSE

The Committee considered the final EAGAR report for penethamate hydriodide and considered whether the wording of the current Schedule 4 entry remained appropriate.

BACKGROUND

The rescheduling of penethamate hydriodide was considered by the Committee under JETACAR Recommendation 6 at the October 2003 meeting. At the time EAGAR was unable to provide a completed assessment report for penethamate hydriodide but did provided an interim recommendation that the substance be included in Schedule 4 for all uses. The Committee endorsed EAGAR's recommendation and agreed to include penethamate for all uses in Schedule 4 of the SUSDP which was consistent with the Government response to JETACAR Recommendation 6.

The October 2003 meeting expressed concern that the proposed inclusion of penethamate hydriodide in Schedule 4 would be contrary to the current policy that salts of substances would not normally be used as the schedule entry. Therefore, penethamate rather than penethamate hydriodide was included in Schedule 4. The Secretariat was asked to determine whether other salts of penethamate exist and report to the February 2004 meeting.

DISCUSSION

The Committee was provided with the EAGAR final assessment for penethamate hydriodide that confirmed its interim advice to the October 2003 meeting.

Members were also informed that a search of the Merck Index only revealed reference to the hydriodide salt of penethamate. Despite the absence of other salts of penethamate, Members noted that there remained a possibility that another salt may at some time in the future be prepared. Therefore, Members agreed that the current scheduling for penethamate remained appropriate in keeping with the Committee's policy on the scheduling of salts and derivatives.

OUTCOME

The Committee noted the EAGAR report for penethamate hydriodide and agreed that the current Schedule 4 status of penethamate remained appropriate.

PHARMACEUTICALS

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

12.1 PYRIDOXINE

PURPOSE

The Committee considered post-meeting comment on the proposed rescheduling decision for vitamin B6 (pyridoxine, pyridoxal or pyridoxamine) (Decision 2003/39-4).

BACKGROUND

Since 1985, pyridoxine has been included in Schedule 4 for recommended daily doses above 50 mg except when labelled with specified warning statement(s). Pyridoxine is not controlled as a medicine in New Zealand.

The 38th NDPSC Meeting (June 2003) considered the outcomes of the three international committees who reviewed the safety of pyridoxine: the UK Expert Group on Vitamins and Minerals (May 2003); the EU Scientific Committee on food (November 2000); and the US Standing Committee on the Scientific Evaluation of Dietary Reference Intakes through its Panel on Folates and other B group Vitamins (1999). The NDPSC agreed that since there was sufficient evidence to clearly characterise a significant risk of neuropathy from prolonged use of pyridoxine at dose of 200 mg/day or greater in adults, such doses of pyridoxine should only be available on the prescription of a medical practitioner. At the lower end of the dose spectrum, the Committee could see no new evidence to alter its earlier conclusions and agreed that the 50 mg cut-off for requiring warning statements remain unchanged. Accordingly, an amendment to the pyridoxine Schedule 4 entry was foreshadowed which included 200 mg as the upper limit for exemption.

The 39th NDPSC Meeting (October 2003) reconfirmed its view that there was a risk of neuropathy from prolonged use of pyridoxine at doses of 200 mg/day and above in adults, and supported adoption of this level as the upper limit for exemption from Schedule 4. The Committee also agreed to recommend that the New Zealand Ministry of Health (NZ MOH) adopt a similar regulatory outcome. Additionally, noting a request to allow time for industry to reformulate their product, it was agreed to consider further information to vary the effective date at the next meeting if submitted.

DISCUSSION

The Committee noted the advice from XXXXXXXXX that 17 ARTG products containing more than 200 mg of vitamin B6 will be rescheduled as Schedule 4 as a result of this decision. The XXXXXXXXX asked the effective date to be extended to 1 January

2005 which would allow sponsors time to reformulate their products in order for them to remain available as non-prescription products. This view was also presented by the industry representative.

One Member expressed his concern on the potential risk of extending the current scheduling status, allowing a daily dose above 200 mg of vitamin B6 to be available without a prescription. It was highlighted that the high dose vitamin B6 products would still be required to be labelled with the warning statement and that an extension of seven months was not unreasonable.

DECISION 2004/40 - 21 – Variation to Amendment (DECISION 2003/39-4)

The Committee reconfirmed its view that there was a risk of neuropathy from prolonged use of pyridoxine at doses of 200 mg/day and above in adults and supported adoption of this level as the upper limit for exemption from Schedule 4. Additionally, noting the request to allow time for industry to reformulate their product, it was agreed to vary the amendment (Decision 2003/39-4) by amending the effective date to 1 January 2005.

Schedule 4 – Amendment (Effective date 1 January 2005)

PYRIDOXINE, PYRIDOXAL OR PYRIDOXAMINE - amend entry to read:

PYRIDOXINE, PYRIDOXAL OR PYRIDOXAMINE for human therapeutic use **except:**

(a) in oral preparations containing 200 mg or less but more than 50 mg of pyridoxine, pyridoxal or pyridoxamine per recommended daily dose when labelled with the warning statement:

WARNING - this medication may be dangerous when used in large amounts or for a long time; or

WARNING - this product contains [*insert pyridoxine, pyridoxal or pyridoxamine as applicable*] which may be dangerous when used in large amounts or for a long time; or

(b) in oral preparations containing 50 mg or less of pyridoxine, pyridoxal or pyridoxamine per recommended daily dose.

12.2 ORLISTAT

PURPOSE

The Committee considered post-meeting submissions in relation to the October 2003 initial decision to reschedule orlistat for the treatment of obesity from Schedule 4 to

Schedule 3 of the SUSDP.

BACKGROUND

Submissions from XXXXXXXXX seeking to reschedule orlistat for the treatment of obesity from S4 to S3 were considered at both the June 2002 NDPSC and the February 2003 NDPSC meetings. The February 2003 submission also sought to have orlistat included in Appendix H. On both these occasions the Committee decided that the information submitted by the sponsor did not provide sufficient evidence to address the Committee's concerns in relation to its safety profile; the necessity for medical assessment to determine patient's suitability for treatment with orlistat; and the view that therapeutic intervention should not be the first-line treatment for obesity.

A third submission by XXXXXXXXX to reschedule orlistat from S4 to S3 for the treatment of obesity, without inclusion in Appendix H, was considered by the October 2003 NDPSC Meeting. After considering the additional information provided by the sponsor and supporters, as well as the submissions expressing concern about the proposed rescheduling, the Committee agreed to include orlistat for the treatment of obesity in Schedule 3 of the SUSDP.

DISCUSSION

The Committee considered two post meeting comments opposing the initial decision to re-schedule orlistat for the treatment of obesity from S4 to S3 of the SUSDP.

The issues raised by the XXXXXXXXX largely reflected the concerns expressed by the NDPSC when it considered the applications from XXXXXXXXX in June 2002 and February 2003. At its October 2003 meeting, the Committee agreed that these concerns had been addressed by the additional information provided by the applicant.

Concern that by blocking fat absorption orlistat may also block the absorption of fat soluble vitamins and nutrients, particularly vitamin A and the related retinoids lutein and zeaxanthin was expressed by XXXXXXXXX. XXXXXXXXX stated that lutein and zeaxanthin have been shown to be deficient in the retinas of people who develop blindness from age related macular degeneration (ARMD) and that recently lutein supplements had been shown to slow the process of ARMD. He was concerned that prolonged use of orlistat may increase the risk of elderly people developing AMRD later in life.

The Committee also noted the Minute from the MEC which advised that the MEC was strongly opposed to any future proposal to include orlistat in Appendix H to the SUSDP and that it considered any further down-scheduling of this substance below Schedule 3 to be inappropriate.

The Committee considered the issues raised by the submissions.

Concern about the wrong public health message

The Committee agreed that, while the preferred first-line treatment for obesity is non-pharmacological therapies such as dietary and lifestyle changes, the availability of orlistat as a S3 product would not impart the wrong public health message (i.e., that earlier pharmacotherapy is appropriate) given the wide range of weight loss products already available on the market. The Committee noted that obesity was a major public health problem and that there was a requirement for professional intervention by the pharmacist at the time of supply. Members agreed that the availability of orlistat as Pharmacist Only medicine provided the consumer with another treatment option.

Concern about the need for medical supervision

The Committee confirmed its view that obesity is a disease which can easily be recognised by consumers and that pharmacists have good training and experience in providing advice and consultation in relation to the management of weight loss and treatment of obesity. In addition the Committee considered that the CMI provided adequate information to enable the product to be used safely.

Concern about potential vitamin deficiencies

The Committee was aware that there is a potential for malabsorption of fat soluble vitamins during treatment with orlistat. The Committee noted that the 4 year study of patients being treated with ‘XXXXXXXXX ‘ (the XENDOS Study), reported that mean plasma levels of fat soluble vitamins remained within the normal reference ranges at all times during the study. Members considered the detail on the levels of fat soluble vitamins in patients the XENDOS study. The Committee also noted that vitamin supplements were administered to those patients in the study (both the orlistat and the placebo groups) who had low baseline vitamin values, or who experienced a decrease in their vitamin values during treatment. The Committee noted that to ensure adequate absorption, the study protocol recommended supplementary doses of vitamins be administered 2 hours before or after the dose of XXXXXXXXX or at bedtime.

The Committee also discussed the advice to consumers on the need for vitamin supplementation presented in the draft Product Information (PI), the Consumer Medicine Information (CMI) and the proposed product label. The Committee noted that the PI and CMI included advice to take a vitamin supplement containing fat soluble vitamins and that this should be taken 2 hours before or after XXXXXXXXX or at bedtime. This information was included under the section “Things to be Careful of”. Members felt that this advice could be given greater emphasis in these documents and agreed to recommend to the MEC that the advice to take a vitamin supplement be moved to the Section “How to take it” and the statement strengthened.

Several Members raised the issue of potential overdoses of fat soluble vitamins. Of particular concern was the risk to pregnant women. The Committee noted that the dosage of vitamins A and D permitted in OTC vitamin preparations was limited and that there were warning statements on vitamin A products. None-the-less Members agreed that the vitamin dosage range should be included in the PI while the specific vitamins should be listed in the CMI. A Member suggested that this range should be based on the vitamin dosages administered in the XENDOS study. The Committee agreed, but noted that the product used in the study was not one available in Australia. The Secretariat was requested to seek information from the company on the multivitamin product and provide these details to the MEC to enable the appropriate dosage range to be established.

The Committee also agreed to recommend to the MEC that the proposed product label should be amended to include a statement to alert to patients to take a multi-vitamin supplement when taking orlistat.

The potential for the use of orlistat to increase the risk of ARMD was discussed by the Committee. It was noted that XXXXXXXXX had not presented any evidence, nor provided references, to any studies to support his claim that deficiencies in lutein and zeaxanthin may increase the risk of ARMD. A Member advised the Committee of one study of 6000 subjects where 13 were found to have decreased lutein levels. One Member noted that the major risk factor for ARMD was smoking. Another Member said that while no evidence had been submitted, the Committee should not dismiss the possibility of such a risk. The Committee agreed that, while theoretically there was a possibility of an increased risk of ARMD, the risk was likely to be low, given low incidence of vitamin deficiencies identified in the available study and the strong advice in the PI and CMI for multi-vitamin supplementation. The Committee agreed that, if such a risk existed, it was more likely to manifest itself in diabetic patients. As orlistat for the treatment of type 2 diabetics remains in Schedule 4, the Committee recommended that XXXXXXXXX letter be referred to ADEC for consideration and advice.

Concern about abuse

Members reconsidered the possibility that orlistat may be abused, especially by those suffering with anorexia or bulimnia. Members noted that there was a reasonably long history of use of orlisat without abuse. In addition the Committee noted that including orlistat in Schedule 3 would require the product to be sold under the supervision of a pharmacist.

Concern about side effects

Members discussed reports concerning the enhancement of warfarin efficacy due to a reduced vitamin K level and its use in the treatment of type 2 diabetes. Members considered that the interaction with warfarin had been adequately addressed by the CMI and PI. The treatment of type 2 diabetes remains a Schedule 4 indication. A Member raised the issue of whether vitamin K supplementation should be recommended given that no vitamin K values in the XENDOS study were below the reference range.

Members agreed that vitamin K supplementation was not necessary.

Conclusion

After considering the additional information provided by the sponsor and supporters, as well as the submissions expressing concern about the proposed re-scheduling, the Committee agreed to confirm its decision to include orlistat for the treatment of obesity in Schedule 3 of the SUSDP.

Clarification

One of the Members pointed out that the proposed S3 entry for orlistat "… containing 120 mg or less of orlistat" should be "… containing 120 mg or less of orlistat per dosage unit". The Committee agreed with this editorial change.

DECISION 2004/40 – 22 – Variation of Amendment (DECISION 2003/39 – 31)

In accordance with subregulation 42ZCZ(3), the Committee agreed to vary the orlistat amendment (Decision 2003/39-31) by adding the words "per dosage unit" to the entry. The reasons for the decision to include orlistat for the treatment of obesity in Schedule 3 of the SUSDP were:

- the safety profile of orlistat based on the a low incidence of adverse effects;
- orlistat was reasonably efficacious for gradual and long term weight loss when used in conjunction with exercise and dietary restriction;
- obesity is a disease which can be easily recognised by the consumer;
- pharmacists in Australia have good training and experience in providing advice and consultation in relation to management of weight loss and treatment of obesity;
- orlistat for use in weight loss has low potential for abuse or overdose;
- the Consumer Medicine Information and the Product Information strongly recommend that patients taking orlistat also take a multivitamin preparation containing fat soluble vitamins; and
- orlistat for the treatment of obesity met the criteria for inclusion in Schedule 3.

Schedule 3 - New Entry

ORLISTAT in oral preparations for weight control purposes containing 120 mg or less of orlistat per dosage unit.

Schedule 4 – Amendment

ORLISTAT - amend entry to read:

ORLISTAT **except** when included in Schedule 3.

12.3 NICOTINE IN NRT

PURPOSE

The Committee re-considered its initial decision to exempt nicotine in gums and transdermal patches for smoking cessation taking into account the post meeting submissions that were received.

BACKGROUND

At its November 2000 meeting, following a recommendation from the Trans Tasman Harmonisation Working Party, the Committee considered whether de-scheduling of nicotine in gums and patches met with the criteria for such a change. At that time NDPSC agreed not to change the scheduling of nicotine. The NCCTG guidelines required the NDPSC to reconsider this matter again after two years.

This matter was again considered by the NDPSC in October 2003. Following consideration of pre-meeting submissions from a variety of stakeholders and consideration of relevant studies, as well as comparison of the regulatory situations in Australia and New Zealand, the NDPSC agreed to exempt nicotine in gums and transdermal patches from the requirements of scheduling. The reasons for this decision were that widening the availability of NRT products should encourage more smokers to quit smoking and that this should improve public health outcomes. The Committee also noted that the decision harmonised the scheduling outcome with New Zealand.

The October 2003 meeting also agreed to consider the proposal to exempt lozenges for consistency with nicotine in chewing gum and transdermal patches. (See Agenda Item 13.14)

The Committee received post meeting submissions from the XXXXXXXXX and the XXXXXXXXX, both of which opposed the de-scheduling of nicotine in NRT on a number of grounds.

DISCUSSION

Concerns about the need for professional support.

The Committee noted that both the XXXXXXXXX and the XXXXXXXXX submissions argued that professional support was essential for the success of NRT.

The Committee considered a number of studies and reports which looked at the effectiveness of various smoking cessation approaches.

The Committee discussed a recent article (*Aust N Z J Public Health 2003; 27:491-5*) which reported on OTC access of NRT products by the Australian community. The article reported that of the 215 current and former smokers, 31.2% had used NRT on their most recent quitting attempt. The majority of NRT use (61%) lasted for less than two weeks. The Committee noted that more than 40% of NRT users reported receiving no instructions from a doctor or pharmacist on how to use the product. The Committee also noted that approximately one-third of NRT use was associated with concomitant smoking. The authors concluded that the data suggest a level of inappropriate use of NRT products in the community, and reinforce the concerns raised by overseas studies of OTC use of NRT products – low levels of advice and support and potentially high levels of inappropriate use.

The Committee also considered a study (*Aust N Z J Public Health* 2003; 27:486-90) which involved the use of free nicotine patches by indigenous people. The Committee noted that no participant completed a full course of patches but that cessation rates for both groups were lower than those in other populations, probably due to the study being conducted in a primary care setting, widespread use of tobacco in these communities and the perception of tobacco use as non-problematic.

Members of the Committee discussed the WHO *Policy Recommendations for Smoking Cessation and Treatment of Tobacco Dependence* (*WHO Policy Document*). While the Committee noted the WHO comments that behavioural treatment can substantially increase the effectiveness of pharmacotherapy, it also noted that the WHO considered that "evidence based medicines……provid(ed) an approximate doubling of the probability of long-term smoking cessation"(*p.xiii).* The Committee further noted the following statements by WHO in the same report;

- "Another intervention would be to help those who wish to quit by making it easier for them to obtain NRT and other cessation interventions. NRT markedly increases the effectiveness of cessation efforts and also reduces an individual's withdrawal costs. Yet in many countries, NRT is difficult to obtain." (*WHO Policy Document p.4*);

- "concomitant NRT use and smoking does not appear to be harmful and there is growing evidence that it facilitates smoking reduction among dependent smokers

who are unable to quit *(Regulation of nicotine replacement therapies: and expert consensus 2001 (WHO Regulation Recommendations p.17*) .

- "detractors against wider availability often use the argument of lower efficacy in a less controlled environment, but meta-analysis of the few well designed, placebo controlled over-the-counter trials to date showed that NRT more than doubled the abstinence rates compared with placebo in over-the-counter conditions" *(the WHO Regulation Recommendations p.23*)

The Committee noted that the WHO also stated that 'Changing the products to general sales does not diminish the added value that health professionals can offer." *(the WHO Regulation Recommendations p.24*)

The Committee also considered the information provided by Treatobacco.net referred to in the WHO Policy document (2003). The Committee noted that this is a peer reviewed source of evidence-based data and practical support for the treatment of tobacco dependence. The website recommends: "the regulatory barriers that prevent effective treatment products being made as widely available as possible should be reformed so that at the very least, addicted tobacco users who wish to stop can acquire tobacco dependence treatment products at least as easily as they can acquire tobacco products." (treatobacco.net - Recommendations printed 10/2/04).

Further, the Committee noted that a key finding of Treatobacco.net is that "Increasing the availability (i.e. moving from prescription-only to pharmacy or general sale, where appropriate) of pharmacological treatments increases usage. This probably increases overall cessation attempts and successful cessation efforts although the data for this are as yet inconclusive." (treatobacco.net – Key Finding printed 10/2/04).

Members also discussed a report of "Community pharmacy personnel interventions for smoking cessation" which compared interventions by community pharmacy personnel to promote smoking cessation amongst their clients who were smokers to usual pharmacy support or any less intensive program. In the two trials with 976 smokers in the UK, one study showed a significant difference in self-reported cessation rates at 12 months (14.3% vs 2.7%, $p<0.001$); the other study showed a positive trend at each follow-up (12.0% vs 7.4%, $p=0.09$) at 9 months. The Committee noted that the limited numbers of studies to date suggest that trained community pharmacists, providing counselling and record keeping support programme for their customers, may have a positive effect on smoking cessation rates. However, the strength of evidence is limited because only one of the trials showed a statistically significant effect.

One of the Members presented the Committee with the Cochrane Review of 110 trails which found that "The effectiveness of NRT appears to be largely independent of the intensity of additional support provided to the smoker. Provision of more intense levels of support, although beneficial in facilitating the likelihood of quitting, is not essential to the success of NRT."

The Committee also discussed the project to be funded by the Commonwealth Department of Health and Ageing through the Guild/Government Agreement Research and Development Fund to evaluate the effectiveness of a smoking cessation programs in Australian community pharmacies, The Committee considered the XXXXXXXXX recommendation that the decision to de-schedule NRT be deferred until the results of that project become available. The Committee decided that the de-scheduling of NRT patches and gums was independent of the project. Members noted that the funding of a research program by the Government was in line with the WHO strategy that governments pursue a range of strategies to encourage smoker to quit.

The Committee noted that while in 2000 the Drug Strategy Branch (DSB) submission did not support the de-scheduling nicotine in NRT, their reasons for this were that there was no clear evidence that wider availability reduced smoking prevalence and concern about its use in children and pregnant and lactating women. Members noted that no post-meeting submission was received from DSB in relation to the current de-scheduling decision. A Member suggested that a significant concern for governments supporting the wider availability of NRT was economic and that this was outside the matters which NDPSC was required to consider under S52E(1) of the *Therapeutic Goods Act 1989.*

After considering all these matters the Committee did not agree with the XXXXXXXXX assertion that "access to NRT without access to healthcare personnel who provide support and advice and information….. is inconsistent with WHO policy." The Committee supported the WHO conclusion; " …..there is no single approach should be emphasised to the exclusion of others because the therapies vary widely in their efficacy, acceptability, cost effectiveness and their cost on an individual and population basis." (*WHO Policy Document p xiii*). The Committee noted that de-scheduling of nicotine in patches and gums would not preclude pharmacies from selling those products or from promoting any support or counselling services for smokers wishing to quit.

Concerns about use in pregnancy

A Member of the Committee advised that nicotine was classified as a Class D substance in relation to use in pregnancy. Members considered that the Class D classification was based on the harmful effects of tobacco smoking. Members understood that " specific effects of nicotine therapy on foetal development is unknown (*Prescribing Drugs in Pregnancy, 4th Edition*). Members noted packets of nicotine patches and gums and the CMI for these products carried appropriate warnings including advice that pregnant women should only use the product under medical supervision.

Members also noted that the WHO comment that "expert opinion is that NRT is considerably safer than smoking in pregnancy" (*WHO Regulation Recommendations p.11*) and had concluded that "the balance of argument appears to favour wider use of NRT by pregnant women" but with close medical supervision.

Concerns about Abuse

The Committee discussed the issue of abuse potential. Members noted that there did not appear to be any significant abuse of NRT products containing nicotine. One Member reported that there had been some reports in NSW of abuse by teenagers, generally of the gum. However, the Member stated that the reports found that the NRT products had been used as a substitute source of nicotine when cigarettes were difficult to obtain. Reports indicated that those abusing NRTs had no intention of giving up cigarettes and were not using it to assist in giving up smoking.

Members noted the comments by WHO *(WHO Regulation Recommendations p.38*) which considered that the "dependence potential of NRT products is relatively low compared with the cigarette." Members noted that the WHO experts found that "the patch releases nicotine slowly, gradually peaking after 4-9 hours whereas nicotine levels from gum, inhalator and lozenge peak after about 30 minutes….This compares with a concentrated bolus of nicotine reaching the brain within 10 seconds of each puff on a cigarette."

The Committee also noted that a number of reports had concluded that, were abuse to occur, the level of harm was likely to be less than would occur from smoking tobacco. Members noted the WHO comment that "The regulatory framework should recognise that the drug nicotine is unique and NRT products are used in an environment dominated by the use of an extremely harmful and highly addictive and widely available nicotine delivery system – the cigarette" (*WHO Regulation Recommendations p.8).* Members also noted that WHO found that "Evidence from the United States has demonstrated public health benefits from increased availability of NRT with no significant potential for abuse or dependence" *(WHO Regulation Recommendations p.23).*

Harmonising of decisions with New Zealand

While this matter came before the Committee as a recommendation from the TTHWP, the Committee noted that the NCCTG guidelines required it to harmonise on the lower schedule where that would not compromise the health and safety of the community. Having considered all the available information, including the packaging and labelling of the products, the Committee concluded that it would not compromise the health and safety of the community to de-schedule nicotine in patches and gums. Further, the Committee agreed that the patches and gums no longer met the criteria for Schedule 2. The Committee noted that this would harmonise the scheduling outcome with New Zealand.

Considerations against S52E of the *Therapeutic Goods Act 1989*

(1) (a) toxicity and safety of a substance

The Committee noted that nicotine could have toxic effects at high doses. The Committee noted that NRT products had been available for some considerable time and are widely

used in the community with minimal problems with toxicity. In addition the Committee noted the wide consumption of nicotine from smoking cigarettes and other smoking products.

(1)(b) the risks and benefits associated with the use of a substance

The Committee considered that making NRT more available to the public would encourage more smokers to quit smoking. The Committee considered that while there was a risk to pregnant women from taking NRT, the risk was small and was addressed by appropriate warning labels on the packaging of NRT products. The Committee agreed that any potential risks were more than balanced by the benefits associated with the use of gums or patches containing nicotine, ie. cessation or reduction in the smoking. The Committee noted that this view was consistent with the WHO advice (*WHO Regulation Recommendations p.11-12).*

(1)(c) the potential hazards associated with the use of the substance

The Committee noted that hazards of nicotine in NRT was considerably less than when the nicotine was consumed from widely available tobacco products. Members also noted the warnings on the labelling and packaging of the products would minimise those potential hazards.

(1)(d) the extent and patterns of use of a substance

The Committee noted that NRT products were widely used, although many of the studies pointed out that the duration for which the products are used is often quite short - only several weeks (e.g. *Aust N Z J Public Health 2003; 27:491-5*).

(1)(e) the dosage and formulation of the substance

The Committee noted that gums and patches come in several strengths and, in keeping with the WHO view that smokers should have access to a wide variety of treatment and assistance options, having a variety of formulations of the NRT products available would provide a choice for those wishing to use a pharmacotherapy to assist them give up smoking.

(1)(f) the need for access to a substance, taking into account its toxicity compared with other substances available for a similar purpose

Smoking is major cause of morbidity and mortality in the Australian community. The Committee noted that the WHO recognises that it is important for the community to have access to a range of options to assist in cessation or reduction of smoking and that NRT is an important tool in efforts to reduce smoking.

(1)(g) the potential for abuse of a substance

The Committee agreed that the potential for abuse was minimal and that this potential risk was further reduced because nicotine was slowly released from the gums and patches. The Committee noted that consumption of these products would not produce the high that would be the primary attraction for those who wished to abuse to the product. The Committee noted the WHO considered the abuse potential to be low. Nor had the Committee seen any evidence of significant abuse.

(1)(h) the purposes for which the substance is to be used

Nicotine in NRT is intended for use as an aid in smoking cessation and reduction programs.

(1)(i) any other matters that the Committee considers necessary to protect public health, including the risks (whether imminent or long-term) of death, illness or injury resulting from its use.

The Committee considered that, given the significant harm caused by smoking to the individual and the community, it was important to make a range of treatment options available to assist to those addicted to smoking cease or reduce the level of their smoking. The Committee noted that this was in line with the recommendations of the WHO.

DECISION 2004/40 – 23 – Confirmation of Amendment (DECISION 2003/39 – 5)

In accordance with sub-regulation 42ZCZ(3) the Committee agreed to confirm the amendment (Decision 2003/39-5) to exempt nicotine in patches and gums from scheduling. The Committee also agreed to correct the amendment to take account that the Schedule 3 amendment for NRT was published in SUSDP 18 Amendment 2. In reaching its decision the Committee, as required, took into account the matters set out in the *Therapeutics Goods Act S52E.* The Committee's reasons for confirming this decision were that:

- widening of the availability of NRT products should encourage more smokers to quit smoking or reduce their level of smoking and that this should improve public health outcomes;
- the safety profile of nicotine in NRT gums and patches was such that it no longer required scheduling;
- the packaging of the product carries appropriate warnings to allow safe use; and
- the potential for abuse is minimal.

Schedule 2 - Amendment

NICOTINE - amend entry to read:

NICOTINE for use as an aid in withdrawal from tobacco smoking:

(a) in lozenges; or

(b) in preparations for inhalation.

Schedule 4 – Amendment

NICOTINE - amend entry to read:

NICOTINE for use as an aid in withdrawal from tobacco smoking (including preparations for nasal administration) **except**:

(a) when included in Schedule 2 or 3;

(b) in chewing gum; or

(b) in preparations for transdermal use.

12.4 PARACETAMOL

PURPOSE

The Committee considered post-meeting comments on the amendment to the Schedule 2 entry for paracetamol.

BACKGROUND

The 39th NDPSC Meeting (October 2003) agreed to the inclusion of new label warning statements for paracetamol in Appendix F of the SUSDP which were proposed by the Medicines Evaluation Committee (MEC) and the consequential amendments to the Schedule 2 entry for paracetamol. It was also agreed that the effective date would be 1 May 2005.

DISCUSSION

Members noted the post-meeting comments from XXXXXXXXX and XXXXXXXXX. Both companies noted that the new Schedule 2 entry for ibuprofen includes the words "to the following effect" prior to warning statements for the primary pack and asked that the entry for paracetamol be amended to include the same words, to ensure homogeneity and clarity between these similarly scheduled analgesic substances.

The XXXXXXXXX Member pointed out that the Introduction to Appendix F states "The wording of warning statements and safety directions specified in this appendix may be varied provided that the intent is not changed". Members agreed that for the consistency,

the words "to the following effect" should also be included in the Schedule 2 entry for paracetamol.

DECISION 2004/40 - 24 – Variation to Amendment (DECISION 2003/39-26)

The Committee reconfirmed the inclusion of the MEC proposed label warning statements for paracetamol in the Schedule 2 entry (Decision 2003/39-26), but agreed to vary this amendment by including the words "to the following effect" where there is a requirement for a warning statement. It also reconfirmed that the mandatory effective date for the new warning statements would be 1 May 2005.

Schedule 2– Amendment

PARACETAMOL – amend entry to read:

PARACETAMOL for therapeutic use **except**:

(a) when included in Schedule 4;

(b) in individually wrapped powders or sachets of granules each containing 1000 mg or less of paracetamol as the only therapeutically active constituent other than effervescent agents, when:

(i) in a primary pack containing not more than 12 such powders or sachets;

(ii) (A) labelled with the statement to the following effect (permitted until 30 April 2005):

WARNING - This medication may be dangerous when used in large amounts or for a long period; or

CAUTION - This preparation is for the relief of minor and temporary ailments and should be used strictly as directed. Prolonged use without medical supervision could be harmful; or

(B) labelled with the statements to the following effect (mandatory from 1 May 2005):

Adults: Keep to the recommended dose. Don't take this medicine for longer than a few days at a time unless advised to by a doctor;

Children and adolescents: Keep to the recommended dose. Do not give this medicine for longer than 48 hours at a time unless advised to by a doctor;

If an overdose is taken or suspected, ring the Poisons Information Centre (Australia 131 126; New Zealand 0800 764 766) or go to a hospital straight away even if you feel well because of the risk of delayed, serious liver damage;

Do not take with other products containing paracetamol, unless advised to do so by a doctor or pharmacist; and

(iii) not labelled for the treatment of children six years of age or less; or

(c) in tablets or capsules each containing 500 mg or less of paracetamol as the only therapeutically active constituent other than effervescent agents, when:

(i) packed in blister or strip packaging or in containers with child-resistant closures;

(ii) in a primary pack containing not more than 25 such tablets or capsules;

(iii) (A) the primary pack is labelled with the statement to the following effect (permitted until 30 April 2005):

WARNING - This medication may be dangerous when used in large amounts or for a long period; or

CAUTION - This preparation is for the relief of minor and temporary ailments and should be used strictly as directed. Prolonged use without medical supervision could be harmful; or

(B) labelled with the statements to the following effect (mandatory from 1 May 2005):

Adults: Keep to the recommended dose. Don't take this medicine for longer than a few days at a time unless advised to by a doctor;

Children and adolescents: Keep to the recommended dose. Do not give this medicine for longer than 48 hours at a time unless advised to by a doctor;

If an overdose is taken or suspected, ring the Poisons Information Centre (Australia 131 126; New Zealand 0800 764 766) or go to a hospital straight away even if you feel well because of the risk of delayed, serious liver damage;

Do not take with other products containing paracetamol, unless advised to do so by a doctor or pharmacist; and

(iv) not labelled for the treatment of children six years of age or less.

12.5 ASPIRIN

PURPOSE

The Committee considered post-meeting comments on the amendment to the Schedule 2 entry for aspirin.

BACKGROUND

The 39th NDPSC Meeting (October 2003) agreed to the inclusion of new label warning statements for aspirin in Appendix F of the SUSDP which were proposed by the Medicines Evaluation Committee (MEC) and the consequential amendments to the Schedule 2 entry for aspirin. It was also agreed that the effective date would be 1 May 2005.

DISCUSSION

Members noted the post-meeting comments from XXXXXXXXX and XXXXXXXXX. Both companies noted that the new Schedule 2 entry for ibuprofen includes the words "to the following effect" prior to warning statements for the primary pack, and asked that the

entry for aspirin be amended to include the same words, to ensure homogeneity and clarity between these similarly scheduled analgesic substances.

Members agreed that for the consistency, the words "to the following effect" should be included in the Schedule 2 entry for aspirin. However, after discussion, Members decided that these words should not be added to paragraphs (b) (iii) or (c) (iv) of the Schedule 2 entry, as the Medicine Evaluation Committee (MEC) has advised retention of the warning statement "*Consult a doctor before giving this medication to children or teenagers with chicken pox, influenza or fever"* pending further evaluation.

DECISION 2004/40 - 25 – Variation to Amendment (DECISION 2003/39-27)

The Committee reconfirmed the inclusion of the MEC proposed label warning statements for aspirin in the Schedule 2 entry (Decision 2003/39-27) but agreed to vary this amendment by including the words "to the following effect" where there is a requirement for a warning statement (apart from the Reyes Syndrome warning statement). It was also agreed that the effective date for the new mandatory warning statements would be 1 May 2005.

Schedule 2 - Amendment

ASPIRIN - amend entry to read:

ASPIRIN **except**:

(a) when included in Schedule 4, 5 or 6;

(b) in individually wrapped powders or sachets of granules each containing 650 mg or less of aspirin as the only therapeutically active constituent other than an effervescent agent when enclosed in a primary pack that:

(i) contains 12 or less such powders or sachets of granules;

(ii) (A) is labelled with the warning statement to the following effect (permitted until 30 April 2005):

WARNING - This medication may be dangerous when used in large amounts or for a long period; or

CAUTION - This preparation is for the relief of minor and temporary ailments and should

be used strictly as directed. Prolonged use without medical supervision could be harmful; or

(B) is labelled with the warning statements to the following effect (mandatory from 1 May 2005):

Don't use [this product / name of the product]:
If you have a stomach ulcer
In the last 3 months of pregnancy
If you are allergic to aspirin or anti-inflammatory medicines;

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
If you are pregnant;

See a doctor before taking [this product / name of the product] for thinning the blood or for your heart. [Can be omitted in products for inhibition of platelet aggregation or with additional active ingredients.]; and

(iii) includes in the directions for use, in capital letters not less than 1.5 mm in height, the warning statements:

CONSULT A DOCTOR BEFORE GIVING THIS MEDICATION TO CHILDREN OR TEENAGERS WITH CHICKEN POX, INFLUENZA OR FEVER.

CAUTION - DO NOT GIVE TO CHILDREN UNDER TWO YEARS OF AGE **EXCEPT** ON DOCTOR'S ADVICE;

(c) in tablets or capsules each containing no other therapeutically active constituent **except** an effervescent agent when:

(i) packed in blister or strip packaging or in a container with a child-resistant closure;

(ii) in a primary pack of not more than 25 tablets or capsules, each containing 325 mg or less of aspirin, or in a primary pack of not more than 16 tablets or capsules, each containing 500 mg or less of aspirin;

(iii) (A) the primary pack is labelled with the warning statement to the following effect (permitted until 30 April 2005):

WARNING - This medication may be dangerous when used in large amounts or for a long period; or

CAUTION - This preparation is for the relief of minor and temporary ailments and should be used strictly as directed. Prolonged use without medical supervision could be harmful; or

(B) is labelled with the warning statements to the following effect (mandatory from 1 May 2005):

Don't use [this product / name of the product]: If you have a stomach ulcer
In the last 3 months of pregnancy
If you are allergic to aspirin or anti-inflammatory medicines;

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
If you are pregnant;

See a doctor before taking [this product / name of the product] for thinning the blood or for your heart. [Can be omitted in products for inhibition of platelet aggregation or with additional active ingredients.]; and

(iv) the directions for use include, in capital letters not less than 1.5 mm in height, the warning statements:

CONSULT A DOCTOR BEFORE GIVING THIS MEDICATION TO CHILDREN OR TEENAGERS WITH CHICKEN POX, INFLUENZA OR FEVER.

CAUTION - DO NOT GIVE TO CHILDREN UNDER TWO YEARS OF AGE **EXCEPT** ON DOCTOR'S ADVICE; or

(d) in tablets or capsules each containing no other therapeutically active constituent **except** an effervescent agent when:

(i) packed in blister or strip packaging or in a container with a child-resistant closure;

(ii) in a primary pack containing 100 or less tablets or capsules, each containing 100 mg or less of aspirin when packed and labelled for the prevention of cardiovascular disease or for the inhibition of platelet aggregation; and

(iii) the primary pack is labelled with the warning statement to the following effect:

For use under medical supervision only.

12.6 ARIPIPRAZOLE

PURPOSE

The Committee considered the inclusion of aripiprazole in Appendix K.

BACKGROUND

Aripiprazole is an atypical antipsychotic agent indicated for the treatment of schizophrenia. It is proposed that the mechanism of its action is mediated through a combination of partial agonist activity at dopamine D_2 receptors and serotonin 5-HT_{1A} receptors and antagonist activity at 5-HT_{2A} receptors.

At the 39th NDPSC Meeting (October 2003), the Committee agreed to include aripiprazole in Schedule 4 of the SUSDP on the grounds that the condition bring treated necessitated appropriate medical diagnosis and the safe use of this medicine required patient management and monitoring by a medical professional (Decision 2003/39-34).

DISCUSSION

Members noted that the following statements/information appeared in the approved Product Information (PI) for XXXXXXXXX tablets containing aripiprazole (similar statements also in the Micromedex DrugDex monograph for aripiprazole):

- As with other antipsychotics, patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are absolutely certain that XXXXXXXXX does not affect them adversely.

- Listed in the treatment-emergent adverse effects in short-term (up to 6 weeks) placebo controlled trials are lightheadedness (10.4% for aripiprazole *vs* 5.7% for placebo) and somnolence (9.8% for aripiprazole *vs* 6.4% for placebo).

- Somnolence is listed as "the only adverse event to have a possible dose relationship, and then most prominent only with 30 mg. Incidence figures presented are placebo, 7.7%;15 mg, 8.7%; 20 mg, 7.5% and 30 mg, 15.3%.

- "Given the primary central nervous system effects of XXXXXXXXX, caution should be used when XXXXXXXXX is taken in combination with other centrally acting drugs and alcohol" and "Patients should be advised to avoid alcohol while taking XXXXXXXXX".

Members' attention, however, was drawn to a different picture emerging in the open literature. In several studies and clinical trials (Keck et al, *Am J Psychiatry* 2003; Potkin et al, *Arch Gen Psychiatry* 2003; Goodnick et al, *Expert Opin Pharmacother* 2002), aripiprazole at doses up to 30 mg/day, caused somnolence (also lightheadedness in some studies) with a maximal incidence of 20% during first week of therapy, and the effect subsides rapidly to a level less than placebo (up to 11%). Furthermore, in a placebo-controlled 26-week study on schizophrenia patients (Pigott et al, *J Clin Psychiatry* 2003), aripiprazole was well tolerated, with no evidence of marked sedation.

Members noted the discrepancy between the information in the published literature and that in the PI. Members discussed whether a sedation warning statement is needed at the time of dispensing aripiprazole. Although there was some concern on how such a message is clearly delivered to consumers without warning statements, a Member suggested that it might be sufficient to allow the communication of warnings about alcohol consumption and the potential for drowsiness to be at the discretion of the dispensing pharmacist.

A Member pointed out that some other scheduled antipsychotics such as clozapine and quetiapine might also need to be examined for their inclusion in Appendix K. PI for Clozaril lists fatigue, drowsiness and sedation as being among the most common side effects observed, with an incidence of around 40%, and for Seroquel somnolence is listed as occurring in 18% of patients *vs* 11% of those receiving placebo. The Committee agreed that antipsychotics not currently listed in Appendix K would be considered as a group for inclusion in this Appendix at the next meeting. It was also agreed that advice should be sought from the College of Psychiatry.

Members also discussed the criteria for inclusion / exclusion of a substance from Appendix K and whether a substance should be automatically included in this Appendix if the PI mentions drowsiness. Introduction of Appendix K into the SUSDP occurred in 1987 (SUSDP No.2). Appendix K is adopted by all jurisdictions. A Member raised the issue of the future of Appendix K under the new Trans-Tasman Therapeutic Products Regulatory Agency (TTTPRA). The Committee understood that the requirement for Appendix K medicines to be labelled with a sedation warning statement had not been included in the new *Mandatory Advisory Statements for Medicines Labels* as Appendix K warning labels are applied at the time of dispensing. Members were also aware that the *Australian Pharmaceutical Formulary and Handbook* (APF) contains ancillary label instructions for dispensed medicines including sedation warning and that there are a number of inconsistencies and anomalies between Appendix K and APF. Members agreed that Appendix K of the SUSDP be referred to the NCCTG for consideration of its future under the TTTPRA.

DECISION 2004/40 – 26 – Confirmation of Amendment (DECISION 2003/39 – 34)

The Committee agreed to confirm aripiprazole in Schedule 4 of the SUSDP (Decision 2003/39-34) on the grounds that the condition being treated necessitated appropriate medical diagnosis and the safe use of this medicine required patient management and monitoring by a medical professional. The Committee deferred the consideration of aripiprazole for inclusion in Appendix K to the June 2004 Meeting.

Schedule 4 - New Entry

ARIPIPRAZOLE.

13. OTHER OUTSTANDING MATTERS FROM PREVIOUS MEETINGS

13.1 MELIA AZEDARACH

PURPOSE

The Committee considered further the inclusion of *Melia azedarach* in Appendix C of the SUSDP.

BACKGROUND

The 35th NDPSC Meeting (June 2002) agreed to foreshadow the inclusion of *Melia azedarach* or its extracts or its derivatives in Appendix C of the SUSDP, on public health and safety grounds. Whilst the Committee was of the view that there was a need to restrict the use of *Melia azedarach*, it recommended that additional information be sought to help resolve the following issues:

- Is there a mechanism for ensuring that only the non-toxic variety is used in products, given that the toxic variety has been found to be botanically indistinguishable from the non-toxic variety?

- Is it safe to establish a concentration cut-off to accommodate existing products?

- What are the long-term effects of *Melia azedarach* in humans and animals given that its limonoids have been found to be highly cytotoxic?

- What is the appropriate approach for veterinary products, given that *Melia azedarach* has also been established to be highly toxic in animals?

The 36th NDPSC Meeting (October 2002) considered the foreshadowed entry *of Melia azedarach* in Appendix C of the SUSDP but agreed to defer the matter to the 38th NDPSC Meeting (June 2003) to allow affected stakeholders an opportunity to provide relevant data to the Committee.

The 38th NDPSC Meeting (June 2003) noted the submissions from XXXXXXXXX, the XXXXXXXXX and the Office of Complementary Medicines (OCM). The OCM did not support the inclusion of *Melia azedarach*, its extracts and derivatives in Appendix C of the SUSDP, and proposed that a more complete safety review be undertaken with input and advice from the Complementary Medicines Evaluation Committee (CMEC). This should allow a more in-depth analysis of papers reporting on the potential toxic compounds found in this plant. Since the data available at the meeting were not sufficient to resolve the issues raised in regard to the toxicity associated with the *Melia azedarach* plant, the Committee agreed to defer further consideration of the foreshadowed inclusion of *Melia azedarach* in Appendix C of the SUSDP to the 40th NDPSC Meeting (February 2004) to allow the OCM sufficient time to complete the safety review on *Melia azedarach*.

DISCUSSION

The Committee noted the minute from the OCM advising that it has not been possible to complete the review due to overriding work priorities. The OCM further advised that the safety review on *Melia azedarach* has been programmed for completion by 7 May 2004.

OUTCOME

The Committee agreed that there was no choice but to further defer the consideration of this matter to the 41st NDPSC Meeting (June 2004).

13.2 MITRAGYNA SPECIOSA

PURPOSE

The Committee considered the foreshadowed inclusion of *Mitragyna Speciosa* in Schedule 9 of the SUSDP.

BACKGROUND

The *Mitragyna speciosa* (also known as Kratom) tree is native to Thailand and Malaysia. Mitragynine, one of the alkaloids found in the leaves of *Mitragyna speciosa*, has psychoactive properties and is used as an opium substitute. *Mitragyna speciosa* leaves are used extensively in Thailand (also in Malaysia) to increase work output and tolerance of direct sunlight, and are usually chewed, smoked or drunk as tea to achieve the desired affect. The leaves were chewed 3 to 10 times a day, with stimulant effects occurring after 5 to 10 minutes. *Mitragyna speciosa* is regulated in the same way as cocaine and heroin in Thailand and carries the same restrictions and penalties as cocaine.

The 37th, 38th and 39th NDPSC meetings (February, June and October 2003) considered the pharmacology, toxicology and the mode of action of mitragynine, the potential for abuse, and the potential impact of its inclusion in Schedule 9 (S9) of the SUSDP. It was recognised that whilst there were no widespread reports of abuse of mitragynine in Australia at this time, the information relating to the use of mitragynine for psychoactive effects, particularly in Asian countries, was well documented and easily found on the internet. At the October 2003 meeting, the Committee agreed to take a pro-active approach and included mitragynine in S9 of the SUSDP based on its potential for abuse (Decision 2003/39 – 23). In addition, the Committee noted information from Poisindex (Micromedex Healthcare) indicating that addiction and withdrawal symptoms had occurred with chronic use of *Mitragyna speciosa*, and agreed to foreshadow the inclusion of the plant species *Mitragyna speciosa* in S9 to allow further public comments to be considered at the February 2004 meeting.

DISCUSSION

The Committee noted the public submissions received from XXXXXXXXX, Messers, XXXXXXXXX, XXXXXXXXX, XXXXXXXXX, XXXXXXXXX, XXXXXXXXX, and XXXXXXXXX and the Office of Complementary Medicines (OCM).

XXXXXXXXX which did some pre-clinical trials with mitragynine in the 1970s, did not object to the inclusion of mitragynine and *Mitragyna speciosa* in Schedule 9. There was no further comment or additional information provided by the Office of Complementary Medicines. Several individuals (Messers XXXXXXXXX, XXXXXXXXX, XXXXXXXXX, XXXXXXXXX, XXXXXXXXX and XXXXXXXXX) opposed the proposal as *Mitragyna Speciosa* is currently grown as a rare ornamental plant with decorative value, or may be made available as herbal tea.

Mr XXXXXXXXX also highlighted the following points:

- Experiments in New Zealand (Jansen & Prast, *J Ethnopharmacol* 1988) showed that mitragynine produced considerable and effective relief of withdrawal symptoms in methadone and heroin users.

- Mitragyna speciosa could represent a billion dollars a year industry for Australian cultivators from mitraphylline which is also present in large amounts in the plants. Mitraphylline is an immuno-stimulant and has proved useful in the ongoing immuno-maintenance of cancers and AIDS patients.

A literature review, which included the Jansen and Prast paper (1988) and other relevant published papers, was considered by the Committee at its previous meeting. The potential effect of mitragynine in relieving withdrawal symptoms in methadone and heroin users is attributed to its opium-like action. In fact, habitual users of mitragynine could also develop marked withdrawal syndromes, which is demonstrated by recent studies through activating mu- and delta- subtypes of opioid receptors. Regarding mitraphylline and its pharmacotherapy effects, the Committee was not aware of any clinical information from the open literature.

The Committee considered that prohibition of *Mitragyna Speciosa* before the occurrence of widespread abuse is far more preferable from a public health and safety point of view. Members were reminded that jurisdictions are able to issue licences to allow Schedule 9 substances to be used for medical or scientific research purposes. It was mentioned by the NZ Member that the Schedule 9 inclusion of mitrogynine and *Mitrogyna speciosa* in Australia might suggest that NZ should also consider its scheduling in NZ.

DECISION 2004/40 - 27

The Committee agreed to include *Mitrogyna speciosa* in Schedule 9 of the SUSDP on the grounds of its potential for abuse.

Schedule 9 - New Entry

MITRAGYNA SPECIOSA.

13.3 HYOSCYAMUS NIGER

PURPOSE

The Committee considered the foreshadowed exemption of *Hyoscyamus niger* in preparations containing 30 micrograms or less of total solanaceous alkaloids.

BACKGROUND

The 38th (June 2003) NDPSC meeting considered a recommendation of the 28th (November 2002) NZ MCC to amend the cut-off in Appendix G of the SUSDP for atropine (100µg), hyoscine (10µg) and hyoscyamine (10µg) to 300µg/L to harmonise with New Zealand. The Committee agreed to amend the cut-offs in Appendix G for atropine to 300 µg, hyoscine to 150µg and hyoscyamine to 100µg to reflect the relative potencies of these substances.

The 29th (May 2003) MCC meeting considered a submission from Weleda seeking reclassification of Hyoscyamus niger from a pharmacy only medicine to a general sale medicine when in packs containing 300µg[1] or less of total solanaceous alkaloids. The MCC agreed to allow *Hyoscyamus niger* as a general sale medicine when in packs containing 30µg or less of total solanaceous alkaloids. The 39th (October 2003) NDPSC Meeting agreed to foreshadow, on the grounds of harmonisation, an amendment to the Schedule 2 entry for *Hyoscyamus niger* to exempt preparations containing 30µg or less of total solanaceous alkaloids from the requirements of scheduling.

DISCUSSION

Members noted that comments from the applicant XXXXXXXXX and the XXXXXXXXX supporting the lower cut-off level. Members understood that the 30 µg total solanaceous alkaloid content per pack was within the general principles of the herbal framework adopted in NZ that a general pack should contain not more than one hundredth of the lowest fatal dose.

DECISION 2004/40 - 28

The Committee agreed to the Schedule 2 amendment for *Hyoscyamus niger* to exempt preparations containing 30µg or less of total solanaceous alkaloids from the requirements of scheduling, on the basis that the product has a wider margin of safety. This amendment also allowed scheduling harmonisation with NZ.

[1] The value "300µg" was corrected to read "30µg" at the June 2004 NDPSC Meeting (Item 1.5.2)

Schedule 2 – Amendment

HYOSCYAMUS NIGER – amend entry to read:

HYOSCYAMUS NIGER 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 total solanaceous alkaloids and a recommended daily dose of 1.2 mg or less of total solanaceous alkaloids; or

(b) in divided preparations containing 0.03 mg of total solanaceous alkaloids or less per dosage unit when labelled with a recommended daily dose of 1.2 mg or less of total solanaceous alkaloids,

except in a pack containing 0.03 mg or less of total solanaceous alkaloids.

Schedule 4 - Amendment

HYOSCYAMUS NIGER – amend entry to read:

HYOSCYAMUS NIGER **except**:

(a) when included in Schedule 2; or

(c) in a pack containing 0.03 mg or less of total solanaceous alkaloids.

13.4 MERCURY

PURPOSE

The Committee considered the foreshadowed inclusion of mercury in Appendix G of the SUSDP.

BACKGROUND

Mercury is found naturally in the environment, and is also an industrial pollutant. The general population is exposed indirectly to mercury through the diet and dental amalgam. The diet is the major source of human exposure to mercury, with seafood containing much higher level of mercury than most other foods. The tolerable limit for total mercury, set at the 16th meeting of the Joint FAO/WHO Expert Committee on Food

Additives (JECFA) and maintained after reconsideration at the 22nd JETCFA meeting, is 0.3 mg per person per week, equivalent to 5 µg/kg bw/week. This limit has also been adopted by Food Standards Australia and New Zealand (FSANZ, 2002).

The 39th (October 2003) NDPSC meeting discussed a request to clarify whether 10 ppm (10 mg/L) of mercury for human therapeutic use is exempt from scheduling under the general exemption in Part 1 – Interpretation of the SUSDP. The Committee was informed that because mercury was included in Schedule 7, the general exemption in Part 1 – Interpretation of the SUSDP for substances at concentrations of less than or equal to 10 mg/kg or 10 mg/L did not apply to mercury. Furthermore, it was highlighted that mercury was not currently listed in Appendix G, suggesting that a safe limit for the use of mercury in dilute preparations for therapeutic use had yet to be determined. An entry for mercury in Appendix G of the SUSDP at a level of 5 µg/kg or 5 µg/L was proposed.

DISCUSSION

Members noted the recommendation made by the Office of Complementary Medicines which highlighted the following points:

- According to the Joint Expert Committee on Food Additives (JECFA) of the Food and Agriculture Organisation and the World Health Organisation (WHO), the current Provisional Tolerable Weekly Intake (PTWI) for total mercury and methylmercury is 5 and 1.6 µg/kg bw/week (0.3 and 0.1 mg/person/week for a 60 kg person) respectively.

- An average mature Australian can be expected to obtain no more than 15%, 23% and 12% of the JECFA PTWI for total mercury intake respectively from the diet, non-food environmental sources (with dental amalgam surfaces) and the typical environment.

- There is then scope for further exposure to mercury via complementary medicines equivalent to an additional 50% of the JECFA PTWI. According to calculations, if the Appendix G level for mercury is set at 1 mg/kg or L, a person would have to consume more than 150 g/week complementary medicine to exceed 50% of the JECFA PTWI for total mercury, which is unlikely.

- If the Appendix G level for methylmercury (short-chain alkyl mercury) is set at 0.3 mg/kg or L, a person would have to consume more than 160 g/week complementary medicine to exceed 50% of the JECFA PTWI for methylmercury, which is unlikely.

- The OCM give the following recommendations for the Appendix G entries: Short-chain alkyl mercury at 300 µg; Inorganic/organic mercury at 1 mg.

Members also noted that the similar Appendix G entry for cut-off concentration of mercury (1 mg/L or kg) was recommended by XXXXXXXXX and XXXXXXXXX. In addition, these submission highlighted that in the US, homoeopathic preparations of

mercury compounds (except mercurius cyanatus) are scheduled as OTC at a 6x potency, concentration of 1 mg/L or kg (as per the Homoeopathic Pharmacopoeia of the United States Revision Service, HPRS 1999).

Members understood that there are marked differences in toxicokinetics between methylmercury and other mercury. Methylmercury (short-chain alkyl mercury) is quite lipid soluble due to a strong Hg-C bond, and almost all is absorbed from the gastrointestinal tract, circulated unchanged and readily crosses the blood-brain barrier and placenta unchanged and has a long half life. Other organic mercury compounds have the Hg-C bonds cleaved in the liver. The toxic effects of methylmercury are well documented with the developing foetus more sensitive than adults. Members were aware of advice from FSANZ that pregnant women should limit their consumption of certain species of fish. It was noted that the OCM was of the opinion that pregnant women should be advised to avoid medicines containing methylmercury. Members were of the view that this issue should be addressed at registration through labelling.

On the basis of the OCM calculations, Members agreed that the proposed cut-off level for mercury at 5 µg was probably too conservative, and agreed to adopt the proposed levels. Members noticed the confusion with the terms "methylmercury" and "short-chain alkyl mercury", and agreed to use "mercury" and "methylmercury" for the entries at this stage.

DECISION 2004/40 - 29

The Committee agreed to include mercury in Appendix G at a cut-off concentration of 1 mg for total mercury, and of 300 µg for methylmercury.

Appendix G – New Entry

MERCURY	1 mg
METHYLMERCURY	300 micrograms

13.5 PORCINE PANCREATIC ENZYME EXTRACT PRODUCTS

PURPOSE

The Committee considered the decision foreshadowed at the October 2003 meeting to include products containing pancreatic enzyme extract in Schedule 4.

BACKGROUND

At its 39th meeting (October 2003), the Committee considered a recommendation made to the Therapeutic Goods Administration (TGA) by the June 2003 ADEC Meeting that, due to potential contamination of Australian marketed pancreatic enzyme products with

porcine parvovirus (PPV), the use of porcine pancreatic enzyme products should be restricted to pancreatic insufficiency only. The Committee agreed to foreshadow the inclusion of pancreatic enzymes in Schedule 4 with no cut-off to lower schedules for the following reasons:

- that contamination of Australian marketed pancreatic enzyme products with PPV and potential risk of human infection cannot be ruled out;

- the available data suggest that the benefits associated with treatment of pancreatic exocrine insufficiency with porcine pancreatic enzymes outweighs the potential risk of PPV contamination of these products; and.

- the risk-benefit ratio for the use of porcine pancreatic enzymes for conditions unrelated to pancreatic insufficiency, as OTC products or complementary medicines is too high, and those products should be withdrawn.

DISCUSSION

The Committee noted that the Complementary Medicines Evaluation Committee (CMEC) at Meeting 43 (November 2003) also discussed the ADEC's recommendation in relation to pancreatic enzyme products. The CMEC advised TGA that products containing pancreatic enzyme extract of porcine origin are suitable for use as an ingredient in listable or registrable complementary medicines, for indications other than pancreatic exocrine enzyme insufficiency, subject to the following regulatory approach:

- that TGA consult further with industry on the most appropriate method for reducing the potential of PPV infectivity in porcine pancreatic enzyme extracts, and

- TGA and industry agree on a practical timeframe for introducing any new requirements, and report back to CMEC. (CMEC considers that this implementation timeframe should be no more than twelve months.).

CMEC further advised the TGA that following the agreed implementation period, sponsors should either:

- ensure that manufacturers of porcine pancreatic extract-containing products validate their manufacturing process for porcine virus inactivation, and if necessary, introduce additional steps for viral inactivation. If gamma irradiation or other steps are introduced, the effect of such step(s) on enzyme activity should be investigated; or

- obtain TGA pre-clearance for PPV by providing adequate data or certification to ensure that pancreatic glands are only collected from pigs that are negative for PPV antibodies and that there have been no reproductive problems in the herds from which the glands are harvested.

The pre-meeting submission from XXXXXXXXX pointed out the discrepancy between recommendations by the NDPSC and the CMEC, and expressed concern as to whether cancellation of these medicines would be immediate or follow a grace period or if the scheduling would lead to cancellation of these products from ARTG. The latter has been referred to TGA Information Officer.

XXXXXXXXX submitted pre-meeting comment highlighting that it fully supports the approach proposed by CMEC. XXXXXXXXX stated that its view is that scheduling is not an appropriate mechanism for achieving the quality and safety of products in the Australia market.

The Committee noted that XXXXXXXXX had pointed out that the Record of Reasons from the October 2003 NDPSC meeting for the foreshadowed amendment did not differentiate between porcine and bovine pancreatic enzymes. XXXXXXXXX noted that there are some listed products containing bovine pancreatic enzyme, which will have met the TGA's requirements regarding Transmissible Spongiform Encephalopathy (TSE). The Committee noted that the XXXXXXXXX had requested the NDPSC to limit the scheduling changes to pancreatic enzymes of porcine origin only.

Members noted that there are four types pancreas-related products (pancreas, pancreatic extract, pancreatin and pancrelipase) on the ARTG, with the majority porcine origin, and only 6 products from bovine.

The Committee noted that in response to a request from OCM for information on the processes that sponsors had in place to guarantee that products were free from PPV only one sponsor had provided an acceptable response. The Committee also noted that OCM was about to write to sponsors again seeking information on the method and timeframe proposed by sponsors to guarantee that their products are free from PPV and an assurance from sponsors that the proposed manufacturing or inactivation process has been pre-cleared by the TGA.

Members queried whether or not there was an acceptable methodology to guarantee the manufacturing process or a suitable inactivation process. Members requested the Secretariat to obtain advice from the TGA on these matters.

The Committee agreed with the OCM that a consistent regulatory approach was important to avoid confusion by sponsors of medicines on the ARTG.

OUTCOME

The Committee deferred consideration of this decision pending advice from TGA and OCM.

13.6 PSEUDOEPHEDRINE

PURPOSE

The Committee further considered the scheduling of undivided, combination and slow release pseudoephedrine preparations in Schedule 2.

BACKGROUND

The June 2002 Meeting agreed to reschedule all OTC single-active immediate release pseudoephedrine preparations from Schedule 2 to Schedule 3, and to consider the scheduling of the remaining S2 pseudoephedrine formulations at the October 2002 NDPSC Meeting.

Preliminary information available at the October 2002 meeting did not provide sufficient evidence to support scheduling action on compounded, undivided and modified release pseudoephedrine preparations in Schedule 2. Nonetheless, the Committee remained concerned over the potential for the remaining Schedule 2 products to be diverted to the illicit drug trade and agreed that it would continue its consideration of the matter at the February 2003 meeting following further public consultation. This approach was viewed as an opportunity for the Committee to be informed of the outcome of ongoing analytical investigations on OTC pseudoephedrine products by the Australian Bureau of Criminal Intelligence (ABCI), and for sponsors to indicate their plans for existing and future product lines.

The NDPSC February 2003, June 2003 and October 2004 meetings further considered the scheduling of undivided, combination and slow release pseudoephedrine preparations in Schedule 2. The Committee agreed to defer consideration of this issue until the latest developments of the National Working Group on the Diversion of Chemical Precursors (NWG) were available.

DISCUSSION

Members noted the information provided by the Treaties and Monitoring Section of the Office of Chemical Safety on the importation of pseudoephedrine since 1991 which represented all imports of raw material and formulated products. It showed that the importation peaked at 1997 (27,500 kg), but has plateaued since 1999 (about 20,000 kg per year). The Secretariat was advised that the figure previously reported to the Committee on importation of pseudoephedrine for 2001 (40,323 kg) was incorrect, and the correct figure is 20,644 kg.

Members also noted a copy of the Draft Resolutions from the NWG November 2003 meeting. Members were advised that the researchers had examined the ease of extraction of pseudoephedrine from a range of products and reported the preliminary results to

NWG. It was understood that extraction from single and/or multiple component products *via* different approaches is effective, and the recovery / yield may be significant. No deliberations or conclusions on this issue were made at the NWG meeting, and the NWG fully expected a second presentation of the final research results on extraction and conversion of pseudoephedrine at the next meeting (March 2004). The NWG meeting also noted the recent report by the House of Representatives Standing Committee on Family and Community Affairs, Road to Recovery, in particular Recommendations 82 and 83. The NWG resolved that the TGA and Customs will address the next working group meeting on the Report recommendations.

Recommendation 83 states: "the Commonwealth government amend its *Standard for uniform scheduling of drugs and poisons* to make all substances containing pseudoephedrine a Schedule 4 Prescription Only Medicine." Members discussed this recommendation and the availability of the Commonwealth Government's response to this report. It was agreed to await the Commonwealth Government's response before considering this recommendation further.

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

- XXXXXXXXX requested the Committee to maintain the current scheduling of undivided, combination and slow release preparations in Schedule 2 for the following reasons:

  - Tighter scheduling of these combination products will not be able to control and prevent illegal behaviour.

  - Tighter scheduling creates a significant disadvantage for legitimate consumers.

  - Time is needed to assess the impact of both the newly established Industry Code of Conduct on Pseudoephedrine and the tighter scheduling (S3) of single active pseudoephedrine products.

  - There is no specific data available upon which to base any decision on rescheduling.

- XXXXXXXXX recommended that the NDPSC resolves to retain the current scheduling for pseudoephedrine combination products, and also believed that reliance on manufacturers to modify formulations to inhibit extraction is not realistic because of the costs involved and the limited benefit.

- XXXXXXXXX did not support the potential rescheduling for pseudoephedrine in undivided, combination and slow release preparations and raised the following points:

  - Scheduling alone will not reduce the supply of methylamphetamine to the illicit drug trade.

- Scheduling should be reserved for determining the appropriate level of access based on the safety profile of the substance and its intended use.

- There are currently not enough data to determine the size of the diversion problem, and sources, extraction and/or conversion of pseudoephedrine formulations being used.

- The XXXXXXXXX Pseudoephedrine Team which includes all sponsors of pseudoephedrine-containing products agreed that all advertisements to healthcare practitioners should include a statement to the effect "Pseudoephedrine containing products may be the target of illicit use". This is an attempt to maintain awareness of the problem in the market place.

- XXXXXXXXX urged the NDPSC to await the outcome of the TGA and Customs report to the NWG on Recommendations 82 and 83 (Road to Recovery report, 2003) at the next NWG meeting before taking any scheduling action.

The XXXXXXXXX Member advised that certain combination pseudoephedrine products/formulations were targeted for conversion in each state, for example, those in XXXXXXXXX were different from those in XXXXXXXXX. It was suggested that once a particular product is put in a higher schedule or where pharmacists are required to keep a record of sales, these people will move into other products for diversion purposes.

The XXXXXXXXX Member informed the Committee that in order to limit illicit manufacture of methamphetamine, NZ had proposed to classify pseudoephedrine and ephedrine as "Controlled Drug C3" (Pharmacy only pseudoephedrine products) and "Controlled Drug C5" (Prescription only pseudoephedrine and ephedrine products). Inclusion of pseudoephedrine and ephedrine in the '*NZ Misuse of Drugs ACT 1975*' provided stronger Customs powers but results in the scheduling of these medicines being unharmonised between Australia and NZ.

The Committee agreed to defer consideration on pseudoephedrine scheduling until the June 2004 meeting to allow the outcomes of the extraction/conversion research and other measures agreed by the next NWG meeting (March 2004) to become available. Members urge the Secretariat to write to the NWG to express their concern about the length of time it is taking to finalise the report on research into PSE extraction and conversion. It was also agreed that all public submissions for pseudoephedrine from previous meetings will be carried forward.

13.10 3,4-METHYLENEDIOXY-N, A-DIMETHYLPHENYLETHYLAMINE (MDMA)

PURPOSE

The Committee considered the foreshadowed amendment to the nomenclature for MDMA.

BACKGROUND

At the NDPSC October 2003 meeting, the Committee was advised that the nomenclature for 3,4-methylenedioxy-N,α-dimethylphenylethylamine (MDMA) in Schedule 9 of the SUSDP may be incorrect. A Member advised that the World Health Organization chemical name for MDMA based on the WHO list (Part One – Psychotropic Substances under International Control), is (+/-)-N,α-dimethyl-3,4-(methylenedioxy)phenylethylamine. There was no INN for this illicit drug. The Committee agreed to foreshadow consideration of the amendment to the nomenclature of MDMA at the February 2004 Meeting.

DISCUSSION

Members were advised that the Secretariat requested confirmation from the TGAL that the name proposed by the Committee is consistent with current naming convention used for other systematic names in the SUSDP. TGAL believe that for consistency, the entry for MDMA should be left as it is, since in the proposed WHO name, an "α" symbol after the "N," is missing, and it has the (+/-) to signify a racemic mixture of the two stereoisomers, which is unnecessary given that SUSDP entries cover all stereoisomers [Secretariat note: Unfortunately, when the WHO chemical name was sent to the TGAL, the "α" symbol was removed.] The Committee noted that the Chemical Abstracts name is *N,α-Dimethyl-1,3-benzodioxole-5-ethanamine*.

DECISION 2004/40 - 30

The Committee agreed to adopt the WHO name for MDMA with removal of the (+/-) symbol. It was also agreed to leave reference to the current existing name in the index of the SUSDP.

Schedule 9 – Amendment

3,4-METHYLENEDIOXY-N,α-DIMETHYLPHENYLETHYLAMINE – amend entry to read:

N,α-DIMETHYL-3,4-(METHYLENEDIOXY)PHENYLETHYLAMINE *(MDMA).

13.13 KAVA AND KAVALACTONES

PURPOSE

The Committee considered the scheduling of kava (*Piper methysticum*) and its active constituents kavalactones.

BACKGROUND

The 39th NDPSC Meeting (October 2003) noted a safety evaluation report prepared by the Kava Evaluation Group (KEG)/Office of Complementary Medicines (OCM) on kava containing medicines, which made recommendations on the regulation of kava as an ingredient in listed medicines. Due to the potential risk of liver toxicity with use of non-aqueous extracts of kava plants at high doses, the Committee considered the need for regulation of alcohol/acetone extracts of kava that were supplied to health care practitioners in bulk as starting materials for extemporaneously compounding, and agreed that a schedule entry to minimise the risk without affecting the current usage of listed complementary products should be made following the review of the listed products on the ARTG. Advice from MEC, CMEC and FSANZ, and comments from industry were invited before the February 2004 meeting.

DISCUSSION

Members noted that NT Menzies School of Health Research has studied the effects of kava since the mid-1980s. The Committee considered the comments by Senior Research Officer, XXXXXXXXX, that kava has been regarded as a hypnotic and strong muscle relaxing effects and that there is a link between kava use and malnutrition. Members also noted that XXXXXXXXX stated that the link between kava use and arrhythmias and sudden cardiac deaths in heavy kava users during exercise (playing football) is uncertain.

The Committee noted that France and Germany recently banned the sale of kava-based product. The action by the various European countries followed the release of a German report which cited 30 cases in Germany and Switzerland, and linked kava products to liver disease. The Committee noted however, that XXXXXXXXX believes there is a big difference between kava in the pill and kava in the bowl and that the serious liver damage (sometimes leading to death) seen in users of the manufactured kava products was not seen in the Aboriginal kava drinkers in Arnhem Land.

A Member advised that WHO was reviewing the safety of kava.

Members were also advised that there was some evidence of idiosyncratic reactions.

Members noted advice from the Food Standards Australia New Zealand (FSANZ) that FSANZ is currently reviewing the regulation of kava as a food in proposal P256 –

Review of Kava (Members noted that as regulated by FSANZ, kava refers to the powdered kava used for the purpose of preparing the traditional kava beverage).

Currently, kava as food in both Australia and New Zealand is regulated by Standard 2.6.3 – Kava, of the Australia New Zealand Food Standards Code. In Australia, Standard 2.6.3 operates in conjunction with the National Code of Kava Management on the Restriction of Sale and Advertising of Kava (NCKM), but the latter does not apply in New Zealand. The NCKM enable States and Territories to introduce more restrictive measures if they are considered necessary. Both the Northern Territory and Western Australia have introduced such legislation.

Members noted that, based on a safety evaluation of both the traditional kava beverage and the use in food of kava extracts prepared by organic solvent extraction, FSANZ is likely to recommend that the use of the traditional kava beverage continue to be allowed by Standard 2.6.3 and that organic extracts of kava (e.g. ethanol or acetone) be prohibited for use in food or as food. [Secretariat note: The Final Assessment Report on Proposal 256 – Review of Kava was released by the FSANZ on 17 March 2004 with the outcomes as predicted.]

Members noted advice from OCM is that the CMEC recommendation 41.3 (August 2003) regarding the forms of kava (*Piper methysticum*) permitted for use in Listed Medicines has been actioned and Schedule 4 to the Therapeutic Goods Regulations 1990 amended so that only specified forms of kava under certain conditions can be listed medicines. Members also noted that all other kava products have been cancelled from the ARTG.

The Committee noted that the XXXXXXXXX supports the CMEC position.

The Committee noted that, while Therapeutic Goods Regulations restricted the type of kava medicinal products which could be marketed in Australia, these regulations did not apply to all kava preparations used in medicines. In particular Members were concerned about starting materials containing kava and kavalactone extracted by solvents other than water and supplied to complementary health care practitioners. The Committee agreed that kava and kavalactones prepared using organic solvents posed a significant safety risk for the community and should be included in Schedule 4. However, Members also agreed that products containing low levels of kavalactones, ie. below 250 mg, did not meet the requirements to be included in a schedule.

Members were unsure about whether drafting the entry to refer to another legislative requirement, ie. the Therapeutic Goods Order, would cause problem for jurisdictions. In particular, Members were concerned that the warnings required by the TGA would not be covered by the draft schedule entry as currently worded. Members agreed, in principle to include kava and kavalactones, other than specified exceptions, in Schedule 4 but referred the wording to the Drafting Advisory Panel for advice to ensure that the scheduling provisions were drafted to achieve consistency with the Therapeutic Goods Regulations.

OUTCOME

The Committee agreed to foreshadow inclusion of kava (*Piper methysticum*) in Schedule 4 of the SUSDP with the exception of specified kava preparations The reasons for the Committee's decision are that:

- the safety of whole or peeled rhizomes and their aqueous preparations appear to meet the criteria for exclusion from scheduling;

- other kava preparations containing less than 250mg kavalactones appear to meet the criteria for exclusion from scheduling; and

- the toxicity of other kava and kavalactones preparations is such that medical advice is necessary for their safe use.

The committee agreed that the entry should be drafted to ensure that specific exemptions were consistent with the Therapeutic Goods Regulations and accurately reflected the Committee's view.

13.14 NICOTINE IN LOZENGES

PURPOSE

To consider the scheduling of nicotine when included in lozenges for use in withdrawal from tobacco smoking.

BACKGROUND

The NDPSC Meeting 32 (August 2001) agreed to include nicotine in lozenges in Schedule 3 of the SUSDP for use in NRT, based on its expected comparable pharmacokinetic and safety profile, and toxicological properties compared to the sublingual tablets. The NDPSC Meeting 38 (June 2003) considered an application from XXXXXXXXX and agreed to include nicotine lozenges in Schedule 2 of the SUSDP on the basis of its overall safety profile, marketing experience and post marketing surveillance which indicated that the lozenge preparation is safe in OTC use. The Committee agreed that its previous concerns, namely the absence of clinical experience and the potential for overdose in children, given the high nicotine bioavailability, had been allayed.

The NDPSC Meeting 39 (October 2003) made an initial decision to exempt nicotine in chewing gum and transdermal patches from the requirements of scheduling

The Committee received submissions from the XXXXXXXXX the XXXXXXXXX and the XXXXXXXXX all of which opposed the de-scheduling of nicotine in lozenges on a number of grounds. The Committee also received a submission from the XXXXXXXXX

supporting the de-scheduling of nicotine in lozenges. Consideration of these post-meeting comments is discussed below and at Item 12.3.

DISCUSSION

Concerns about the need for professional support.

The Committee noted that both the XXXXXXXXX and the XXXXXXXXX submissions agued that the professional support is essential for the success of all NRTs.

The Committee considered the XXXXXXXXX, XXXXXXXXX and the XXXXXXXXX submissions, a number of studies which looked at the effectiveness of various smoking cessation approaches, including behavioural counselling and support and pharmacological products WHO documents, and analysis of the available research. Details of the Committee's considerations are recorded under Agenda Item 12.3. After considering all these matters the Committee did not agree with the XXXXXXXXX assertion that "access to NRT without access to healthcare personnel who provide support and advice and information is inconsistent with WHO policy." The Committee noted that de-scheduling of nicotine in patches and gums would not preclude pharmacies from selling those products or from promoting any support or counselling services for smokers wishing to quit.

Concerns about use by pregnant women

Members discussed concerns about use by pregnant women of nicotine in products intended to assist in withdrawal from tobacco smoking. Details of those discussions are included under Agenda Item 12.3. The Committee supported the WHO recommendations that in certain circumstances NRT should be made available to pregnant women ("*Regulation of nicotine replacement therapies: and expert consensus" 2001, p. 39 (WHO Regulation Recommendations))*

The Committee noted that the packaging for nicotine lozenges carries a warning that the product should not be used in pregnancy except under medical supervision.

Concerns about Abuse

The Committee discussed the issue of abuse. The Committee noted the concerns expressed by the XXXXXXXXX that lozenges would be considered as sweets thereby leading to abuse. Members noted that there did not appear to be abuse of NRT products containing nicotine. One Member reported that there had been some reports in XXXXXXXXX of abuse by teenagers, generally of the gum. However, the Member stated that the reports found that the NRT products had been used as a substitute source of nicotine when cigarettes were difficult to obtain. Reports indicated that those abusing NRTs had no intention of giving up cigarettes and were not using it to assist in giving up smoking. One Member stated that the taste of lozenges would also be a deterrent.

Members noted that this view was supported by the WHO experts (the WHO Regulation Recommendations p.39)

Members considered the comments by WHO (WHO Regulation Recommendations p.38) which considered that the "dependence potential of NRT products is relatively low compared with the cigarette." Members noted that the WHO experts found that "the patch releases nicotine slowly, gradually peaking after 4-9 hours whereas nicotine levels from gum, inhalator and lozenge peak after about 30 minutes. This compares with a concentrated bolus of nicotine reaching the brain within 10 seconds of each puff on a cigarette." The Committee also noted that a number of reports had concluded that the likelihood of abuse was small, and agreed that, were abuse to occur, the level of harm was likely to be less than would occur from smoking tobacco.

Harmonisation with New Zealand

The Committee was advised that de-scheduling of nicotine in lozenges would result in the scheduling not being harmonised with the controls in New Zealand. A Member advised the Committee that to date no application had been made to de-schedule nicotine in lozenges in New Zealand. The Committee agreed to recommend that New Zealand deschedule nicotine in lozenges.

Considerations against S52E of the Therapeutic Goods Act 1989

S52E(1) (a) toxicity and safety of a substance

The Committee noted that products to aid in smoking cessation programs had been available for some considerable time with minimal problems with toxicity. While the Committee recognised that the lozenges had not been available for as long as some other NRT products, the Committee was not aware of any evidence that the safety profile of lozenges differed from that of other NRTs.

S52E (1)(b) the risks and benefits associated with the use of a substance

The Committee considered that by making NRTs, including lozenges, more available to the public would encourage more smokers to quit smoking. The Committee noted that nicotine in NRTs was generally well tolerated although there may be some minor side effects.

The Committee considered the potential risks to pregnant women from taking nicotine in lozenges, but noted that product labels carried warnings to pregnant women. The Committee agreed that any risk to pregnant women was more than balanced by the benefits associated with the use of lozenges containing nicotine, i.e., cessation or reduction in the smoking of tobacco products where pregnant women were unable to quit using non-pharmacological means. The Committee noted that this view was consistent with that of the WHO.

S52E (1)(c) the potential hazards associated with the use of the substance

The Committee agreed with the WHO view that the hazards of nicotine in all NRT products (including lozenges) were considerably less than the hazards associated with consumption from widely available tobacco products. Members also noted the warnings required on the labelling and packaging of the products.

S52E (1)(d) the extent and patterns of use of a substance

The Committee noted that NRT products containing nicotine were widely used, although many of the studies pointed out that the duration for which the products are used is often quite short, only several weeks. (e.g. *Aust N Z J Public Health 2003; 27:491-5*).

S52E (1)(e) the dosage and formulation of the substance

The Committee noted that lozenges come in several strengths and, in keeping with the WHO view that smokers should have access to a wide variety of treatment and assistance options, having a variety of formulations of the NRT products available would provide a choice for those wishing to use a pharmacotherapy to assist them give up smoking. WHO stated that "Broadening the range of nicotine delivery systems has proven useful in increasing the number of cigarette smokers who can choose acceptable formulation to help them quit." *(WHO Regulation Recommendations p. 25).*

S52E (1)(f) the need for access to a substance, taking into account its toxicity compared with other substances available for a similar purpose

Smoking is major cause of morbidity and mortality in the Australian community. The Committee noted that the WHO recognises that it is important for the community to have access to a range of options to assist in cessation or reduction of smoking and that lozenges, together with other NRTs, are important tools in efforts to reduce smoking.

S52E (1)(g) the potential for abuse of a substance

The Committee considered that the potential for abuse of nicotine lozenges was minimal particularly as the lozenges would not deliver the 'high' which characterises most substances of abuse. Nor had the Committee seen any evidence of significant abuse. The Committee agreed with the WHO and the writers of other studies that, should abuse occur, the risks of harm would be considerably less than from consumption of nicotine from tobacco products.

S52E (1)(h) the purposes for which the substance is to be used

Nicotine in lozenges is intended for use in smoking cessation and reduction programs.

S52E (1)(i) any other matters that the Committee considers necessary to protect

public health, including the risks (whether imminent or long-term) of death, illness or injury resulting from its use.

The Committee considered that, given the significant harm caused by smoking to the individual and the community, it was import to make a range of treatment options available to assist to those addicted to smoking cease or reduce the level of their smoking. The Committee noted that this was in line with the recommendations of the WHO.

DECISION 2004/40 - 31

The Committee agreed to exempt nicotine in lozenges for use as an aid in withdrawal from tobacco smoking from scheduling. In reaching its decision the Committee, as required, took into account the matters set out in section 52E of the *Therapeutics Goods Act* 1989. The reasons for the Committee's decision were that:

- widening of the availability of NRT products should encourage more smokers to quit smoking or reduce their level of smoking and that this should improve public health outcomes;
- the safety profile of nicotine in lozenges to aid in withdrawal from tobacco smoking was such that it no longer required scheduling;
- the packaging of the product was required to carry warnings for pregnant women; and
- the potential for abuse was minimal.

Schedule 2 - Amendment

NICOTINE - amend entry to read:

NICOTINE for use as an aid in withdrawal from tobacco smoking in preparations for inhalation.

Schedule 4 – Amendment

NICOTINE - amend entry to read:

NICOTINE for use as an aid in withdrawal from tobacco smoking (including preparations for nasal administration) **except**:

(a) when included in Schedule 2 or 3;

(b) in chewing gum;

(c) in lozenges, or

(d) in preparations for transdermal use.

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

14.1 SUSDP, PART 4

14.1.1 SODIUM FLUORIDE MOUTHWASH

PURPOSE

The Committee considered an application seeking to increase the scheduling exemption for fluoride in mouth rinse preparations from 0.01 to 0.022%.

BACKGROUND

XXXXXXXXX have submitted an application requesting consideration of an exemption from scheduling for oral mouth rinse preparations containing 0.022% fluoride (0.05% sodium fluoride). These preparations are currently included in Schedule 2.

The 39th NDPSC Meeting (October 2003) considered TTHWP Recommendation 9/1, and agreed to replace the term "dentifrice" in the fluorides scheduling entries with "pastes, powders or gels for the cleaning of teeth" to harmonise with NZ. This decision was foreshadowed for consideration at the February 2004 meeting. (See Agenda Item 1.8.1.2.1).

DISCUSSION

Members noted that, in response to the call for comments on the proposal to amend the fluoride entries in the Schedules, XXXXXXXXX had argued that, for consistency, all topical dental hygiene products should have the same cut off levels for exemption from scheduling, ie. 1000 mg/kg. The Committee did not support this proposal. (See Agenda Item 1.1.8.1.2.1)

Members noted that the submission from XXXXXXXXX to amend the cut off level for exemption from scheduling of mouth rinses did not address all issues required for rescheduling. Members also noted that, as XXXXXXXXX did not nominate a specific product or pack size in relation to this submission, the proposed exemption would apply all products or pack sizes of dental hygiene products.

The Committee noted that the current classification of fluorides means that toothpaste products that can be freely sold in grocery stores with sodium fluoride levels of 0.22%, while oral rinses that contain 0.05% are classified as pharmacy medicines.

Members noted that the submission presented by XXXXXXXXX stated that the US FDA has set the fluoride limit at 0.05% w/w sodium fluoride for oral rinses and that this level

of fluoride has been extensively used safely in markets such as the US, UK, New Zealand and Australia.

Members noted that the data submitted by XXXXXXXXX in relation to safety of fluoride mouth rinses are consistent with the literature and that cited by the NHMRC (*Review of Water Fluoridation and Fluoride Intake from Discretionary Fluoride Supplements, 1999 (NHMRC Fluoridation Report)*) i.e. that mouth rinses containing 0.02-0.05% sodium fluoride do not appear to pose any significant adverse effects in adults. However, Members noted that the NHMRC review has raised concerns at the possibility of adverse effects from excessive chronic fluoride ingestion by children (resulting in dental fluorosis).

The Committee noted that according to the NHMRC Guideline, "fluoride mouth rinses contain fluoride at a concentration of 0.05% (230 ppm).

The Committee discussed the possible use of the fluoride mouth washes by children and expressed concern that this could potentially lead to an increase in fluoride ingestion and the development fluorosis. However, as the level of 0.022% fluoride is still significantly lower than that in toothpaste the Committee considered that it is unlikely to pose any increased safety issues. The Committee noted that the *NHMRC Fluoridation Report* had recommended a number of ways to reduce excessive fluoride intake.

Members noted the US guidelines for OTC anti-caries drug products which may be allowed to be marketed in the USA without prior approval by the FDA include sodium fluoride in a range of concentrations from 0.01 to 0.05%, depending on the pH of the solution provided that the pack contained no more than 120 mg total fluoride per package, the package was labelled with warnings to "Keep out of reach of children" and the directions emphasised that the product was only for use in adults and children six years of age and older.

DECISION 2004/40 - 32

Members agreed that the level of exemption of "other dental hygiene products" could be increased to 0.022% fluoride (0.05% sodium fluoride) provided there was a limitation on the pack size (not to exceed 120 mg per package), the products were fitted with child resistant closures and the products labelled as not recommended for use in children, particularly in those under six years of age. The reasons for the Committee's decision were;

- the evidence from Australia and overseas supported the view that 0.022% did not pose a safety risk in adults; and

- the potential safety problems with children could be adequately addressed by the proposed measures to restrict access by children to the products.

A Member raised the issue of extending the time period for current products to comply with the requirement for child resistant packaging but the Committee agreed that this should not be granted.

Schedule 2 – Amendment

FLUORIDES - amend entry to read:

FLUORIDES for human therapeutic use (except in preparations containing 15 mg/kg or 15 mg/L or less of fluoride ion):

(a) as sodium fluoride, in preparations for ingestion containing 2.2 mg or less of sodium fluoride per dosage unit; or

(b) in preparations for topical use containing 2.5 per cent or less of fluoride ion **except**:

(i) pastes, powders or gels for the cleaning of teeth, included in Schedule 3;

(ii) pastes, powders or gels for the cleaning of teeth, containing 1000 mg/kg or less of fluoride ion; or

(iii) other dental hygiene products containing 220 mg/kg or 220 mg/L or less of fluoride ion, in packs containing not more than 120 mg total fluoride, 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.

Schedule 3 – Amendment

FLUORIDES – amend entry to read:

FLUORIDES in pastes, powders and gels containing more than 1000 mg/kg of fluoride ion.

Schedule 4 - Amendment

FLUORIDES - amend entry to read:

FLUORIDES in preparations for human therapeutic use **except**:

(a) when included in Schedule 2 or 3;

(b) pastes, powders or gels for the cleaning of teeth, containing 1000 mg/kg or less of fluoride ion;

(c) other dental hygiene products containing 220 mg/kg or 220 mg/L or less of fluoride ion, in packs containing not more than 120 mg total fluoride, fitted with a child-resistant closure and labelled with warnings to the following effect:

(i) Do not swallow; and

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

(d) in other preparations containing 15 mg/kg or 15 mg/L or less of fluoride ion.

Schedule 5 – Amendment

FLUORIDES – amend entry to read:

FLUORIDES in preparations containing 3 percent or less of fluoride ion **except**:

(a) when included in Schedule 2, 3 or 4;

(b) pastes, powders or gels for the cleaning of teeth, containing 1000 mg/kg or less of fluoride ion;

(c) other dental hygiene products containing 220 mg/kg or 220 mg/L or less of fluoride ion, in packs containing not more than 120 mg total fluoride, fitted with a child-resistant closure and labelled with warnings to the following effect:

(i) Do not swallow; and

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

(d) in other preparations containing 15 mg/kg or 15 mg/L or less of fluoride ion.

Schedule 6 - Amendment

FLUORIDE – amend entry to read:

FLUORIDES **except**:

(a) when included in Schedule 2,3,4 or 5;

(b) pastes, powders or gels for the cleaning of teeth, containing 1000 mg/kg or less of fluoride ion;

(c) other dental hygiene products containing 220 mg/kg or 220 mg/L or less of fluoride ion, in packs containing not more than 120 mg total fluoride, fitted with a child-resistant closure and labelled with warnings to the following effect:

(i) Do not swallow; and

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

(d) in other preparations containing 15 mg/kg or 15 mg/L or less of fluoride ion.

14.1.2 TRIAMCINOLONE

PURPOSE

The Committee considered an application seeking rescheduling of intranasal triamcinolone acetonide from Schedule 3 to Schedule 2 for the short term treatment of allergic rhinitis.

BACKGROUND

Triamcinolone is a synthetic fluorinated corticosteroid with mainly glucocorticoid activity. Intranasal triamcinolone is registered in 64 countries including the UK and USA. It has been included in the Australian Register of Therapeutic Goods since 1998, but has never been marketed in Australia.

Intranasal triamcinolone acetonide is classified as a Prescription Only Medicine in several countries, including Canada, Sweden and the USA. In the UK, and application seeking Pharmacy Status was submitted in December 1999, this was subsequently approved. Intranasal triamcinolone acetonide is listed as a restricted medicine in New Zealand.

At 28th NDPSC Meeting (August 2000), the Committee agreed that it was appropriate to schedule triamcinolone nasal spray to Schedule 3 for the short-term prophylaxis or treatment of seasonal allergic rhinitis in adults and children aged 12 years of age and over. Its safety profile was considered to be similar to other nasal corticosteroids included in Schedule 3 at that time. Inclusion in Appendix H was also approved by the Committee.

XXXXXXXXX has submitted an application seeking rescheduling of the current indications for Schedule 3 triamcinolone acetonide for intranasal use to Schedule 2, and to expand the Schedule 2 indications to also include perennial allergic rhinitis, thereby becoming "allergic rhinitis". The recommended maximum daily dose is 220g[1] for adults and children 12 years of age and over and a maximum pack size 120 actuations of 55g[2] per actuation

[1] The value "220g" was corrected to read "220mcg" at the June 2004 NDPSC Meeting (Item 12.1).
[2] The value "55g" was corrected to read "55mcg" at the June 2004 NDPSC Meeting (Item 12.1).

DISCUSSION

The Committee noted that extensive trials assessing the efficacy and safety of intranasal triamcinolone acetonide for the treatment of allergic rhinitis have been conducted in adults and children, which indicate no evidence of harmful effects when used for up to 12 months. It has an equivalent safety and efficacy profile to other Schedule 2 intranasal corticosteroids (beclomethasone, budesonide and mometasone furoate) for allergic rhinitis.

Members noted that international post-marketing data for intranasal triamcinolone available since its launch in 1997 did not show any new or worrisome adverse event profile in extensive Periodic Safety Update Reports. Members also noted an ADRAC summary for triamcinolone in preparations other than nasal spray (topical creams, pastes, ointments and solutions for injections) which revealed application site reactions, congenital abnormalities, dyspnoea, dermatitis, face oedema, pruritus, maculopapular rash and urticaria in less than 10% of reported cases with only 1 report of adrenal insufficiency. Of the 4 reports of congenital abnormalities, triamcinolone was not the sole suspected causative agent.

The Committee agreed that allergic rhinitis is a condition which is suitable for self-diagnosis and short-term treatment. To avoid confusion, Members agreed that "short term treatment" should be replaced with a specified time, namely "up to 6 months". Members also agreed that the maximum dose permitted in Schedule 2 should reflect the doses used in the safety and efficacy data considered by the Committee.

DECISION 2004/40 - 33

The Committee agreed to reschedule triamcinolone for use for up to 6 months for intranasal use for allergic rhinitis from Schedule 3 to Schedule 2 for the following reasons:

- Allergic rhinitis is regarded clinically as a condition which is suitable for self diagnosis and treatment;

- Clinical trial and post marketing safety fulfils the criteria for inclusion in Schedule 2; and

- The potential for abuse is extremely low.

Members also agreed to change to name from triamcinolone acetonide to triamcinolone for consistency with the AAN and INN nomenclature.

Schedule 2 – New Entry

TRIAMCINOLONE in aqueous nasal sprays delivering 55 micrograms or less of triamcinolone per actuation when the maximum recommended daily dose is no

greater than 200 micrograms and when packed in a primary pack containing 120 actuations or less, for prophylaxis or treatment of allergic rhinitis for up to 6 months in adults and children 12 years of age and over.

Schedule 3 - Amendment

TRIAMCINOLONE ACETONIDE – amend entry to read:

TRIAMCINOLONE for the treatment of mouth ulcers, in preparations containing 0.1 per cent or less of triamcinolone in a pack of 5 g or less**.**

Schedule 4 - Amendment

TRIAMCINOLONE – amend entry to read:

TRIAMCINOLONE **except** when included in Schedule 2 or 3.

14.2 SUSDP, PART 5

14.2.1 APPENDIX H

There were no items were considered.

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

15.1 NEW SUBSTANCES

15.1.1 ADALIMUMAB

PURPOSE

The Committee considered the scheduling of the new medicine adalimumab.

BACKGROUND

Adalimumab is a tumour necrosis factor α (TNFα) neutralising human IgG monoclonal antibody. TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF are found in the synovial fluid of rheumatoid arthritis patients and are thought to play a significant role in pathological inflammation and joint destruction. Infliximab and etanercept have a similar mechanism of action.

The October 2003 ADEC meeting recommended the approval of an application by XXXXXXXXX to register XXXXXXXXX for subcutaneous injection every second week, containing the new medicine adalimumab XXXXXXXXX, for the indication:

XXXXXXXXX is indicated for reducing signs and symptoms and inhibiting the progression of structural damage in adult patients with moderate to severely active rheumatoid arthritis when the response to disease-modifying anti-rheumatic drugs has been inadequate.

XXXXXXXXX can be used alone or in combination with methotrexate.

ADEC also recommended that approval be subject to the finalisation of the Product Information to the satisfaction of the TGA.

DISCUSSION

The Committee noted the October 2003 ADEC minutes, which reported that:

[paragraphs deleted]

The Committee noted the approved Product Information for XXXXXXXXX.

The Committee also noted that adalimumab was classified as a prescription medicine in New Zealand.

DECISION 2004/40 - 34

The Committee agreed to include adalimumab in Schedule 4 of the SUSDP:

- on the grounds that the condition being treated necessitated appropriate medical diagnosis and the safe use of this medicine required patient management and monitoring by a medical professional; and

- to harmonise with New Zealand.

Schedule 4 - New Entry

ADALIMUMAB.

15.1.2 ENFUVIRTIDE

PURPOSE

The Committee considered the scheduling of the new medicine enfuvirtide.

BACKGROUND

Enfuvirtide (T20) is a synthetic 36 amino acid peptide that corresponds to residues 127-162 in the extracellular portion of the transmembrane segment (gp41) of the HIV

envelope glycoprotein. It blocks HIV cell fusion and viral entry. It is the first agent in a new class defined as fusion inhibitors targeting viral cellular entry, and is likely not to be cross resistant to currently available therapies. It is the first antiretroviral agent that is not delivered orally (administered by subcutaneous injection).

The August 2003 ADEC meeting recommended the approval of an application by XXXXXXXXX to register XXXXXXXXX for injection, containing the new medicine enfuvirtide XXXXXXXXX vials for the indication:

> Enfuvirtide is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in antiretroviral experienced patients with treatment failure due to resistant virus.

ADEC also recommended that approval be subject to the finalisation of the PI and the sponsor submitting to TGA the final reports of any carcinogenicity studies undertaken with enfuvirtide.

DISCUSSION

The Committee noted the August 2003 ADEC minutes, which reported that:

[paragraphs deleted]

The Committee noted the approved Product Information for XXXXXXXXX.

DECISION 2004/40 - 35

The Committee agreed to include enfuvirtide in Schedule 4 of the SUSDP on the grounds that the condition being treated necessitated appropriate medical diagnosis and the safe use of this medicine required patient management and monitoring by a medical professional.

Schedule 4 - New Entry

ENFUVIRTIDE.

15.1.3 ESCITALOPRAM

PURPOSE

The Committee considered the scheduling of the new medicine escitalopram.

BACKGROUND

Escitalopram is a selective serotonin reuptake inhibitor (SSRI); it is the S(+)- enantiomer of citalopram which is listed in Schedule 4.

The August 2003 ADEC meeting recommended the approval of an application by XXXXXXXXX to register XXXXXXXXX containing the new medicine escitalopram oxalate XXXXXXXXX, XXXXXXXXX, XXXXXXXXX and XXXXXXXXX for the treatment of major depression.

DISCUSSION

The Committee noted the August 2003 ADEC minutes, which reported that:

[paragraphs deleted]

The Committee also considered including escitalopram in Appendix K as somnolence was a statisically significant adverse rection. However, it was considered that the precaution statement in the PI was sufficient. The Committee also considered that this approach was consistent with the treatment of other SSRIs, such as fluvoxamine and venlafaxine, where the October 2003 NDPSC meeting did not support the inclusion of these substances in Appendix K as the available evidence indicated that they had a low potential to cause sedation or affect motor skills at the recommended doses and the inclusion of a sedation warning in the CMI and PI was considered sufficient.

The Committee noted the approved Product Information.

The Committee also noted that escitalopram was listed as a prescription medicine in New Zealand.

DECISION 2004/40 - 36

The Committee agreed to include escitalopram in Schedule 4 of the SUSDP:

- on the grounds that the condition being treated necessitated appropriate medical diagnosis and the safe use of this medicine required patient management and monitoring by a medical professional; and

- to harmonise with New Zealand.

Schedule 4 - New Entry

ESCITALOPRAM.

15.1.4 CHOLERA VACCINE

PURPOSE

The Committee noted the approval of a new cholera vaccine.

BACKGROUND

The August 2003 ADEC meeting recommended the approval of an application by XXXXXXXXX to register XXXXXXXXX Cholera Vaccine which in each 3 mL vial contains:

[paragraph deleted]

for the indication:

> Cholera caused by serogroup 01 Vibrio cholerae: Active immuisation of adults and children from two years of age who will be visiting areas epidemic or endemic for cholera who are at high risk of infection.

[paragraph deleted]

OUTCOME

The Committee noted that cholera vaccines are listed in Schedule 4 of the SUSDP and are classified as prescription medicines in New Zealand.

15.1.5 ADEFOVIR DIPIVOXIL

PURPOSE

The Committee considered the scheduling of the new medicine adefovir dipivoxil.

BACKGROUND

Adefovir is structurally similar to the antiretroviral tenofovir. Adefovir is an acyclic nucleotide analogue of adenosine monophosphate.

The August 2003 ADEC meeting recommended the approval of an application by XXXXXXXXX to register XXXXXXXXX tablets containing the new chemical entity adefovir dipivoxil in 10 mg tablets for the treatment of chronic hepatitis B in adults with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease. This indication is based on histological, virological, biochemical and serological responses in adult patients with HbeAg+ and HbeAg -/HBV DNA +- chronic hepatitis B compensated liver function and in adult patients with clinical evidence of lamivudine-resistant hepatitis B virus with either compensated or decompensated liver function.

ADEC also recommended that approval be subject to finalisation of the Product Information to the satisfaction of the TGA and the sponsor be required to submit the final reports for efficacy studies (XXXXXXXXX) to the TGA within three months of completion of the reports.

DISCUSSION

The Committee noted the August 2003 ADEC minutes, which reported that:

[paragraphs deleted]

DECISION 2004/40 - 37

The Committee agreed to include adefovir in Schedule 4 of the SUSDP on the grounds that the condition being treated necessitated appropriate medical diagnosis and the safe use of this medicine required patient management and monitoring by a medical professional.

Schedule 4 - New Entry

ADEFOVIR.

15.1.6 LEVOSIMENDAN

This item was withdrawn.

15.2 FOR INFORMATION (SUBSTANCES ALREADY SCHEDULED)

15.3 OTHER ADEC MATTERS FOR CONSIDERATION

15.3.1 QUININE

PURPOSE

The Committee considered the scheduling of quinine in light of ADEC's recommendation that all indications for quinine, other than malaria, should be removed.

BACKGROUND

Quinine is available in Australia as quinine bisulphate and quinine sulphate for oral use and quinine dihydrochloride for *iv* use. There are 12 products listed on the ARTG containing quinine. All of the available oral products currently carry indications for the treatment of, or symptomatic relief of, nocturnal cramps and/or muscle cramps, and for the treatment of malaria. One product is indicated for the treatment of myotonica congenita and the diagnosis of myasthenia gravis. Three products are Listed medicines for use in Australia or for export only.

Prior to 1994 quinine was available in the US both on prescription and over the counter (OTC). In 1994, the FDA reviewed the efficacy and safety of quinine for nocturnal leg cramps, specifically in regard to OTC use, and short periods of treatment (7 days or less). The FDA concluded that the data do not indicate that quinine is safe or efficacious when used for nocturnal leg cramps, and therefore limited quinine marketing to prescription only.

Submissions supporting an amendment to the SUSDP to delete quinine from all schedules other than Schedule 4 were received from the XXXXXXXXX the XXXXXXXXX. The XXXXXXXXX did not support any relaxation of the current scheduling due to concerns on its efficacy for the treatment of nocturnal leg cramps, and side effects such as thrombocytopenic purpura and retinal toxicity.

The XXXXXXXXX and XXXXXXXXX sought the right to comment further after the meeting.

DISCUSSION

The Committee noted that at its 230th Meeting (October 2003), ADEC considered a proposal from ADRAC to remove all indications for quinine-containing products except malaria. Members noted that ADRAC had received 214 reports (out of a total 598 adverse reactions reports with quinine, 36%) of thrombocytopenia with quinine, including 4 reports with fatal outcomes. In 153 of these reports, quinine was the sole suspected medicine. Members were advised that ADEC considered that the use of quinine for any treatment, other than malaria, was not evidence-based, including the treatment of cramps resulting from narcotic withdrawal.

The Committee noted that ADEC had concluded that the risk/benefit ratio of quinine for cramps is too unfavourable to justify its use and provided this advice to the Therapeutic Goods Administration (TGA). The Committee also noted that following the ADEC advice, the Drug Safety Evaluation Branch of the TGA advised sponsors of prescription products that all indications other than malaria were to be deleted from quinine containing products.

The Committee were advised that at its February 2004 meeting, the Medicines Evaluation Committee (MEC) noted that there was only one quinine-containing OTC product with

the ARTG indications for "to alleviate the unpleasant withdrawal symptoms normally experienced when giving up smoking" and that MEC has requested the sponsor to provide data for consideration at the April 2004 MEC meeting to support the safety of the product in terms of the potential for quinine to cause severe haematological reactions.

The Committee noted that hypersensitivity appears to be the mechanism by which adverse reactions occur and that there is no dose threshold.

However, Members also noted that the Food Standards Code (FSC) permits quinine to be included in foods. The FSC requires labels of tonic water to state clearly that the product contains quinine, but does not require the quantity to be stated on the label. Maximum levels of quinine permitted by the FSC are 100 mg/kg in tonic and similar drinks, and 300 mg/kg in wines and other alcoholic beverages.

Members noted the comments from the XXXXXXXXX and the XXXXXXXXX which support quinine being included in Schedule 4 only because the evidence for its efficacy for the treatment or prevention of cramps is controversial, and because of a number of articles associating quinine with disseminated intravascular coagulation and haemolytic-uraemic syndrome.

The Office of Complementary Medicines (OCM) advised NDPSC that quinine is one of four main alkaloid constituents (quinine, quinidine, cinchonine and cinchonidine) in the bark of *Cinchona spp* trees, and *Cinchona* bark is employed in traditional herbal medicines. Members noted that there are 31 entries for products containing *Cinchona ssp.* on the ARTG - 27 of them for homoeopathic remedies. All are labelled with indications other than for the treatment of malaria.

The Committee noted the comment from CMEC that if the ADEC review encompasses all of the *Cinchona spp* alkaloid constituents, many more listed products would be affected. For example, the leaf of Olea europaea (Olive) contains the less active alkaloid cinchonine and cinchonidine and appears in 160 products in the ARTG.

Members also noted that the inclusion of quinine in Schedule 4 would preclude the use of *Cinchona spp* in Listed Medicines (unless the quinine concentration was less than 10 mg/kg), as well as the use of Cinchona spp by traditional practitioners.

Two Members advised that they were not aware of any problems with herbal products.

Members considered that the risk/benefit ratio for quinine was such that products containing quinine for the treatment of cramp should be restricted to prescription only. Members also noted the levels of quinine available in foods, particularly tonic water, and that while there had been some reports of tonic water causing thrombocytopenia or provoking repeated attacks, these reports appear to have involved sensitive individuals. Members therefore agreed that products containing quinine with a recommended daily dose of 50 mg or less should be exempted and that this would be consistent with the levels of quinine permitted in foods.

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The Committee agreed to amend the SUSDP by rescheduling quinine to Schedule 4 with an exemption from scheduling for products with a recommended daily dose of 50 mg or less of quinine. The reasons for this decision were:

- that there was no proven benefits for the use of quinine for any condition other than the treatment of malaria.
- there were considerable risks associated with the use of quinine; and
- safe and effective use requires assessment and monitoring by a medical practitioner.

Members noted that as a consequence of this decision the warning statements for quinine in Appendix F were no longer required.

Schedule 4 – Amendment

QUININE – amend entry to read:

QUININE for human internal use **except** in preparations containing 50 mg or less of quinine per recommended daily dose.

Schedule 3 – Amendment

QUININE – delete entry

Appendix F – Amendment

QUININE – delete entry

16. OTHER MATTERS FOR CONSIDERATION

16.1 TEMAZEPAM

PURPOSE

The Committee considered the proposal that temazepam capsules (including gelcaps) be rescheduled from Schedule 4 to Schedule 8 of the SUSDP.

BACKGROUND

Temazepam is a short-acting benzodiazepine which is effective in the treatment of anxiety and insomnia. Temazepam is used as a hypnotic in the short-term management of

insomnia and for premedication before surgical or investigation procedures. Temazepam (Euhypnos, Nocturne, Normison, Temaze, Tentabs) is currently available in both tablet and soft gelatin capsule forms (gelcaps).

Liquid (gel)-filled temazepam capsules are widely abused on the illicit drugs market for iv or ia use, resulting in reports of ischaemia, in some cases necessitating amputation. Similar problems in the UK in the 1990s led to the gelcap formulation being completely removed from the market which is reported to have prevented these harms occurring.

The Australian Drug Evaluation Committee (ADEC) February 2002 meeting recommended to the TGA that the registration of temazepam gel-filled capsules should be cancelled because of the public health safety issues arising from misuse of the capsules. The ADEC advised that the continuing availability of the capsule dosage form, in addition to the tablet dosage form, is outweighed by the emergent risks of injection of capsule contents.

A PBS authority requirement was imposed on 10 mg temazepam gelcaps from May 2002 to restrict PBS prescribing to certain restricted conditions.

DISCUSSION

Members noted that the Australian Pharmaceutical Advisory Council (APAC) has recently received a report in relation to the increasing occurrence of significant adverse events associated with misuse of temazepam gelcaps among injecting drug users (IDUs). Members were advised that the report stated that:

- the IDUs either, bought the gelcaps on the street, or, obtained scripts from doctors. They injected gelcaps because the effect was quicker and more intoxicating. IDUs, used gelcaps as a heroin replacement, or used them to withdraw from other drugs, to deal with stress or psychological distress and/or to sleep.

- a recent survey of benzodiazepine using IDUs in Kings Cross revealed that the majority of respondents injected up to 200 mg in gelcap form on a daily basis. They were all aware of the risks of injecting and most had suffered some complications in the past including abscesses, cellulitis, skin ulcers, nerve damage and distal limb amputation. A number used deep veins in the groin and neck because they could no longer access peripheral veins.

The Committee noted that the September 2003 meeting of the Intentional Misuse of Pharmaceuticals Subcommittee of APAC recommended that temazepam gelcaps (the formulation) be removed from the Australian Register of Therapeutic Goods (ARTGs), given evidence of continuing intravenous injection and the resulting consequence of serious health harm, notwithstanding the PBS authority requirement imposed on 10 mg temazepam gelcaps from May 2002. The Committee were advised that deregistration would have the effect of making the capsules unavailable to the approved indications and that the TGA is in the process of obtaining expert external legal advice as to whether it is

able, under the *Therapeutic Goods Act 1989*, to deregister a product if harm follows deliberate misuse of the sort as described above.

The TGA Principal Medical Advisor proposed that the NDPSC consider rescheduling temazepam capsules from Schedule 4 to Schedule 8.

Members noted the pre-meeting comments from XXXXXXXXX and the XXXXXXXXX which recommended following options (in the order of importance):

i) Voluntary withdrawal by all manufacturers.

ii) Transfer temzepam capsules to Schedule 8.

iii) Transfer temazepam capsules to Schedule 9

iv) Leave in Schedule 4 and introduce a permit system.

v) Cancel the registration of all brands of temazepam capsules from the ARTGs.

vi) Do nothing since the number of Pharmaceutical Benefits Scheme (PBS) dispensing of temazepam capsules dropped markedly following the introduction of the restriction to 'Authority' prescription in May 2002. However, these statistics did not include Repat and Private prescription.

The Committee noted that the XXXXXXXXX had expressed support for all temazepam capsule products to be removed from the Australian market since the readily availability of temazepam tablets provided a satisfactory alternative. The Committee also noted the XXXXXXXXX example of a sponsor who voluntarily withdrew its brand of temazepam capsules from the ARTG in January 2004 for reasons of quality use of medicines and that XXXXXXXXX preferred approach would not be the rescheduling from Schedule 4 to Schedule 8.

The Committee noted the concern expressed by the XXXXXXXXX that a product that has no safety issues when used appropriately may be rescheduled simply because of its potential for misuse. XXXXXXXXX pointed out that:

- Temazepam capsules did not pose any form of risk to the legitimate patient.
- Scheduling should be reserved for determining the appropriate level of access based on the safety profile of the substance and its intended use.
- Scheduling alone will not reduce the supply of temazepam capsules to the injecting user.

Members considered the views of XXXXXXXXX, the only sponsor of temazepam capsules, which objected to any proposed changes to the rescheduling of these products on the basis that:

- usage of temazepam 10 mg capsules (Euhypnos and Normison, 25's) has decreased significantly since the "Authority only" restriction on the PBS. Large pack sizes of 50's and 100's were voluntarily deleted by XXXXXXXXX in 2003 and are no longer available in the marketplace. More time is needed to assess the impact of these changes;

- rescheduling is not an effective way to address any abuse problem. Studies have shown that in the absence of temazepam, illicit drug users will switch to other benzodiazepines (Bobertson JR, 1994. *BMJ* 308 (6936); 1082.). There are also reports of crushed tablet injection, and in one study, the larger particulate size of the crushed tablet blocked the pulmonary artery and resulted in a fatal pulmonary embolus (Vella EJ, 1993. *BMJ* (307); 26.);

- there is no scientific, objective evidence upon which to base any decision of rescheduling. Rescheduling will not address the real problem of abuse and will only disadvantage legitimate patients, prescribers, pharmacists, manufacturers, sponsors and their employees;

- rescheduling of temazepam capsules will set a precedent for dealing with all therapeutic goods that can be abused. Many prescription medicines can cause harm if used outside their registered indications and dosage form recommendations.

- temazepam capsules are safe and effective for their registered indications and routes of administration. Prescribers and pharmacists must take some responsibility to ensure that prescribing and dispensing is limited to legitimate use.

Members noted XXXXXXXXX views, but considered that the continuing problem of significant harm from abuse of temazepam gelcaps needs to be addressed.

The Committee noted that temazepam gelcaps was a relatively cheap product and so considered that the PBS restrictions on prescribing may have only limited impact on the abuse of temazepam gelcaps.

Members noted that abuse was one of the matters which the Committee was required to consider when making a scheduling decision. Members also considered the possibility that banning the product may lead to drug users turning to other products. One Member advised that there was already evidence of this.

One Member suggested that, as there was only one company involved, the company should be approached and asked to consider voluntarily withdrawing the product. The Committee noted that the Chair of APAC had already discussed the matter with the company although Members were not sure of the details of that discussion. One Member offered to discuss voluntary withdrawal of the product with the company.

OUTCOME

The Committee agreed to defer a decision on rescheduling of temazepam gelcaps until the next meeting to allow time to explore the voluntary withdrawal of the product by the sponsor.

INFORMATION ITEMS (PHARMACEUTICALS)

22. AMENDMENTS TO THE SUSDP

22.1 EDITORIAL CHANGES AND ERRATA

22.1.1 MOMETASONE AND MOXIDECTIN

PURPOSE

The Committee considered a request for editorial amendments from XXXXXXXXX regarding the entries for mometasone and moxidectin.

BACKGROUND

The NDPSC 38 Committee meeting agreed to reschedule mometasone to Schedule 2, for the short-term prophylaxis or treatment of allergic rhinitis for up to 6 months in adults and children 12 years of age and over.

The NDPSC 38 Committee meeting agreed to include external use preparations for the treatment of non-companion animals containing 0.5% or less of moxidectin in Schedule 5 of the SUSDP.

DISCUSSION

Members discussed the previous XXXXXXXXX Member's proposed minor amendments to the entries for mometasone and moxidectin. These were the removal of the term 'short term' from the entry of mometasone and the use of a comma in the entry for moxidectin after the word animal.

DECISION 2004/40 - 39

The Committee agreed to amend the entries for mometasone and moxidectin to correct typographical errors. The moxidectin Schedule 5 amendment has been incorporated under Item 6.2.

Schedule 2 – Amendment

MOMETASONE – amend entry to read

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

22.1.2 NZ POISONS INFORMATION CENTRE INFORMATION LINE

PURPOSE

The Committee considered correspondence from XXXXXXXXX advising of the change to the NZ Poisons Information Centre number.

BACKGROUND

NDPSC (Oct 2003) 39 considered the Medicines Evaluation Committee's (MEC) package of warning statements for over the counter (OTC) analgesics for inclusion in Appendix F of the SUSDP.

The Committee discussed the concerns raised in public submissions about the inclusion of the PIC phone number in the proposed new warning statement number 99. Members agreed to include the Appendix E section regarding PIC in the introduction section of Appendix F to allow some flexibility.

XXXXXXXXX advised that the NZ PIC number included in Appendix F is no longer in operation.

DECISION 2004/40 – 40

The Committee agreed to amend the Appendix E and F Poisons Information Centre telephone number entries to remove the inactive NZ phone number. The Appendix F entry was amended editorially as it was included in Amendment 18/3.

Appendix E and F, Introduction –Amendment

Poisons Information Centre Telephone Numbers – amend paragraph to read

Companies should use the poisons information centre telephone number appropriate to the country(ies) of sale for the product, that is Australia or New Zealand or both. These are 13 1126 for Australia and free-call number 0800 764 766 for New Zealand.

Companies wishing to use a poisons information centre telephone number other than the national telephone numbers for Australia and New Zealand in warning statement No. 99 in Part 1 of this Appendix must meet the following criteria:

1. The poisons information service whose number is used must be attended by adequately trained staff for 24 hour emergency poisons information; and
2. Calls must be logged and submitted for incorporation into the official collection of poisoning data.

22.1.3 HALOFUGINONE

PURPOSE

For the Committee to consider a request to delete the entry for halofuginone from Appendix F of the SUSDP.

BACKGROUND

The Office of Chemical Safety (OCS) have advised that they have notes that there is an entry for halofuginone in Appendix F of the SUSDP and as this is a veterinary feed additive it may be deleted. The OCS advised that there is an appropriate entry in the FAISD Handbook.

DISCUSSION

The Committee discussed the proposition from the OCS and agreed that it is an agvet chemical and it should not be included in Appendix F of the SUSDP

DECISION 2004/40 - 41

The Committee agreed to the delete the entry for Halofuginone from Appendix F of the SUDSP.

Appendix F, Part 3 - Amendment

Halofuginone – delete entry

24. ATTACHMENTS

Attachment 1 – Case Reports Of Naphthalene Poisoning (Item 4.2)

ATTACHMENT 2 - CASE REPORTS OF NAPHTHALENE POISONING (ITEM 4.2)

Exposure	Subject Age	Outcome[#]	Ref
Oral Exposures			
Oral, "part of a mothball" (notes 34 cases of poisoning by ingestion)	21 months	acute haemolytic anaemia resolving after several transfusions - Negro, Canada	[i]
Ingestion of 1 or more moth balls	2 years	haemolytic anemia, survived, - race not given, USA	[ii]
Ingestion of half a moth ball	17 months	haemolytic anemia, survived - Negro, USA	[iii]
Ingestion of one moth ball	6 years	haemolytic anemia, survived - Indian, India	[iv]
Ingestion of 1 or more moth balls	2 years, 2 years 2.5 years, 2.25	haemolytic anemia, all survived, - Negro, USA	[v]
Ingestion of moth balls/flakes, (7 cases) Playing where naphthalene products were available (5), wearing treated clothing (2)	1.5-39 mths (mean 23 months)	haemolytic anemia, all survived - USA	[vi]
INHALATION/DERMAL - CHILDREN			
"very small amounts in diapers"	"infants"	haemolytic anaemia - Canada	[i]
Primarily by inhalation from clothes, blankets, diapers etc. Cases occurred in autumn/winter from bedding/clothing stored with mothballs. In many cases no skin contact occurred.	0-39 days	haemolytic anemia, 2 deaths, not all cases were G6PD deficient (9 with normal values), - Greek, Greece	[vii]
Diapers stored with moth balls, rinsed before use but still smelt of moth balls	6 days	Died from haemolytic anaemia - NOT Greek, Italian or other genetically predisposed population, USA	[viii]
Naphthalene impregnated clothing	14 days, 9 days	Haemolytic anaemia, survived. Both G6PD deficient - Negro, USA	[ix]
Naphthalene impregnated clothing	11 days	haemolytic anaemia, survived - Chinese, USA	[x]
Naphthalene impregnated clothing	47 days	twins, haemolytic anaemia, survived - Greek, Australia	[xi]
INHALATION/DERMAL - ADULTS			
naphthalene treated blankets	young adult males (army recruits)	6 cases of severe haemolysis 1 of which was fatal - Greek, Greece	[xii]

[#] In almost all cases treatment consisted of blood transfusions.

[i] Jacobziner, H. (1964) Naphthalene poisoning. *NY State Journal of Medicine*. 64, 1762-1763
[ii] MacGregor, R.R (1954) *Canadian Medical Association Journal*, 70, 313-314
[iii] Zinkham, W.H. & Childs, B. (1958) *Paediatrics*, 22, 461-471
[iv] Santhanakrishnan, B.R., Ranganathan, G & Raju, V.B. *Indian Journal of Paediatrics*, 40, 195-197
[v] Zueler, W.W. & Apt, L. (1949) *Journal of the American Medical Association*, 141, 185-190
[vi] Santucci, K & Shah, B. (2000) *Academy of Emergency Medicine*, 7,1, 42-47
[vii] Valaes, T., Dioxiadis, S.A., & Fessas, P. (1963) *Journal of Paediatrics*. 63, 904-915
[viii] Schafer, W.B. (1951) *Paediatrics*. 7, 172-174
[ix] Dawson, J.P., Thayer, W.W. & Desforges, J.F. (1958) *Blood*, XIII, 12, 1113-1125
[x] Cock, T.C. (1957) *American Journal of Diseases of Children.* 94, 77-79
[xi] Grigor, W.G., Robin, H., Harley, J.D. (1966) *Canadian Medical Association Journal*. 2, 1229-1230
[xii] Younis, D., Veltsos, A., Platakos, Th., & Vafidis, S. (1957) *Archives of the Institute Pasteur Hellinique*, 521