Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

National Drugs and Poisons Schedule Committee

Record of Reasons

54th Meeting
14-15 October 2008

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GLOSSARY

ABBREVIATION	*NAME*
AAN	Australian Approved Name
AC	Active Constituent
ACCC	Australian Competition and Consumer Commission
ADEC	Australian Drug Evaluation Committee
ADI	Acceptable Daily Intake
ADR	Adverse Drug Reactions
ADRAC	Adverse Drug Reactions Advisory Committee
AGRD	Australian Guidelines for the Registration of Drugs
AHMAC	Australian Health Ministers' Advisory Council
APMF	Australian Paint Manufacturers Federation
APVMA	Australian Pesticides and Veterinary Medicines Authority
AQIS	Australian Quarantine and Inspection Service
ARfD	Acute Reference Dose
ASCC	Australian Safety and Compensation Council
ASMI	Australian Self-Medication Industry
ARTG	Australian Register of Therapeutic Goods
BAN	British Approved Name
CAS	Chemical Abstract Service
CHC	Complementary Healthcare Council of Australia
CMEC	Complementary Medicine Evaluation Committee

CMI	Consumer Medicine Information
COAG	Councils of Australian Governments
CRC	Child-Resistant Closure
CRIH	Chemical Review and International Harmonisation
CTFAA	Cosmetic, Toiletry & Fragrance Association of Australia
CWP	Codeine Working Party (NDPSC)
DAP	Drafting Advisory Panel
DPSC	Drugs and Poisons Schedule Committee (now NDPSC)
DPSSC	Drugs and Poisons Schedule Standing Committee (now NDPSC)
DSEB	Drug Safety and Evaluation Branch (now OPM)
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
FWP	Fluorides Working Party
GHS	Globally Harmonised System for Classification and Labelling of Chemicals.
GIT	Gastro-intestinal tract
GP	General Practitioner

HCN	Health Communication Network
INN	International Non-proprietary Name
ISO	International Standards Organization
JETACAR	Joint Expert Advisory Committee on Antibiotic Resistance
LC_{50}	The concentration of a substance that produces death in 50 per cent of a population of experimental organisms. Usually expressed as mg per litre (mg/L) as a concentration in air.
LD_{50}	The concentration of a substance that produces death in 50 per cent of a population of experimental organisms. Usually expressed as milligrams per kilogram (mg/kg) of body weight
MCC	Medicines Classification Committee
MEC	Medicines Evaluation Committee
MOH	Ministry of Health (NZ)
NCCTG	National Coordinating Committee of Therapeutic Goods
NDPSC	National Drugs and Poisons Schedule Committee
NHMRC	National Health and Medical Research Council
NICNAS	National Industrial Chemicals Notification & Assessment Scheme
NOEL	No Observable Effect Level
NOHSC	National Occupational Health & Safety Commission
NPMB	Non-Prescription Medicines Branch
NZ	New Zealand
OCM	Office of Complementary Medicines
OCS	Office of Chemical Safety
ODBT	Office of Devices, Blood and Tissues
OLSS	Office of Laboratories and Scientific Services

OOS	Out of Session
OPM	Office of Prescription Medicines
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
PSC	Poisons Schedule (Standing) Committee (now NDPSC)
PSSC	Poisons Schedule Sub-Committee (now NDPSC)
QCPP	Quality Care Pharmacy Program
QUM	Quality Use of Medicines
RFI	Restricted Flow Insert
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
SVT	First aid for the solvent prevails
TCM	Traditional Chinese Medicine
TGA	Therapeutic Goods Administration
TGAL	TGA Office of Laboratories and Scientific Services

TGC	Therapeutic Goods Committee
TGO	Therapeutic Goods Order
TTHWP	Trans-Tasman Harmonisation Working Party
TTMRA	Trans-Tasman Mutual Recognition Agreement
UK	United Kingdom
USFDA	United States Food and Drug Administration
USA	United States of America
WHO	World Health Organization
WP	Working Party
WS	Warning statement

1.7 PROCEDURAL MATTERS

Nil.

1.8 NDPSC WORKING PARTIES

1.8.1 CODEINE WORKING PARTY INCLUDING CODEINE COMBINATIONS & DEFINITION OF "COMPOUNDED"

PURPOSE

The Committee considered:

- the foreshadowed consideration of codeine / ibuprofen including proposed pack size limits; and
- progress by the Codeine Working Party (CWP) regarding the SUSDP definition of "compounded" and a review of the scheduling of all codeine combinations.

BACKGROUND

The June 2005 NDPSC Meeting discussed the scheduling of codeine / ibuprofen following concern about a bi-layer tablet reportedly being cut in half to access the codeine. Given that the product was reformulated at that time, the Committee agreed that concerns of abuse had been resolved.

The June 2007 NDPSC Meeting noted some pharmacist concern about apparent increasing incidence of codeine / ibuprofen abuse. It was understood that the codeine was being easily separated from the ibuprofen by simple dissolution in water. The Committee asked the TGA to investigate these claims. The February 2008 NDPSC Meeting noted that the results of the TGAL investigation into dissolution were not yet available and therefore agreed to foreshadow consideration at the June 2008 NDPSC Meeting.

The June 2008 NDPSC Meeting considered three related issues: the definition of "compounded"; the abuse potential of OTC compounded codeine; and the specific scheduling of codeine / ibuprofen. The Committee agreed to foreshadow consideration for the October 2008 Meeting of a reduction in the Schedule 2 codeine / ibuprofen pack size limit and to include a Schedule 3 pack size limit. Further, the Committee also decided to form a working party (the CWP) to review the availability of all OTC codeine combination analgesics and the definition of "compounded".

DISCUSSION - SUBMISSIONS

The submissions section has been divided into the following:

- Codeine Working Party

- Pre-meeting comments
- Additional information - definition of "compounded"
- Additional information - codeine scheduling (particularly the ibuprofen combination)
- June 2008 New Zealand Medicines Classification Committee (MCC) Meeting

CODEINE WORKING PARTY

Members noted the following from the Minutes of CWP Meetings to date (1 August 2008 and 16 September 2008).

Terms of reference

- To look at the current definition for the term "compounded", including the genesis of this definition, to make a comparison of definitions used in comparable documents overseas and possible amendment of the current wording.
- To consider the consistency of the cut-offs in terms of current pack size limits, especially when in combination with different active ingredients (e.g. ibuprofen vs. paracetamol).
- In the context of the appropriateness of current scheduling cut-offs, to consider the risks of the potential for abuse with OTC codeine versus the benefits of codeine being available OTC, not excluding other matters listed under 52E.

Recommendations

"Compounded" definition

- That NDPSC note that the CWP was considering the following options but, while generally in favour of option 2, were not in a position to make a recommendation at this time. The opinion of XXXXX was being sought and should allow the CWP to present a recommendation to the February 2009 NDPSC Meeting.
  - **Option 1**: Retention of current definition (noting that the CWP had already agreed that XXXXX did not meet this definition).
  - **Option 2**: Replace the definition of "compounded" in Part 1 with the following (i.e. adopt parts of the UN Convention on Psychotropic Substances 1971 – see below):

    "Compounded" in relation to a substance means combined with one or more other therapeutically active substances in such a way that it ~~cannot be separated from them by simple dissolution or other simple physical means~~ presents no, or a negligible, risk of abuse and the substance cannot be recovered by readily applicable means in a quantity liable to abuse, so that the preparation does not give rise to a public health and social problem.

– Option 2 may be amended following XXXXX feedback. XXXXX was also requested to comment on whether a definition should continue to exist within the SUSDP or if it should instead be picked up through a TGA guideline document.

Codeine scheduling

- That NDPSC note that the CWP was deferring any recommendations regarding the broad issue of codeine scheduling while it sought additional information to properly address the issue of supply of OTC codeine (particularly in terms of risks and benefits). XXXXX. The CWP agreed that, other than correcting inconsistencies, no further recommendations on the scheduling of codeine/ ibuprofen combinations be made until the review was complete.

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PRE-MEETING COMMENTS

Pre-meeting comments were received from XXXXX. Members particularly noted the following points from these comments.

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Codeine Dissolution

- There are distinct differences in the dissolution patterns of paracetamol / codeine and ibuprofen / codeine. These should be taken into consideration in any ongoing discussion of extractability and compounding (i.e. that water extraction of codeine from codeine /ibuprofen combination tablets was a practical method of obtaining codeine, but that this method was less feasible for codeine combinations with paracetamol or aspirin).
- Whilst the British Pharmacopoeia and US Pharmacopoeia do not require codeine dissolution testing, it is the case that individual products registered with TGA do include dissolution testing.

Safety of OTC codeine / paracetamol

- Advice from ADRAC indicates that more than 70 per cent of all ADR entries for paracetamol / codeine are for prescription products. The proportion of remaining ADRs relate that in any way relates to codeine abuse has not been determined. As the concerns regarding codeine / ibuprofen relate to OTC availability it was asserted that any comparison of ADRs for paracetamol / codeine against ibuprofen / codeine should exclude prescription products or those ADRs not specifically related to codeine abuse i.e. there is far less concern regarding OTC paracetamol / codeine products than has sometimes been implied.
- Asserted that any proposed study looking at the incidence and issues associated with codeine abuse should differentiate the varying strengths of codeine combinations and the manner in which they are accessed in order to be relevant.

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General issue of codeine

- Noted with appreciation that no final decision was made by the June 2008 NDPSC Meeting and welcomed the proposal to form the CWP. Also reconfirmed support of various points from their June 2008 comment including:
  - Information presented so far did not amount to a prima facie case justifying further consideration. Interested parties, including industry, have not had access to the information and thus cannot comment on its credibility. The Committee should ensure that it "hears all parties" and that the matters considered under section 52E should not be confined to (e) "dosage / formulation" and (g) "potential for abuse".
  - It was ready to discuss practical ways to limit or avoid misuse of ibuprofen / codeine products, should the Committee find evidence to justify this.
- Reiterated criticism of the quality of the pre-June 2008 evidence (i.e. lacked probative value, being largely anecdotal / untested (nor testable because of its anonymous nature)).
- Accepted that there was data before the June 2008 NDPSC Meeting "that in the interim there was evidence that abuse/misuse was occurring", but noted that the Record of Reasons did not disclose if the various matters reported were in any way tested in regard to validity, integrity, robustness or ability to be extrapolated to population levels. It is not possible to conclude that the evidence before the Committee amounts to regulatory failure which could justify the foreshadowed scheduling actions. In particular asserted:
  - that the views attributed to jurisdictional members was hearsay at best;
  - that it was impossible to know who reviewed what "23 cases" and whether the report had been peer reviewed; and
  - that the same could be said for the other anomalised statements.
- Asserted that the critical issue was evidence demonstrating the magnitude and nature of the risks and the extent of abuse of codeine combinations. An understanding of these issues would dictate the appropriate actions to be taken.

Foreshadowed ibuprofen / codeine proposal

- The Committee should establish, by a robust and transparent process, the risks and benefits of its foreshadowed action to limit pack sizes. Consideration of the foreshadowed proposal, if taken before the Committee has the CWP's findings, would be pre-emptive.
- A restriction on pack sizes may not necessarily be appropriate once the evidence has been properly assessed. The evidence of abuse appears to be restricted to specific and small patient subpopulations and it was not clear how pack size restrictions would benefit these groups. Medical intervention and / or other regulatory measures may deliver better public health outcomes. It would also be difficult to monitor the

success of any intervention if the problem it was intended to curb was not adequately quantified at the outset.

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- Codeine / ibuprofen is a target for obtaining large amounts of OTC codeine for direct abuse, not for diversion to produce morphine or diamorphine.
- Noted that there was one non-prescription combination that contained more codeine than XXXXX being XXXXX, which is only available in small packs and is in Schedule 3. XXXXX was unaware of inappropriate use of or excessive demand for this product.
- Considered that currently registered OTC ibuprofen / codeine should be Schedule 3 for ≤ ~50 tablets (with no Appendix H listing, it being wholly inappropriate to advertise substances that are known to be abused) and Schedule 4 above this. If this were to take place, there would be considerable pressure to demand that paracetamol / codeine and aspirin / codeine be identically scheduled to provide for a level commercial playing field. However, the evidence to date does not indicate that there was an issue with the latter two combinations under the current scheduling arrangements.

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Recommendations

- No change to the pack size limits or scheduling of OTC ibuprofen / codeine.
- That there be transparency in the sharing of information upon which decisions are based and the process by which decisions are made, including the activities of the CWP. New data being gathered on the incidence / risk of codeine usage should be taken into account.
- Any response to the risk of potential misuse / abuse of OTC ibuprofen / codeine should be appropriate in scale and nature, and not likely to impact adversely on the health of the community or result in inconvenience and hardship to the majority of consumers.
- If any changes are made to the scheduling of OTC ibuprofen / codeine the changes should apply equally to other OTC codeine combinations at the same time.

Discussion

- Agreed that the potential risk of misuse / abuse of OTC codeine existed and asserted that they were committed to being actively involved in addressing the issue. Asserted, however, that the currently available data indicate that levels of misuse and abuse were low and there was no convincing evidence that it was increasing. Any response to this issue should be founded upon robust data and reliable evidence.

- Contended that, in the absence of data demonstrating that more than a small minority were at risk of the potential side-effects of very large quantities of ibuprofen, it was inappropriate to deny the majority of the community the opportunity to decide on the level of pain relief most appropriate for them.
- Asserted that a balanced response to a real, however small, problem could include specific action at the point of sale to minimise the risks of misuse / abuse, whilst maintaining continued access to OTC codeine combinations. The focus should be on education and responsible promotion.
- This submission discussed the following in detail:
  - **pack size limits** - The potential impact of the changes foreshadowed in relation to pack size limits for codeine / ibuprofen combinations;
  - **extent of misuse / abuse of OTC ibuprofen / codeine** - Further evaluation of the issue is required;
  - **risk / benefit** - Balancing the level of risk of misuse and abuse of OTC codeine combinations against the needs of the overall community;
  - **reducing the potential risk of misuse / abuse** - The non-steroidal anti-inflammatory drug (NSAID) / codeine label requirements are in the process of being updated to (new wording highlighted): "Do not use for more than a few days at a time unless a doctor has told you to. Keep to the recommended dose. Excessive use can be harmful.";
  - **company response to potential risks from OTC ibuprofen-codeine** - Educational programmes, commissioning of research, marketing ethically and responsibly. Advised that it intended to undertake a Pharmacy Education Programme and the commissioning of an independent prospective epidemiological study to better understand the potential and incidence for misuse / abuse;
  - **collaboration** - Advocated collaboration in the formulation and implementation of a response to the risk of misuse / abuse.

XXXXX

- Reiterated its June 2008 suggestions for mitigating any ongoing problems from misuse of codeine / ibuprofen:
  - **jurisdictional uniformity**: Consistency and uniformity across all jurisdictions must become a priority and need to apply to all aspects including scheduling as well as any guidance or recommendations issued by pharmacy boards. Other issues requiring uniformity include storage criteria and the handling by pharmacists such as mandatory Schedule 3 recording of sales;
  - **limit large pack sizes**: As codeine combination products are mostly intended for short term therapy, the availability of larger pack sizes can be more restrictive;

- **revise the codeine content for Schedule 2**.

- Asserted that there is a need to investigate issues relating to all codeine combinations before making any significant decisions affecting codeine / ibuprofen. Also asserted that codeine / ibuprofen must continue to be available OTC for short term management of stronger pain.
- It also sought to be involved in the CWP. XXXXX .
- Asserted that public awareness and education remain a priority to better inform about the appropriate use of short term analgesics and intentional / unintentional misuse of codeine.
- Was concerned that currently there is no system to capture evidence and reporting of misuse of codeine combinations in a consistent and coordinated manner. Reliance has been on anecdotal reports by community pharmacists relating to purchasing patterns and trends by consumers and other 'alerts' based on reports of presentations at hospitals.
- The pharmacist intervention required when a consumer makes frequent or large quantity requests can be complicated because this could be intentional or unintentional misuse. It is more difficult to provide advice to those who are misusing intentionally. Consequently the approach taken by pharmacists is to limit or deny the sale of the product.
- Intentional misusers of codeine who prefer the ibuprofen combination are usually concerned primarily with obtaining the codeine and are either not well informed about possible GI side effects or consider them merely an inconvenience of remote importance.
- Reiterated its June 2008 assertion that the Illicit Drug Reporting System report showed that the codeine preparations identified as being most commonly used (in an illicit sense) were predominantly paracetamol combinations.

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Recommendations

- That the current scheduling of ibuprofen / codeine be maintained.
- Uniformity of ibuprofen / codeine controls across all States and Territories should be addressed prior to consideration of scheduling (i.e. pack size). In particular there is a NSW variation which allows packs of 72 ibuprofen / codeine to be sold as Schedule 2.

Discussion

- Asserted that ibuprofen / codeine should be available OTC as it is often needed quickly to alleviate moderate short term pain.

- Noted that the potential for misuse / abuse of codeine was not limited to ibuprofen combinations. All codeine products, including prescription only products, should be examined as a class.
- Asked that their earlier comments be re-examined should the Committee revisit these issues (see below).
- Did not believe that the evidence set out in the June 2008 NDPSC Record of Reasons adequately established a pattern of abuse of these products in the Australian community.
- Assumed that the CWP will have the opportunity to appropriately gather and evaluate concrete evidence as it exists, rather than give unwarranted value to hearsay, media sensationalism and flimsy surveys.
- Asserted that public education initiatives are key to improving consumer medicine behaviour and was working to develop a national program that will educate consumers regarding appropriate analgesic use, including potential risks associated with using OTC analgesics (particularly codeine) for longer than recommended periods. Asserted that, together with an enhancement of robust supply protocols, staff education and simple interventions, this will be more effective in promoting quality medicine use than the foreshadowed pack-size scheduling changes.
- Noted that a number of June 2008 comments suggested that ProjectSTOP could be extended to apply to ibuprofen / codeine. While this may be a possible application of the technology, the regulatory, privacy and administrative challenges it presents would deter the sector applying this measure as an initial response.
- Commented on matters raised in the June 2008 Record of Reasons including:
  - "*NSAIDs are among the leading sources of ADRs in Australia and the rest of the world*". While the potential for gastrointestinal (GI) adverse events is well known in NSAIDs, the risk of ibuprofen inducing GI adverse events is significantly lower than other commonly used NSAIDs. Asserted that it is now thought ibuprofen has a similar risk of inducing GI adverse effects to paracetamol.
  - "*Although the majority of the information presented to date had been individual case reports, this was likely to be the result of the lack of appropriate reporting systems rather than the absence of a problem of misuse*". Given the media coverage one would imagine that there would be an associated increase in ADRAC reporting. ADRAC reporting is dependant on the health professionals consulted following the reaction rather than the regulation that surrounds the supply of the medicine. Asserted that it was therefore unwise and dangerous to presume that adverse outcomes from overuse of ibuprofen / codeine were under reported.
  - "*Photographic evidence was provided of price promotion and large, publicly accessible dump-bin amounts of codeine and ibuprofen combinations being available in certain pharmacies*". Notes that this was concerning and inconsistent with the direction the industry was taking. Price promotion in community

pharmacies is guided by the Price Information Code (enforceable in Queensland and NSW) and the ASMI Code of Practice. Pharmacists engaging in unprofessional conduct are accountable to the pharmacy board in their jurisdiction. Standard 4 in the Quality Care in Pharmacy Program (QCPP) guides the promotion and advertising of medicines and prohibits goods being sold in a manner which promotes excessive or inappropriate use.

XXXXX

- Asserted that codeine combinations must remain available as OTC medicines. These are safe and effective when used appropriately and pharmacists are both suitably trained and best placed to manage their supply.
- Supported the formation of the CWP.
- Noted that all available OTC products containing ibuprofen are required to be labelled with "Do not use for more than a few days at a time unless a doctor has told you to. Do not exceed the recommended dose. Excessive use can be harmful.".
- Given that all ibuprofen products were only intended for short term use, asserted that restrictions should be placed on the pack sizes of Schedule 3 codeine / ibuprofen - 48 dosage units was suggested (i.e. enough for a patient to be treated for eight days at the recommended maximum dose). Imposing a Schedule 3 pack size limit in the order of 24 dosage units would be too restrictive at this point in time.
- Suggested that new sub-entries to be created in the Schedule 3 codeine entry individually specifying each "single non-opiate analgesic substance" with which codeine is currently compounded (i.e. aspirin, ibuprofen and paracetamol). In this case the Schedule 3 pack size limit for codeine / paracetamol and codeine / aspirin should initially be 100 dosage units (subject to review should evidence emerge suggesting abuse of these combinations).
- Asserted that the safety of the public would be better served by excluding codeine / ibuprofen from Schedule 2. This could be achieved by specifying paracetamol / aspirin as the single non-opiate analgesic substances with which codeine may be combined under the existing Schedule 2 entry.
- Furthermore, it was noted that there appeared to be differences in the scheduling of these combinations across the various jurisdictions and regarded harmonisation as an essential component of this review process.

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Recommendations

- All Schedule 2 codeine combinations stored behind the counter; and
- All Schedule 3 codeine supplies recorded as a prescription if, after discussion between patient and pharmacist, safety and therapeutic need are established.

Discussion

- Limiting pack sizes will change little as long as these Schedule 2 products remain accessible for self-selection. Asserted that as long as the check out system for self selected Schedule 2 and unscheduled ibuprofen products continues, patients will continue to die from GI bleeds and suffer renal failure.
- Asserted that pharmacists have to be serious about Schedule 3 control i.e. must have a serious patient interview and properly record all supplies so that consumption can be monitored despite changes in the duty pharmacist. Deliberate abusers know when stricter pharmacists are on duty and when assistants rotate.
- Asserted that there was a myth that ibuprofen was harmless.

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- Ibuprofen / codeine had been his pharmacy's worst 'problem product' for several years. Despite practising a 'high professional intervention' style of pharmacy and placing these products in a position designed to assist the pharmacist observe people selecting them, until recently has struggled to control sales to those suspected of overusing.
- Noted that extraction of codeine from codeine / ibuprofen is simple and details are easily found on the internet.
- Undertook a 3 month project monitoring codeine / ibuprofen sales and can advise:
  - ~ 80 per cent of sales were to regular long-term users without their doctors' knowledge (i.e. not consistent with Schedule 2 use). Up to half of these were potentially for recreational purposes – this being the proportion of monitored sales made by a group who would take it in turns to present at the pharmacy or ask other people to do the same. The addresses of the ringleaders were known to local police as premises where drug dealing had taken place and on occasions these 'mules' were observed handing their codeine / ibuprofen purchases to these ringleaders.
  - One individual was quite open about abusing codeine /ibuprofen, mistakenly believing (because the product was Schedule 2) that it was harmless and that the pharmacist was not legally able to prevent their sale.
- In response this pharmacy ceased carrying the 72 tablet packs (which contain 12 days supply and are therefore not consistent with non-prescription supply in any case) and treated the sales of all other pack sizes as Schedule 3 (keeping them out of sight of the public and requiring the pharmacist to personally sanction all sales). This has resulted in the improved opportunity to informally monitor sales and counsel patients, greater prescriber knowledge of 'long-term' use of codeine / ibuprofen Plus by patients, and a substantial reduction in sales to 'long-term chronic' users.
- Noted that the success in using Schedule 3 provisions to control sale of these Schedule 2 products has relied heavily on being the only pharmacy in a 43,000 km2

local government area and therefore on more than 95 per cent of customers being regular users of the pharmacy with virtually no opportunity to 'shop around' for products.

- For the vast majority of pharmacies, it would not be feasible to exercise the necessary level of 'sales control' simply by making these products Schedule 3. For most pharmacies to realistically control sales of these widely misused products, it will require making them Schedule 3 Recordable and making them subject to 'Project STOP' monitoring. Making them Schedule 3 is, therefore, the very minimum measure required.

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Recommendation

- Make packs of ≤ 12 Schedule 2, packs ≤ 24 Schedule 3 and bigger packs Schedule 4 (if stocked at all). If a person is getting these products on a regular basis they should see their doctor for a script.

Discussion

- Advised that there was a significant abuse problem of codeine / ibuprofen in her area. As a consequence the 72 packs were no longer stocked.
- Advised that a customer had asked this pharmacist to limit her supply of codeine / ibuprofen due to a problem with codeine addiction. At least 4 other customers are being counselled on a regular basis who also have a problem with this combination.
- Was concerned that the current controls would see many more people present with perforated ulcers or kidney disease.

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Recommendation

- Changes need to be made to the scheduling of ibuprofen / codeine. Pharmacists come under considerable pressure to supply this combination and at the moment there is little to back up pharmacist's advice that use should be short term only.

Discussion

- Has a pharmacy located in a remote rural setting which has been an excellent position from which to observe the problem of ibuprofen / codeine abuse (i.e. no other pharmacy for 200 km).
- Become aware of particular individuals overusing ibuprofen / codeine in late 2006 / early 2007. These individuals followed similar patterns, usually presenting every 1-2 days for 24 packs in an attempt to avoid contact with the pharmacist. During the same period the pharmacy also had many customers being treated by a doctor for pain who were using large amounts of OTC pain relievers but were more upfront about

their usage. These customers often requested supply with time frames inconsistent with safe usage but were more easily managed regarding this.

- In early 2008 the pharmacy decided to record sales of all ibuprofen / codeine as well as large packs of paracetamol / codeine (though these were causing far fewer problems). Ibuprofen / codeine sales decreased significantly after instituting these recording procedures. Pharmacy staff have referred significant numbers of patients to GPs for review or denied further supply because of overuse and inappropriate use of ibuprofen / codeine. Recording all sales of ibuprofen / codeine has allowed earlier detection of inappropriate use and has found most customers to be unaware of the potential problems of long term or inappropriate use of codeine (despite current warnings on packaging).
- Longer term and resistant customers have proved more difficult to treat presumably because of significant addiction, mixed messages sent by large pack sizes (like 48 and 72) and lack of recording in all pharmacies.
- Asserted that the pharmacy was only seeing the "tip of the iceberg".

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ADDITIONAL INFORMATION – DEFINTION OF "COMPOUNDED"

"Compounded" is a term which is only used in the SUSDP in reference to narcotic substances when combined with another, non-opiate, analgesic substance. This allows, under Schedule III of the *Single Convention on Narcotic Drugs 1961* (Single Convention), for certain preparations of narcotics to be supplied in a less restrictive (i.e., other than Schedule 8) manner. When first adopted, the Single Convention set down the following in Schedule III as conditions for when opiates may be exempted:

(a) *compounded with one or more other ingredients in such a way that the preparation has no, or negligible, risk of abuse, and in such a way that the drug cannot be recovered by readily applicable means or in a yield which would constitute a risk to public health; and*

(b) *containing not more than 100 milligrams of the drug per dosage unit and with a concentration of not more that 2.5% in undivided preparations.*

In 1966, subparagraphs (a) and (b) were deleted and replaced by "*When compounded with one or more other ingredients and containing not more than 100 milligrams of the drug per dosage unit and with a concentration of not more than 2.5% in undivided preparations*". That is to say, the public health qualifications of negligible risk, recovery by readily applicable means and yields constituting a public health risk were all removed. While this may have been because none of these terms were defined in Article 1, such an amendment does not exclude a signatory from applying its own interpretation of "compounded" as it deems appropriate.

Article 3 of the Convention on Psychotropic Substances 1971 states the following in relation to exempted substances: "*If a preparation containing a psychotropic substance other than a substance in Schedule I is compounded in such a way that it presents no, or a negligible, risk of abuse and the substance cannot be recovered by readily applicable means in a quantity liable to abuse, so that the preparation does not give rise to a public health and social problem, the preparation may be exempted from certain of the measures of control provided in this Convention in accordance with paragraph 3*." It should be noted that this Convention was adopted five years after similar wording was removed from the Single Convention.

The inclusion of a definition of "compounded" in the SUSDP was first agreed at the August 1991 Meeting. The current definition is:

"**Compounded**" in relation to a substance means combined with one or more other therapeutically active substances in such a way that it cannot be separated from them by simple dissolution or other simple physical means".

Members also noted the following definitions of "compounded" in use by various jurisdictions.

- New Zealand: *Misuse of Drugs Act, Third Schedule, Class C, Part VI* "Compounded with one or more other pharmacologically active ingredients in such a way that the substance cannot be recovered by readily applicable means or in a yield which would constitute a risk to health."
- Queensland: *Health (Drugs and Poisons) Regulation 1996* "Compounded, for a substance combined with a therapeutically active substance, means the way the substances are combined prevents their separation by simple dissolution or in another simple physical way".
- Victoria: *Drugs, Poisons and Controlled Substances Act 1981* "Compound in relation to a poison or controlled substance means a medicament prepared in accordance with a formula and being a combination of-
  - a poison or controlled substance; and
  - any other substance or substances - in such a way that the poison or controlled substance cannot be readily separated from the other substance or substances, and to compound and derivative expressions have corresponding meanings;".
- No other States or Territories define "compounded" in relevant Acts or associated regulations. However, these jurisdictions may pick up the SUSDP definition through adoption by reference to Part 1.
- USFDA legislation does not define "compounded", except in relation to positron emission tomography drugs. The UK's Medicines and Healthcare products Regulatory Agency and the European Medicines Agency do not define the term "compounded" in legislation. However, definitions may be contained in tertiary documents, as it is in Australia (i.e. the SUSDP).

- Health Canada has advised that it does not have a definition for “compounded” that reflects the intent of the UN Convention. However, Section 36 of Canada’s Narcotic Control Regulations authorizes the “compounding” or dispensing of certain preparations containing codeine by pharmacists in the absence of a prescription, and Canada believed these measures were in line with the intent of the UN Convention’s requirements.

Members also recalled the following from Members discussion at the June 2008 NDPSC Meeting.

- Members recalled that Australia is a signatory to the UN Single Convention on Narcotic Drugs and, unless in a preparation that meets the definition of "compounded", codeine falls into Schedule II of the Convention and therefore into Schedule 8.
- The original concern brought to the Members attention regarding codeine / ibuprofen combinations was whether or not they fit the SUSDP definition, particularly in relation to ‘simple dissolution’. The Committee agreed that there was an issue of formulation and compliance with the SUSDP definition.
- A Member stated that, given the dissolution testing, there was now reasonable evidence that currently available codeine / ibuprofen formulations might not comply with Schedules 2 or 3 conditions. Another Member stated, however, that the Committee scheduled substances, not products, and the issue of whether a product was compliant with a particular schedule was a matter for the sponsor and the registration authority.
- A Member put forward that, as there were differing definitions of "compounded", it was reasonable for the Committee to set aside consideration of this matter until the issue of the definition of "compounded" could be investigated further.

Members also noted the following points from comments to the June 2008 NDPSC Meeting.

- Several comments asserted that, as codeine was more soluble than all simple analgesics, it was possible that all codeine combinations would be Schedule 8. A comment asserted that this was not in the best interest of the Australian public and it was a matter of public health that these combinations remain available OTC. Another comment asserted that a better approach to address the issue of appropriateness of the physical properties of a particular formulation was an issue for the regulator to address.
- A comment noted that using methods to reduce the solubility of codeine may affect a product’s ability to meet the TGA’s dissolution requirements.
- A comment put forward that developing an objective definition for the term “compounded” was not an effective way of discouraging illicit diversion. Criminals be likely to find more sophisticated ways of extracting the substance.

- Another comment asserted that a clear and unambiguous statement regarding the definition of "compounded" was required.
- Several comments asserted that the issue of compounding was a secondary consideration to the concerns surrounding potential abuse as it did not appear that extraction of codeine was the preferred means by which the implied abuse was occurring.
- It was asserted that while the definition of "compounded" was intended to protect the community, up-scheduling of all codeine containing analgesics would place an undue burden on the healthcare system.

ADDITIONAL INFORMATION – CODEINE SCHEDULING (PARTICULARLY THE IBUPROFEN COMBINATION)

The following considerations were on the assumption that the “compounded” definition issue could be resolved.

Members recalled the following points from XXXXX advice to the June 2008 NDPSC Meeting.

- Dissolution testing of various codeine combinations found that the dissolution of paracetamol was relatively similar to that of codeine. Aspirin / codeine combinations showed a greater disparity between products (due to differences in formulation); however the dissolution profile of aspirin was still such that the bulk of it was dissolved at a similar rate to the codeine (except in one product). Ibuprofen, however, was easily separated from codeine by dissolution in water at room temperature, with only 10 per cent of the ibuprofen dissolving compared with ~90 per cent of the codeine. It was noted that this difference in dissolution profiles could further be manipulated by lowering the pH (ibuprofen has a very low solubility below pH 6).
- Conclusion that water extraction of codeine from codeine / ibuprofen was a practical method of obtaining codeine, but that this method was less feasible for paracetamol / codeine or aspirin / codeine.

Members also recalled the following points from Members discussion at the June 2008 NDPSC Meeting.

General issue of Codeine

- A Member noted that many people who abuse combination codeine products did not attempt to separate the codeine from the other analgesic. Another Member pointed out that people also access codeine inappropriately as a Schedule 4 medicine. Another Member recalled the WHO analgesic ladder and stated that the vast majority of the population did seem to get benefit from access to OTC codeine combinations.
- It was agreed that a review of the availability of all codeine combinations was warranted to look at the broader issues relating to the supply of codeine, rather than focussing on codeine / ibuprofen alone.

Codeine / ibuprofen

- The Committee agreed that the issue of misuse / abuse of codeine / ibuprofen was only a segment of the overall issue. The Committee agreed that, in the interim, there was evidence that abuse / misuse was occurring with codeine / ibuprofen and that, pending the full review of the scheduling of codeine, consideration of limiting Schedule 2 and 3 pack sizes of codeine / ibuprofen combinations be foreshadowed for consideration at the October 2008 Meeting.
- A Member stated that, as mentioned in several submissions, there was little evidence that police and other law enforcement agencies were aware of a problem relating to the abuse / misuse of codeine / ibuprofen. Another Member stated that this problem may well be hidden as there was little or no illegal activity involved, i.e., was being obtained and used legally, albeit in excessive amounts. The Member stated that the data provided to the Committee by medical practitioners working in the field of addiction medicine suggested that the problem was real and causing significant harm.
- It was noted that industry submissions had shown that ADR monitoring data did not appear to show significant problems or an increase in reports for codeine / ibuprofen despite widespread use and increase in sales. However, a Member noted that this may be due to reporting mechanisms for ADRs not being routinely used for OTC products.
- A Member noted that the number of tablets taken (from case reports) seemed to correlate with available pack sizes. Considering the combination was indicated for temporary relief of pain, the maximum allowable pack size could be reduced without inconvenience.
- It was noted that in two jurisdictions all codeine combinations, both Schedule 2 and 3, were required to be kept behind the counter, away from self selection aisles. However, this was not the case for other jurisdictions and it was recalled that the NSW scheduling for codeine combinations allowed the larger pack sizes to be sold as Schedule 2.
- A Member felt that rescheduling codeine / ibuprofen to Schedule 3 might be the best way to maintain the balance between legitimate users being able to access the substance, while providing pharmacist intervention to help to reduce the amount of inappropriate use. The Committee considered that including the combination in Schedule 3 might not prevent people from pharmacist shopping.
- The Committee noted that there may be alternative methods of creating a product formulation available which can be used to either increase the solubility of the ibuprofen or decrease the solubility of the codeine component in these combination products. For example the codeine component may be able to be chelated to reduce its solubility or the ibuprofen component micronised to increase its solubility.
- The Committee also noted jurisdictional advice on the abuse / misuse of codeine, including a suggestion that, as the problem was with the codeine causing dependence

and, thus, overuse, the Committee really should look at the inappropriate use of all codeine combinations rather than focusing on codeine / ibuprofen alone.

Members also noted the following points from comments to the June 2008 NDPSC Meeting:

Abuse / misuse risk

- A comment asserted that the scale of homebake production was relatively small and, regardless, it was unlikely that the matter at hand had anything to do with issues of diversion. However, several comments agreed that there was likely to be low levels of misuse of all codeine analgesics, including the ibuprofen combination.
- A comment noted that use of codeine / ibuprofen combinations at the recommended dose and duration (i.e., short term) was not habit forming and prolonged use of the combination was not considered appropriate without medical supervision. Patients using this medication regularly should be referred to medical care for investigation of the underlying cause of their pain.
- Several comments asserted that anecdotes of misuse were infrequent and unverifiable and that it had proven difficult to quantify the extent of the problem. Several comments asserted that media reports of misuse appeared to have been sensationalised. Another comment asserted that while some studies looking at the potential for misuse of OTC codeine had identified that this may occur, all had concluded that patient and physician education or further research into the issue was required.
- Several comments reported cases of codeine / ibuprofen misuse causing serious GI injuries or electrolyte disturbances, including one detailed review of 23 serious cases attributed to exposure to high doses of ibuprofen. A comment asserted the profile and behaviour in these cases was unlike other illicit drug users in that most patients started taking the combination for its approved indications and then self-escalated to doses above those recommended.
- A comment stated that, while there had been a significant increase in sales of these combinations, there had seemingly been no increase in the amount of ADRs reported. It was contended that the level of ADRs for codeine / ibuprofen was no greater than for codeine / paracetamol. Several comments asserted that the small number of anecdotal reports of codeine / ibuprofen misuse causing serious ADRs only occurred after gross misuse.
- A comment asserted that, while there was little evidence that appropriately used OTC codeine combinations cause adverse events, codeine / ibuprofen was particularly open to misuse due to high codeine content and the lack of toxicity in overdose when compared to codeine / paracetamol.
- A comment noted that the Australian Medicines Handbook states that codeine should be prescribed only with extreme caution to patients with a history of drug abuse or dependence, alcoholism, emotional instability. A comment suggested that for this

patient group ready access to OTC codeine may make it difficult for them to control their medication use without risk. Additionally, such patients are often reluctant to disclose or discuss their problems.

- A comment advised that a similar issue (availability of OTC codeine) was considered by the UK Committee on the Safety of Medicines in 2005. The recommendation of that Committee was that codeine remain available as an OTC combination, that warning statements be established for product labels and that there be agreement on responsible promotional activities.
- A new warning statement was noted that required OTC NSAIDs to be labelled with "Do not use for more than a few days at a time unless a doctor has told you to. Keep to the recommended dose. Excessive use can be harmful". This would be on codeine / ibuprofen from October 2008.

Benefit

- Several comments asserted that codeine / ibuprofen is an important part of the OTC range of analgesia options. Availability as OTC was appropriate to the management of a range of short-term conditions which may otherwise require unnecessary medical intervention. A comment asserted that, as the type of pain this combination was indicated for was often acute, it must be attended to quickly to avoid adverse outcomes and allow people to function in their daily lives.
- A comment advised that the current Therapeutic Guidelines for analgesics state that 30 mg of codeine phosphate is required for an analgesic effect and 2 tablets of a current codeine / ibuprofen combination contained only 25.6 mg codeine phosphate. The comment also asserted that several international guidance documents state that doses of codeine below 30 mg were likely to be ineffective. However, addiction to codeine can still occur at lower doses.
- A comment noted that both codeine and ibuprofen are well tolerated at therapeutic doses and the use of any substance in excessive quantities would cause ADRs. A comment asserted that the Committee had previously determined that the risk / benefit profile of ibuprofen was such that it was suitable for general sale and that the risk / benefit profile of codeine was such that it is contained in many different Schedule 2 medicines.

Role of Pharmacist

- A comment asserted that pharmacists have a duty of care role and are ideally placed to detect of purchasing patterns which may imply inappropriate medicine use. If detected pharmacists (and staff) should refuse sale and refer the patient to a medical practitioner.
- A comment asserted that, as pharmacists play a key role in helping to educate patients about their medications and providing appropriate access to them, an education campaign specifically targeted at codeine / ibuprofen combinations could be developed, rather than scheduling the combination more restrictively.

- A comment discussed whether it was fair to expect pharmacists to have to identify drug seeking behaviour and thus deny access to such persons. Many of these patients do not fit the stereotypical profile of a drug dependant person.

Advertising

- A comment noted that there had been concerns about the level of advertising of codeine / ibuprofen. The comment asserted that all advertisements for such products have been approved through the correct channels and that in-store promotions and TV advertising adhere to the ASMI code of practice. It was also asserted that there was no evidence that TV advertising leads to short-term sudden peaks in consumption and purchasing patterns are generally consistent. It was also stated that it was not practice to support price discounting on large packs of codeine / ibuprofen.
- Codeine / ibuprofen has a long history of use and sales of the products had remained stable for the last 12 months, despite heavy advertising. It was also stated that an increase in sales did not equate to an increase in abuse.

Opposing scheduling changes

- A comment asserted that determining whether these products are Schedule 8 based on differences in dissolution rates of the actives would not be a sensible outcome as ibuprofen / codeine was clearly intended for the management of short-term, self-limiting conditions.
- Several comments asserted that making codeine / ibuprofen prescription only would inconvenience the great majority of consumers who use this combination as recommended while 'protecting' only a small number from potentially causing themselves harm. A number of general public comments also requested that codeine / ibuprofen should not be Schedule 8 as it would place an undue burden on legitimate users.
- A comment asserted that the impact on the public health system, should this combination not be available OTC, would be significant, putting more strain on emergency departments and general practitioners.
- A comment asserted that an education campaign would be a better approach. Another comment asserted that any upscheduling of ibuprofen / codeine could push the small minority of abusers to maintain their habit with the much more toxic codeine / paracetamol or codeine / aspirin combinations.
- Several comments opposed scheduling change because of an asserted lack of data. It was asserted that, with little evidence other than anecdotal reports, it was illogical to further restrict the public's access to a clinically effective treatment which would also create an unnecessary burden on the public health system. One comment asserted that there was not even enough evidence to justify further enquiry into the matter.
- Generally, a number of stakeholders have commented that the Committee does not have sufficient evidence in front of it to amend the scheduling of OTC compounded codeine. Subregulation 42ZCN(c) of the *Therapeutic Goods Regulations 1990* states

that the Committee is not bound by rules of evidence. Further, the following excerpt is taken from the NDPSC v Roche judgement in relation to making decisions in the absence of any new data:

- *"… the functions of the Committee include making decisions in relation to the classification and scheduling of substances. Nothing in the Act or the Regulations suggests that, having made a scheduling decision, the Committee becomes functus officio [having performed its office] with respect to that substance unless and until new data about the risks and benefits of using the substance become available… it is appropriate for the Committee to monitor the impact of decisions made by it under s 52D(2) and, provided that it follows the procedures mandated for scheduling decisions, to reconsider earlier decisions as it deems appropriate. Moreover, the Committee is not bound by the rules of evidence and may obtain information about an issue in any way it deems appropriate (reg 42ZCN)."*

Support for scheduling change

- Several comments suggested that ensuring uniform scheduling across all States and Territories for OTC codeine may be an appropriate initial response to any misuse.
- Several comments asserted that the current controls on codeine / ibuprofen combinations had failed to control misuse / abuse.
- Several comments suggested limiting pack size:
  - A comment noted that the numbers of tablets taken per day seemed to correlate with pack size. Pack size reduction, especially the 72 dose pack, may need to be considered given the indication is for temporary relief of pain.
  - A comment suggested revising the upper limit of codeine for Schedule 2. Other comments suggest moving all Schedule 2 ibuprofen / codeine to Schedule 3. Several comments also suggested a pack size limit also be applied (i.e. 12 dosage units).
  - A comment recommended that codeine / ibuprofen combinations should be rescheduled to Schedule 4 and that pack size should be limited to 18 tablets.
- A number of other options were mentioned limiting codeine content, monitoring access via a program similar to Project Stop, movement of stock out of self-selection areas and increased recording requirements on sales.

Other suggestions

- Several comments stated that an education campaign to pharmacists and pharmacy staff about the misuse of codeine may be warranted. A company advised that it intended to develop an eduction program for all pharmacy staff which would help educate consumers about their pain, how to manage it appropriately and what to do if it persists and also to identify consumers showing drug seeking behaviour and help them to manage such situations.

JUNE 2008 NEW ZEALAND (MCC) MEETING

Members noted the following from the June 2008 MCC consideration of codeine in OTC combination products:

Recommendation

- That combination medicines containing < 15 mg of codeine / dose unit (and which comply with all other requirements for pharmacy-only sale) should be reclassified from pharmacy-only medicines to prescription medicines.

Other MCC conclusions

- Further consultation should be undertaken prior to the next MCC meeting about suitable cut-off points and pack size limits for pharmacy-only and restricted medicine levels of access based on the following proposal for codeine combination products:
  - Pharmacy-only: ≤ 12 mg codeine / dose unit in packs of ≤ 50 with a maximum recommended treatment period of 7 days.
  - Restricted: > 12 mg and ≤ 15 mg codeine / dose unit in packs of ≤ 25 doses.
  - Prescription: > 15 mg codeine / dose unit.

  It was assumed that these cut-offs all relate to anhydrous codeine content, rather than codeine phosphate content.
- Lower pack size limits for prescription medicine classification would be established after upper limits for pharmacy-only and restricted medicines had been finalised.
- Pharmaceutical companies should be asked to provide package information about rebound headaches and about the potential for addiction.
- Pharmacy professional bodies and pharmacy marketing groups should be notified that it is inappropriate to display codeine-containing products in dump bins and the Pharmacy Council should be asked to provide guidance to pharmacists about the display of these products.

Other discussion

- The initial concerns related to codeine were those of abuse and misuse. While manufacture of homebake appeared to have peaked in the 1990s and had been largely superseded by other drugs of abuse, there appeared to be a growing number of cases of intentional abuse of codeine in combination products containing ibuprofen or paracetamol. There was also evidence of unintentional abuse due to increasing doses in order to maintain a desired effect or for attempted control of rebound headache.
- Members noted that differences in metabolism meant some people experienced much greater effects from codeine than others.
- While it was possible to take large quantities of codeine in combination with ibuprofen, similar quantities of codeine in combination with paracetamol would lead to hepatotoxicity and likely death. However, it was noted that there had been

instances of deaths which were believed to have been attributed to consumption of codeine in combination with ibuprofen.

- It was also noted that there had been problems associated with babies who were breastfed by mothers taking codeine at recommended doses for postnatal pain.
- The Chairman of the MCC reported that Australia was keen to establish a framework with small packs being sold at pharmacy-only level and larger packs at a more restrictive level of classification. The October 2008 NDPSC Meeting noted that while individual opinions to this effect arose at the June 2008 NDPSC Meeting, no such conclusion was reached by the Committee at that time.
- In Britain there had been voluntary control on pack sizes. The upper limit had been reduced to 32 tablets and information on rebound headaches and potential for addiction was included in the product information.
- It was agreed that there was insufficient information at this stage to make a recommendation about cut-off levels for OTC sale and that more information should be sought prior to the next meeting. The proposal for cut-offs (see above) were intended to elicit responses about cut-off points from sponsor companies and other parties. However, it was agreed that a maximum of 15 mg / dose unit or 30 mg per recommended dose should be applied immediately as an upper limit for OTC sale. Recommended doses and dose units above this level should be classified as prescription medicines.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The relevant matters under section 52E (1) relevant, to this item, included (b) risks and benefits; (d) extent and patterns of use; (e) dosage and formulation; (f) need for access; and (g) potential for abuse.

"Compounded" definition

The Members noted that the current definition of “compounded” was problematic. A Member noted that while no uniform definition had been adopted internationally, the general intent of the Single Convention (and thus the definition of “compounded”) was management of diversion, rather than individual overuse. The Member therefore supported the CWP’s ‘Option 2’ wording, as this replaced the current, inflexible criteria with a more outcomes based standard, in line with the original intent of the UN Single Convention.

The Committee generally agreed that consideration of the “compounded” definition should be gazetted for the February 2009 NDPSC Meeting, as it was likely that the CWP’s final recommendations on this issue will be tabled at that time.

Codeine scheduling

With regard to the foreshadowed consideration of ibuprofen / codeine pack size, a Member noted that the pre-meeting comments included proposals that could be considered at this Meeting. The Committee generally agreed, however, that any changes could have significant impact on the Australian market and that it would be more appropriate to await completion of the CWP's review before coming to a decision. A Member also raised a concern that if ibuprofen / codeine pack sizes were restricted in isolation, abuse might shift to other combination codeine products.

On the issue of scheduling of codeine, a Member supported the CWP's intent to seek further data but noted that it may be that there may be little additional data to be found. Should the CWP find this to be the case, then the Committee would need to proceed on the basis of the currently available data.

The New Zealand Member advised that when the issue of OTC codeine pack sizes was considered in New Zealand, it was clear that the currently available data was limited. The Committee agreed, however, that the case reports already provided to it (and, through the Record of Reasons, to the public) were valuable and should not be dismissed as either insubstantial or inconclusive. Furthermore, randomised controlled trials are used to evaluate efficacy and safety, but are not appropriate for determining abuse potential.

A Member suggested that perhaps the CWP could seek access to a specific data set, such as the Hunter Area Toxicology Service database, to obtain additional case reports.

A Member additionally asserted that there was evidence (primarily case reports) before the Committee that OTC products were currently causing real harm. The Member felt that the Committee needed to consider whether this constituted a public health risk requiring immediate action, rather than an issue that could reasonably be delayed, pending further data collection and analysis by the CWP.

The Committee agreed that the issue of codeine scheduling should be deferred, pending advice from the CWP XXXXX. A Member asserted that it needed to be made very clear that the Committee had not necessarily determined that the current scheduling was appropriate, but rather, that the Committee needed to attempt to obtain further data in order to inform any decision it might make on this issue.

Several Members noted that in reviewing the risks of OTC codeine, there should also be a review of the asserted benefits of OTC codeine. A number of Members raised the point that little published data on efficacy of codeine at doses less than 30mg was available. However, the Committee noted that questions of efficacy were for the regulator and should not be a primary consideration of the Committee when scheduling, given that it is not specifically one of the provisions of 52E.

A Member asserted that the issue of consistency across the jurisdictions on supply controls, raised in a number of submissions, was not a matter for NDPSC but should be noted by the Jurisdictional Members.

A Member separately noted that there had been some public confusion with respect to allowable amounts of codeine in Schedule 2 and 3. The SUSDP schedule entries relate to codeine base (i.e., anhydrous codeine) but most products are labelled in terms of codeine phosphate, the salt most commonly used in Australia (e.g. 15 mg of codeine phosphate is equivalent to ~ 11.7 mg of codeine base).

RESOLUTION 2008/54 - 5

The Committee:

- noted the CWP's progress on the definition of "compounded", including the likelihood of recommendations being tabled for consideration at the February 2009 NDPSC Meeting on that issue;
- agreed to defer consideration of ibuprofen / codeine pack sizes until the CWP had progressed further while noting the importance of resolving this issue without undue delay; and
- XXXXX.

1.9 PROPOSED ROUTINE CHANGES TO THE SUSDP

Nil.

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

2.1 SUSDP, PART 1

2.1.1 INTERPRETATION OF AEROSOL CONCENTRATION IN THE SUSDP

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

2.1.2 REVIEW OF REFERENCES IN THE SUSDP

PURPOSE

The Committee noted updates to references to publications and organisations included in SUSDP No.23.

BACKGROUND

As a result of the judgement in the *Roche vs NDPSC* matter, new editions of and amendments to the *Poisons Standard* (the SUSDP and its Amendments) have been determined to be legislative instruments and as such are required to be registered on the Federal Register of Legislative Instruments (FRLI).

Following the June 2008 NDPSC Meeting, advice was received from the TGA Office of Legal Services (OLS) that references in a legislative instrument must be up-to-date and specific to a particular version before it is registered on the FRLI.

OLS has also advised that wording to the effect "as specified or amended from time to time" is only appropriate to use in an Act. All subordinate legislation and quasi legal documents (such as the SUSDP) must use full titles (including publication dates) when referencing.

The Secretariat therefore undertook a review of all references to publications contained in the SUSDP No.23. The Secretariat also took the opportunity to review references to organisations.

DISCUSSION - SUBMISSIONS

The Committee agreed that:

- it did not need to consider amendments to references where these involved an update to current versions/nomenclature and/or straight forward editorial amendments; and
- such amendments are to be undertaken by the Secretariat without consideration by the NDPSC, but should be submitted to NDPSC Meetings for information as SUSDP editorial items.

The Committee noted that a number of references to publications and organisations would be updated to include the current version and/or correct nomenclature.

With regard to the Poisons Information Centre (PIC), the Committee considered the inconsistent wording used in the references to the PIC. The Committee agreed that there should not be a mandate in all references to use the Australian and New Zealand national PIC telephone numbers, although these should be included in the reference as examples. The Committee agreed that all references to PIC, with the exception of Appendix E – Introduction, Appendix F – Introduction and Appendix F – Part 1, warning statement 99,

are to be worded 'a Poisons Information Centre (e.g. phone Australia 131 126; New Zealand 0800 764 766)'.

With regard to the entry 'chemistry sets' in Appendix A, the Australian Standard referenced had been superseded and the Secretariat was yet to determine the correct replacement Standard. The Committee agreed that the Secretariat would make the necessary amendments to the reference without further consideration by the Committee.

With regard to the reference *Required Advisory Statements for Medicine Labels(September 2008)* (RASML), the Secretariat sought legal advice as to whether an entry under Part 1 – Interpretation could include the full title and version of a reference with subsequent references referring to the title as defined in Part 1 – Interpretation, but without including the version. Legal advice confirmed that this approach was appropriate. The Committee agreed that the Secretariat would make the necessary amendments to the reference without further consideration by the Committee.

With regard to the *Australian Code for the Transport of Dangerous Goods by Road or Rail Sixth Edition* (ADG Code)*:*

- the Australian jurisdictional representatives confirmed that their respective State/Territory adopted this Code. As such, these Members noted that this reference source would be included in the SUSDP when referencing 'Dangerous Good of Class 5.1 (oxidising substances)'; and

- the Secretariat sought legal advice as to whether an entry under Part 1 – Interpretation of the SUSDP could include the full title and version of a reference with subsequent references referring to the title as defined in Part 1 – Interpretation, but without including the version. Legal advice confirmed that this approach was appropriate. The Committee agreed that the Secretariat would make the necessary amendments to the reference without further consideration by the Committee.

With regard to "approved name" under Part 1 – Interpretation, the Committee was asked to consider whether or not the inclusion of all the reference sources was still warranted. The Committee agreed to defer consideration until February 2009 pending advice from the TGA, APVMA and NICNAS.

RESOLUTION 2008/54 – 6

The Committee:

- noted the review of the references to publications and organisations in SUSDP No.23 and that a number of references would be amended to reflect the current title/version/nomenclature;
- agreed to delete inappropriate wording from references in line with advice;

- agreed to amend references to 'Poisons Information Centre' for clarity and consistency, except for when included at Appendix E – Introduction, Appendix F – Introduction and Appendix F, Part 1 – warning statement 99.
- agreed to defer consideration of "approved name" under Part 1 – Interpretation until February 2009;
- agreed that in the future the Secretariat would make any necessary 'editorial' amendments to references with referral to the Committee only for its information.

PART 1, INTERPRETATION – NEW ENTRY

"Australian Code for the Transport of Dangerous Goods by Road and Rail" means the sixth edition of the document of that name.

PART 1, INTERPRETATION - AMENDMENTS

"Appropriate authority" - Amend entry to read:

"Appropriate authority"

(a) in the Australian Capital Territory, ACT Health;

(b) in New South Wales, the Director-General of New South Wales Health;

(c) in the Northern Territory, the Chief Health Officer of the Department of Health & Families;

(d) in Queensland, the Chief Executive of Queensland Health;

(e) in South Australia, the Chief Executive of the Department of Health;

(f) in Tasmania, the Secretary of the Department of Health and Human Services;

(g) in Victoria, the Secretary to the Department of Human Services;

(h) in Western Australia, the Chief Executive Officer of the Department of Health.

"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 the Australian Standard AS 1928-2007 entitled *Child-resistant packaging – Requirements and testing procedures for reclosable packages* (ISO 8317:2003, MOD);

(b) a closure approved by an 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 AS 1928-2007 entitled *Child-resistant packaging – Requirements and testing procedures for reclosable packages* (ISO 8317:2003, MOD);

(b) is reclosable and complies with the requirements of at least one of the following Standards:

(i) the International Organization for Standardization Standard ISO 8317:2003 entitled *Child-resistant packaging – Requirements and testing procedures for reclosable packages*;

(ii) the British Standards Institution Standard BS EN ISO 8317:2004 entitled *Child-resistant packaging - Requirements and testing procedures for reclosable packages*;

(iii) the Canadian Standards Association Standard CSA Z76.1-06 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 blister or 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 entitled *Child-resistant packages.*

"Non-volatile content" – Amend entry to read

"Non-volatile content" in relation to a paint or tinter means that portion of a paint or tinter determined to be the non-volatile content by Method 301.1 of Australian Standard AS 1580-301.1-2005 entitled *Paints and related materials – Methods of test – Non-volatile content by mass.*

"Required Advisory Statements for Medicine Labels" – Amend entry to read

"Required Advisory Statements for Medicine Labels" means the document of that name, as published by the Therapeutic Goods Administration in September 2008.

subparagraph (2)(k) - Amend entry to read:

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

PART 2, LABELS AND CONTAINERS – AMENDMENTS

subparagraph 7(1)(d) – Amend entry to read:

(d) if the poison is a dry chlorinating compound containing more than 10 per cent of available chlorine, **except** for preparations certified by a relevant State or Territory authority as not being a Dangerous Good of Class 5.1 (oxidising substances) as specified in the *Australian Code for the Transport of Dangerous Goods by Road and Rail*, with the cautionary statement –

FIRE AND EXPLOSION HAZARD

written:

(i) on a separate line or lines immediately below the cautionary statement "KEEP OUT OF REACH OF CHILDREN" as required by sub-paragraph 7(1)(c); and

(ii) in bold-face sanserif capital letters of uniform thickness; and

(iii) in letters at least four tenths the height of the letters used for the signal word or words; and

(iv) with nothing, other than a Class label as specified in the *Australian Code for the Transport of Dangerous Goods by Road and Rail*, written on the same line;

subparagraph 7(1)(h) – Amend entry to read:

(h) if the poison meets the criteria for a 'flammable liquid' in the *Australian Code for the Transport of Dangerous Goods by Road and Rail*, with the cautionary statement –

FLAMMABLE

written on the main label in bold-face sanserif capital letters of uniform thickness, unless already present in accordance with the requirements of the *Australian Code for the Transport of Dangerous Goods by Road and Rail Rail;*

subparagraph 13(2) – Amend entry to read:

(2) is labelled in accordance with the *National Occupational Health and Safety Commission's National Code of Practice for the Labelling of Workplace Substances* [NOHSC: 2012 (1994)].

Paragraphs 21 and 21a **–** Amend entries to read**:**

21. If a poison, other than a Schedule 5 poison, is sold or supplied in a container with a nominal capacity of 2 litres or less, the container must comply with Australian Standard AS 2216-1997, entitled *Packaging for poisonous substances***.**

21a. Notwithstanding subparagraph 21, a poison which is in Schedule 6 and is an essential oil may be packed in an amber glass container which does not comply with the tactile identification requirements of Australian Standard AS 2216-1997, entitled *Packaging for poisonous substances,* if:

(1) the other safety factors are not diminished; and

(2) the container has a restricted flow insert and a child-resistant closure.

subparagraph 22(1) – Amend entry to read:

(1) comply with sub-section 1.4 (General Requirements) of Australian Standard AS 2216-1997 entitled *Packaging for poisonous substances*; and

subparagraph 23(1)(b)(i) – Amend entry to read:

(i) comply with sub-section 1.4 (General Requirements) of Australian Standard AS 2216-1997 entitled *Packaging for poisonous substances,* excluding paragraph 1.4.3;

paragraph 24 – Amend entry to read:

24. Notwithstanding sub-paragraphs 21, 22 and 23 a poison may be packed in a container that does not comply with the tactile identification requirements of Australian Standard AS 2216-1997 entitled *Packaging for poisonous substances* or the requirements of paragraphs 22(2) or 23(1)(iii) if:

(1) the other safety factors are not diminished;

(2) the container is for a specific purpose; and

(3) an appropriate authority has approved the use of the container for that purpose.

paragraph 27 – Amend entry to read:

27. The tactile identification or embossing required by paragraphs 21, 22 or 23 of this Standard or Australian Standard AS 2216-1997 entitled *Packaging for poisonous substances* do not apply to a container that is an aerosol container, a collapsible tube, or a measure pack which is a flexible sachet.

PART 4, THE SCHEDULES

SCHEDULE 6 - AMENDMENT

GLYCOLIC ACID – Amend entry to read:

GLYCOLIC ACID (including its salts and esters) in cosmetic products or when packed and labelled for use as an agricultural chemical **except**:

(a) in cosmetic preparations for salon use only which are labelled in accordance with the *National Occupational Health and Safety Commission's National Code of Practice for the Labelling of Workplace Substances* [NOHSC:2012 (1994)];

(b) in preparations containing 5 per cent or less of glycolic acid; or

(c) in preparations containing 20 per cent or less of glycolic acid with a pH of 3.5 or greater.

PART 5 – APPENDICES

APPENDIX E, PART 1 - AMENDMENTS

Standard Statements – Amend entries to read:

Basic

A For advice, contact a Poisons Information Centre (e.g. phone Australia 131 126; New Zealand 0800 764 766) or a doctor (at once).

Z First aid is not generally required. If in doubt, contact a Poisons Information Centre (e.g. phone Australia 131 126; New Zealand 0800 764 766) or a doctor.

Eyes

E2 If in eyes, hold eyelids apart and flush the eye continuously with running water. Continue flushing until advised to stop by a Poisons Information Centre (e.g. phone Australia 131 126; New Zealand 0800 764 766) or a doctor, or for at least 15 minutes.

Skin

S2 If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water. Continue flushing with water until advised to stop by a Poisons Information Centre (e.g. phone Australia 131 126; New Zealand 0800 764 766) or a doctor.

S3 If on skin, remove any contaminated clothing, wash skin thoroughly with soap and water, then methylated spirit if available. Contact a Poisons Information Centre (e.g. phone Australia 131 126; New Zealand 0800 764 766) or a doctor.

S4 If on skin, immediately remove any contaminated clothing, wash skin with methylated spirit or PEG (polyethylene glycol) 300 or 400 if available, then flush under running water until advised to stop by a Poisons Information Centre (e.g. phone Australia 131 126; New Zealand 0800 764 766) or a doctor.

S5 If skin contact occurs, immediately remove contaminated clothing. Flush skin under running water for 15 minutes. Then apply calcium gluconate gel. Contact a Poisons Information Centre (e.g. phone Australia 131 126; New Zealand 0800 764 766).

Special Purpose

SP1 If swallowed, splashed on skin or in eyes, or inhaled, contact a Poisons Information Centre (e.g. phone Australia 131 126; New Zealand 0800 764 766) or a doctor at once. Remove any contaminated clothing and wash skin thoroughly. If swallowed, activated charcoal may be advised. Give atropine if instructed.

APPENDIX F, PART 3 - AMENDMENTS

POISON	WARNING STATEMENTS	SAFETY DIRECTIONS
Chlorinating compounds – subparagraph (g) – Amend entry to read**:**		
(g) 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), as specified in *the Australian Code for the Transport of Dangerous Goods by Road and Rail* **except** in preparations for use in toilet cisterns only, containing 15 g or less of trichloroisocyanuric acid.	10,22	12,13,14,15, 17,18,19,21
Dichloroisocyanurates - subparagraphs (e), (h), (j) – Amend entries to read:		
(e) in dry preparations 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), as specified in *the Australian Code for the Transport of Dangerous Goods by Road and Rail.*	10,18,22	1,4,8,12,13,14, 15,16,17,18,19, 20,21,22,26
(h) 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), as specified in *the Australian Code for the Transport of Dangerous Goods by Road and Rail* **except** in preparations containing 21 g or less of sodium dichloroisocyanurate for use in toilet cisterns only.	10,22	12,13,14,15,17, 18,19,21

(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) as specified in *the Australian Code for the Transport of Dangerous Goods by Road and Rail* in preparations containing 5 g or less of sodium dichloroisocyanurate for use in toilet bowls only.		
	(i) during storage	10,22	12,13,14,15,17, 18,21
	(ii) during use	5	1,4,7,12

2.2 SUSDP, PART 2

Nil.

2.3 SUSDP, PART 3

2.3.1 SCHEDULES 5 & 6 STORAGE STATEMENTS

PURPOSE

The Committee noted progress by the working group developing a draft Code of Practice for National Retail Storage of Schedule 5 and Schedule 6 Products.

BACKGROUND

Having agreed with a STANZHA (State/Territory and New Zealand Health Authorities) recommendation to include a paragraph in Part 3 – Miscellaneous Regulations of the SUSDP relating to retail storage of Schedule 5 and Schedule 6 poisons, the October 2005 NDPSC Meeting deemed that further consultation with stakeholders was necessary. The issue of Schedule 5 and Schedule 6 storage statements was subsequently discussed at the February, June and October 2006 NDPSC Meetings. The October 2006 NDPSC Meeting agreed to establish a working group to develop a draft guidance document on minimising access by children to Schedule 5 and Schedule 6 products in the retail setting.

The February 2007 NDPSC Meeting considered the progress of the working group and agreed that the working group would continue developing the draft code in consultation with States/Territories and that industry was encouraged to move forward on this issue. Members further agreed to seek legal advice as to whether the Committee could adopt such a code.

The October 2007 NDPSC Meeting noted a draft code and was advised that States and Territories had provided some feedback. That Meeting agreed to a number of changes to the draft Code, including a preamble that it was a hierarchy of control and that each dot point option was equal in their effectiveness. The Committee agreed to open the draft to public consultation until late March 2008. The working group could then consider and incorporate suggested changes into the draft Code. A copy of the draft Code was made available on the NDPSC website (http://www.tga.gov.au/ndpsc/drs5s6cop.htm).

At the June 2008 NDPSC Meeting, the Committee noted that large industry organisations had not responded to the public consultation process for the draft code, and hence there was a need to recontact these key stakeholders. The Committee noted some editorial comments proposed by Members, in particular the observation by the working group that the scope of the draft Code had an explanation statement for Schedule 5 products but not for Schedule 6 products. The Committee also discussed the way forward on this matter, particularly considering that there was, as yet, no agreement by States and Territories regarding whether compliance with the code meant compliance with State and Territory legislation. The working group was charged with developing a discussion paper with a series of questions on implementation aspects for States and Territories to respond to before further consideration by the Committee.

DISCUSSION - SUBMISSIONS

The Committee was informed that the working group had held a teleconference on 8 October 2008 and formulated the following set of questions for consideration by jurisdictions:

- If the Code goes beyond your current jurisdictional legislative requirements, could the Code be introduced without a regulatory impact statement? If not, would you be willing to undertake such consultation, and how long would that take? Would you also require a legislative change? If so, would you be willing to undertake such a change, and how long would that take? How could it be otherwise referenced in your jurisdiction? If it was referenced in SUSDP only, could it be used as a compliance tool in your jurisdiction?
- If the Code does not meet the prescribed requirements of your current legislation, could it be used as a compliance tool in your jurisdiction? If so, would referenced in the SUSDP be sufficient? If not, could it be otherwise referenced? If not, would you require a legislative change, and if so, would you be willing to undertake such a change and how long would that take?

The Committee also noted that the June 2008 pre-meeting comments from XXXXX had been formally considered by the working group and resultant recommended changes had been incorporated in the draft Code. The Committee additionally noted the following comments made by the working group while developing this new draft Code:

- It was inappropriate to make recommendations on the outstanding issue of whether the Code should include Schedule 5 products at this stage (pending response from the jurisdictions).
- Based on jurisdictional differences there appeared to be two circumstances: Those in which the Code went beyond the jurisdictional legislation and those in which the Code did not meet the prescribed requirements of the jurisdictional legislation.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The following matter under 52E(1) was considered particularly relevant to this consideration: (i) any other matters that the Committee considers necessary to protect public health i.e. restricting access of children to Schedule 5 and 6 poisons in a retail setting.

A Member noted that the issue of Schedule 5 and Schedule 6 storage initially arose from industry concerns but, given the lack of engagement in the recent consultation on the draft Code, industry appeared to no longer be interested. In response, other Members noted that industry had been patient and cooperative and had played its part and that it was now up to the jurisdictions to progress this matter.

A Member indicated that while XXXXX supported the prevention of children from accessing Schedule 5 and Schedule 6 poisons, XXXXX was unlikely to adopt the code or to consider changes to current XXXXX legislation.

A Member indicated that South Australia would pick-up the code by reference if it were included in the SUSDP but would want the Code to cover Schedule 5 and Schedule 6 poisons, noting that this appeared to be in line with industries original push for harmonisation across Australia. A Member suggested that the questions devised by the working group should also include a question on whether the draft Code should apply to Schedule 5 and Schedule 6 poisons or whether it should be restricted to Schedule 6 poisons only.

A Member indicated that in order for Victoria to adopt the code it would need to conduct a Regulatory Impact Statement (depending on how the Code was referenced by the SUSDP) and would need evidence that the Code would be effective. However, if the Code was included in the SUSDP i.e. as an Appendix, then it would be incumbent on Victoria to adopt it. It was noted that if the Code could be added as an Appendix, this may make it easier to legislate in some other jurisdictions as well.

XXXXX emphasised the need for formal responses from the jurisdictions to all the questions and entreated the jurisdictions to canvas all ideas on how to adopt the Code in their response in order to progress this issue. Members were reminded that if the Committee cannot get agreement then there will not be national consistency. Another Member strongly encouraged the States and Territories to consider a flexible code.

The Committee agreed that the current version of the draft Code available on the TGA website should be replaced by the more recent version incorporating the working group's recommended changes.

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The Committee noted progress of the working group and also noted a commitment by jurisdictions to provide written responses to the working group's questions to the Secretariat as a matter of urgency.

2.4 SUSDP, PART 5

2.4.1 APPENDIX A – LEACHING OF POISONS

PURPOSE

The Committee considered the application of some Appendix A general exemptions to products where poisons may leach into food.

BACKGROUND

There are a number of Appendix A general exemptions which may apply to tableware type products that would come into contact with food – ceramics, glass (including crystal ware), glazed pottery, porcelain and vitreous enamels. There is also an entry for "fritted glazing or enamelling preparations". However, this exemption is constrained by the requirement that "the poison is confined as a non-migratory component" (i.e. if the poison can leach out the product would not qualify for the Appendix A).

The June 2008 NDPSC Meeting considered the application of some Appendix A general exemptions (for ceramics, glass (including crystal ware), glazed pottery, porcelain and vitreous enamels) when in products where poisons may leach into food. The Committee decided to defer consideration of these Appendix A general exemptions to allow time for additional information to be sought.

History of these entries in Appendix A

The December 1965 Poisons Schedule Sub-Committee (PSSC) Meeting proposed a list of general exemptions (which included ceramics, vitreous enamels and glazes). The February 1971 PSSC Meeting agreed to include the "list of exemptions" in the SUSDP. No discussion or reasoning for inclusion on the list was given.

The August 1973 PSSC Meeting considered lead hazards from pottery glazes and agreed to amend the "glazes" entry in the "list of exemptions" to "glazed pottery". The Committee also agreed to a new entry in the then Appendix A (equivalent to the current Appendix F) for glazing preparations containing lead compounds "Unless adequately

fired, utensils glazed with this preparation must not be used as containers for food or beverages; to do so may cause lead poisoning". This is still the current Appendix F entry, but only applies to glazing preparations containing scheduled levels of lead, not to glazed pottery which is covered by the Appendix A exemption.

The February 1991 Drugs and Poisons Schedule Standing Committee (DPSSC) Meeting agreed that all types of "clay-ware" (pottery, ceramics and porcelain) should have Appendix A exemptions (noting that pottery and ceramics were already covered). The Committee also agreed that glassware should be covered, as glass often contained a scheduled poison (e.g. lead in crystal).

DISCUSSION - SUBMISSIONS

The release of lead (Pb) and cadmium (Cd) limits under Section 5 of AS/NZS 4371:1996 *Ceramic Tableware* are:

	Pb (mg/L)	**Cd (mg/L)**	**Pb (mg/dm^2)**	**Cd (mg/dm^2)**
Flatware	-	-	0.8	0.07
Hollow-ware	4.0	0.3	-	-

Section 4E (Importation of glazed ceramic ware) of the *Customs (Prohibited Imports) Regulations 1956* reads:

(1) The importation into Australia of an article of glazed ceramic ware of a kind normally used for or in connexion with the storage or consumption of food is prohibited if the article is an article of a kind specified in an item in Schedule 7* and, when tested with the prescribed solution in accordance with the method specified in that item (in column 3), releases to the solution lead or cadmium in an amount per volume of solution in excess of the amounts of lead and cadmium per volume of solution respectively specified in that item (in columns 4 and 5).

(2) For the purposes of sub regulation (1), the prescribed solution is a solution consisting of four per centum by volume of glacial acetic acid in water, being water that conforms with British Standard 3978 published on 18 February 1966.

*The limits in Schedule 7 to the *Customs (Prohibited Imports) Regulations 1956* basically reflect those in Queensland's table of former leaching limits for heavy metals discussed below.

Members recalled that the June 2008 NDPSC Meeting's decision to defer consideration was to allow time for the following additional information to be sought:

- what were the current State and Territory controls for leaching;
- whether the leaching issue should be addressed in regards to: lead and cadmium only; other specific substances of concern (e.g. other heavy metals); or all scheduled poisons;
- was there jurisdictional support for either: adopting specific sections of AS/NZS 4371:1996; the (different) lead and cadmium limits in the Customs (Prohibited

- Imports) Regulations; or specific cut-off values for lead and cadmium in the Appendix A entries (in which case, what value should be used).

Members noted the following from jurisdictional responses:

Current Controls for leaching

South Australia (SA)

- There is no specific reference to leaching in the controlled substances legislation. The *Controlled Substances Act 1984* allows the Minister to prohibit any substance / device that should not be sold etc., pending the evaluation of its harmful properties. The Minister must then refer this to the Controlled Substances Advisory Council. This mechanism is not practical or appropriate for dealing with leaching of poisons from products exempted under Appendix A. The means used to deal with the specific case of lead leaching from imported tagines was for the Minister for Consumer Affairs to declare these to be dangerous goods pursuant to section 25 of the *Trade Standards Act 1979*. The limits for release of lead or cadmium referred to in the declaration were those specified in section 4E of the *Customs (Prohibited Imports) Regulations 1956*.

Queensland

- No controls (other than a general requirement under the *Food Act 2006* that "equipment" must not be sold if it would be likely to make food unsafe). XXXXX

Victoria

- The *Drugs, Poisons and Controlled Substances Act 1981* does not include provisions to control leaching of poisons. Control of leaching from consumer products is through the Consumer Affairs Victoria (CAV) Product Safety Section. CAV have instituted bans on a number of consumer products containing lead including candle wicks, painted chopsticks and children's toys (the lead in toy's ban was consistent with the ban through the Commonwealth Australian Competition and Consumer Commission (ACCC)). There are also standards for lead and cadmium in the Food Standards Code adopted under the *Victorian Food Act 1984*. Provisions in the Food Act prevent the sale of equipment used to prepare food that would render that food unsafe.

New South Wales (NSW)

- No specific controls for leaching of poisons from food/drink containers in NSW legislation. There used to be a "public health" requirement for cooking utensils, but this was removed when the Public Health Act was reviewed some years back and now appears to rely on the controls through the Customs Import Regulations. The NSW Office of Fair Trading has the capacity to ban such products, but require expert opinion to determine which levels are dangerous. XXXXX. The ACCC also has this on a list of standards to be explored for possible insertion under the Trade Practices Act in the next 12 months or so.

Tasmania

- The Tasmanian Office of Consumer Affairs (OCA) does not pick up AS/NZS 4371:1996. Advice XXXXX was that lead/cadmium in ceramic tableware was a consumer affairs issue and not a Poisons Act matter. The OCA acts collaboratively where the ACCC or State / Territory offices have identified a problem that is then considered by the State Product Safety Committee which can make a recommendation for the Minister to institute a ban under the Sale of Hazardous Goods Act. If there was seen to be a significant problem a proposal could be put to the ACCC for adoption of AS/NZS 4371 under the Trade Practice Act, ensuring a uniform approach.
- Appendix I is adopted separately from the Poisons Act under the Public Health Act and there is no provision for the exemptions made in Appendix A. Therefore action could be taken where ceramic work paints contain cadmium or lead above the Appendix I limits.

Should the leaching issue be addressed in regards to lead and cadmium only?

Summary of SA, Queensland, Tasmania

- Lead and cadmium only. It was noted that there are applicable standards in relation lead and cadmium leaching from ceramics and tableware. It was also asserted that there was no evidence that leaching of other scheduled poisons was a public health issue.

Victoria

- The history of Appendix A suggests that certain products were not seen as appropriate to be regulated through the scheduling system. Many of the entries, including the tableware type products, are consumer products and not designed with the primary function of being a delivery mechanism for scheduled poisons. Victorian drugs and poisons legislation is about regulating supply and use of drugs and poisons rather than regulating the safety of consumer products such as pottery. CAV and ACCC have dealt successfully with instances (apparently uncommon) of leaching of lead from consumer products in the past and have the networks and mechanisms to institute bans and recalls. They seem to have this type of product safety issue in hand. There are also controls on leachable lead on imports through Australian Customs import regulations. Given this, Victoria was not convinced that leaching controls for lead, cadmium or other substances from consumer articles currently exempt under Appendix A should be implemented through the SUSDP.

NSW

- As lead and cadmium seem to be the substances of main concern in this regard, and as there are at least 2 accepted test methods for these, it would be appropriate to address these substances at least.

Support for adopting a specific section of AS/NZS 4371:1996 *Ceramic Tableware*.

SA

- Supported adopting section 5 *Limits of release of lead and cadmium*.

Queensland

- Had no preference. However, supported the June 2008 SA statement "…it would be necessary for experts e.g. NICNAS/OCS to advise on the most appropriate lead and cadmium limits (in collaboration with Customs)".
- Queensland also provided the following table of the former XXXXX Queensland leaching limits for heavy metals (cadmium and lead) XXXXX:

Description of article	**Liquid capacity**	**Cd (mg/L)**	**Pb (mg/L)**
cooking utensils (glazed ceramic ware)		0.7	7.0
cooking utensils (other)		0.7	7.0
food receptacle (glazed ceramic ware):			
(a) hollow ware	≥ 1100 ml	0.2	2.0
(b) hollow ware	< 1100ml	0.7	7.0
(c) flat ware	any	2.0	20.0
food receptacle (other)		2.0	20.0

- XXXXX had raised the issue of "tightening" these requirements to reflect ISO6486-2:1999 *Ceramic ware, glass-ceramic ware and glass dinnerware in contact with food – Release of lead and cadmium – Part 2: Permissible limits*, including reducing the allowable lead level in small hollow ware from 7 mg/L to 2 mg/L and in large hollow ware from 2 mg/L to 1 mg/L.
  Members noted that ISO6486-2:1999 set limits for the release of lead and cadmium from ceramic ware, glass-ceramic ware and glass dinnerware intended to be used in contact with food and beverages (preparation, cooking, serving and storage of food and beverages) but excludes articles used in food manufacturing industries or those in which food is sold. It also excluded porcelain enamel articles. This version superseded the 1981 version which, as mentioned in the preface to AS/NZS 4371:1996, was the version that in part informed the development of AS/NZS 4371:1996, together with BS 4034:1990 *Specification for vitrified hotelware*.
- Queensland also provided the following table on allowed levels in various standards (including BS6748-1986 *Specification for limits of metal release from ceramic ware, glassware, glass ceramic ware and vitreous enamel ware* which replace parts 1 and 2 of BS4860-1972 *Specification for permissible limits of metal release from glazed ceramic ware*):

Vessel	BS4860-1972 (mg/L)	BS6748-1986	ISO6486-2: 1999	AS/NZS4371: 1996
Small hollow-ware < 1100 ml	Pb 7.0 Cd 0.7	-	Pb 2.0 mg/L Cd 0.5 mg/L	Pb 4.0 mg/L* Cd 0.3 mg/L Vol not specified
Large hollow-ware > 1100 ml	Pb 2.0 Cd 0.2	-	Pb 1.0 mg/L Cd 0.25 mg/L	As above – Only 1 definition
Flatware	Pb 20 Cd 2.0	Pb 0.8mg/dm^2 Cd 0.07mg/dm^2	Pb 0.8 mg/dm^2 Cd 0.07 mg/dm^2	Pb 0.8 mg/ dm^2 Cd 0.07 mg/ dm^2
Large hollow-ware > 3 L & cookware category 3	-	Pb 1.5mg/L Cd 0.1mg/L	-	-
Large hollow-ware < 3 L category 2	-	Pb 4.0mg/L Cd 0.3mg/L	-	-
Cups and mugs	-	-	Pb 0.5 mg/L Cd 0.25 mg/L	-
Cookware	-	-	Pb 0.5 mg/L Cd 0.05 mg/L	-

*The definition of hollow ware has changed from volume to depth.

Victoria

- Noting the Victorian comment (i.e., recommendation to not address the leaching issue through scheduling) and without knowledge of when each of the various standards were put in place or most recently reviewed, Victoria reported that CAV indicated it would turn to Australian Standards for methodologies and guidance on leaching standards.

NSW

- Ideally the Appendix A entries should not include items which are likely to produce harmful concentrations of any poison in food or drink, but it was doubtful that there was a practicable way of wording this which would not be unduly restrictive.
- Supported that ceramics for use as food or drink containers should be included in Appendix A only if they comply with the relevant sections of either AS/NZS 4371:1996 or BS 4860:1972 (which has different cut-offs) referred to in the Customs (Prohibited Imports) Regulations.
- There seemed no point in specific cut-off values in the Appendix A entries as the leaching would be dependent on the poisons mobility from the particular product rather than only on its concentration. Presumably some ceramics with a higher concentration of lead/calcium leach smaller quantities than do other ceramics with a lower concentration in the ceramic item. Specific limits on the amount leached into

the contents of the container would also be meaningless without specific testing methods. It would be preferable to use the already established testing methods.

- As there are apparently no recent Australian reports of similar leaching problems with glass/crystalware, NSW would not support such a restriction on the "Glass (including crystal ware)" Appendix A entry at present.
- The dictionary definitions seem to say that "ceramics" includes pottery and porcelain, so was not sure why separate Appendix A entries for "Glazed pottery" and "Porcelain" were needed. [Members noted that this distinction arose from the February 1991 Meeting. The minutes of that Meeting unfortunately provided no further details as to reasons for the decision.]

Tasmania

- Agreed that there was a need to get expert advice.
- Noted the NSW advice that the Customs Regulations appear to be moving to AS/NZS 4371:1996 and it would make some sense to fall in with this approach if the Committee wished to adopt a reference in Appendix A.

Members also recalled the following points from the June 2008 NDPSC Meeting discussion:

- It would not be appropriate to introduce controls into Appendix I for non-paints.
- The Committee considered qualifying various Appendix A entries (ceramics, glass (including crystal ware), glazed pottery, porcelain and vitreous enamels) with "in which the poison is confined as a non-migratory component of the ceramic". It was generally agreed, however, that this would be too general, as it was not the Committee's intent to remove the Appendix A exemption from industrial or decorative products which would not come into contact with food.
- Members considered a more specific qualifying statement "except for use in premises, equipment or utensils used for the manufacture, processing, preparation or serving of products intended for human or animal consumption unless the poison is confined as a non-migratory component of the…". A Member noted, however, that the evidence presented had only referred to an issue of leaching with lead and cadmium and recommended that the Committee's consideration focus on these substances rather than all scheduled poisons. The Member also noted that, while there were standards available for lead and cadmium, similar standards were not available for the other scheduled poisons.
- A Member suggested replacing "…unless the poison is confined as a non-migratory component of the…" with "unless compliant with AS/NZS 4371:1996 Ceramic tableware". Members noted, however, that AS/NZS 4371:1996 included many standards (i.e. relating to water absorption/ chipping/ thermal shock/ marking) that were not scheduling issues, and that any moves along these lines would need to refer only to a specific section of AS/NZS 4371:1996 (such as the leaching test requirement regarding lead and cadmium). Members also noted that the lead and

cadmium limits in this standard were not simple cut-offs, but were a spectrum of cut-offs depending on type, shape and size of the tableware in question.

- A Member asserted that while there was evidence that Appendix A needed to be tightened, further input from the jurisdictions was required before this issue could be progressed.
- A Member advised that Australian manufacturers generally voluntarily comply with AS/NZS 4371:1996. The Member was unable to find evidence to suggest that this standard was currently picked up by any legally enforceable regulation.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The relevant matters under section 52E (1), to this item, included: (a) toxicity and safety; (c) potential hazards; (d) extent and patterns of use; and (h) purposes for use.

The Committee was advised that ACCC was examining approaches for controlling poisons in utensils including possible adoption of AS/NZS 4371:1996, but any decision on adoption was not expected to occur soon (if it occurred at all). For this reason, it was therefore suggested that the Committee adopt the appropriate sections of AS/NZS 4371 into the relevant Appendix A entries.

The Committee was advised that the current situation in Western Australia (WA) was that there were some controls in food industry regulations (referring to the British Standards mentioned above, but also accepting compliance with other standards, which were not specified). Enforcement action in WA was currently through trade regulations. The Member advocated that leaching from Appendix A exempted products should therefore be dealt with as a consumer affairs issue and that no change to the current Appendix A entries was necessary.

Several Members felt that such issues were best dealt with via consumer affairs legislation. Another Member asserted that the intent of the Appendix A entries for ceramics, glass (including crystal ware), glazed pottery, porcelain and vitreous enamels was most likely to denote that these consumer products were not intended to be regulated through the scheduling system.

Another Member, also supportive of treating this as a consumer affairs issue, noted that the most efficient and practical way to enforce rapid recall of such products was through the *Trade Practices Act 1974*, noting further that States and Territories do not have recall powers through drugs and poisons legislation. Another Member noted the uncertainty regarding whether ACCC will end up adopting AS/NZS 4371 and advocated that the Committee seek advice at the end of 2009 as to whether such adoption had taken place.

A Member advised that the recently released Productivity Commission Research Study on Chemicals and Plastics Regulation had recommended that the ACCC research the issue of chemicals in consumer articles to ensure a uniform approach and suggested that this leaching issue would be a good case study to assist ACCC in their research.

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The Committee decided that the current general exemptions in Appendix A for ceramics, glass (including crystal ware), glazed pottery, porcelain and vitreous enamels remained appropriate.

The Committee further agreed to refer the problem of lead / cadmium leaching (in products likely to come into contact with food) from ceramics, glass (including crystal ware), glazed pottery, porcelain and vitreous enamels to the Australian Competition and Consumer Commission.

AGRICULTURAL/VETERINARY, INDUSTRIAL AND DOMESTIC CHEMICALS

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

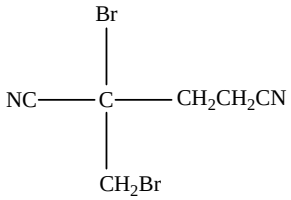
3.1 METHYLDIBROMO GLUTARONITRILE (MDBGN)

PURPOSE

The Committee considered post-meeting comment on the June 2008 methyldibromo glutaronitrile Resolution (2008/53-20).

BACKGROUND

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



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

The June 2008 NDPSC Meeting considered the scheduling of MDBGN and decided:

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

DISCUSSION – SUBMISSIONS

Members were advised that XXXXX pre-meeting comment to the June 2008 NDPSC Meeting was inadvertently omitted from the tabled papers. The Secretariat has subsequently reviewed its processes to ensure this does not happen again. Members particularly noted the following from this comment:

- MDBGN is currently used as a preservative in cosmetic and therapeutic products in Australia in both rinse-off and leave-on formulations.
- An assertion that Australian regulators should always strive for minimum effective regulation using a risk management approach which includes adoption of international standards where these exist. This submission did not support the adoption of unique Australian requirements in the absence of scientific evidence and / or cost benefit analysis.
- Noted that the European Union (EU) Cosmetic Directive restricted the use of MDBGN to rinse-off products at ≤ 0.1 per cent. New Zealand had recently adopted this Directive in its Cosmetics Group Standards.
- Therefore supported harmonising with these standards i.e., limit use to rinse-off cosmetics to ≤ 0.1 per cent MDBGN. Members noted, however, that the EU replaced the ≤ 0.1 per cent allowed level following a decision to ban MDBGN for use in cosmetics (see below).
- XXXXX post-meeting comment below did not repeat the request to allow ≤ 0.1per cent in rinse-off cosmetics.

Member's also noted the following from XXXXX subsequent post-meeting comment:

- Asserted that the June 2008 pre-meeting gazette notice was not specific enough to inform industry that the "consideration of scheduling including a possible ban for cosmetic use" also included consideration of certain therapeutic uses (such as primary sunscreens).
- Noted that the June 2008 decision to add MDBGN to Appendix C was based on the EU decision to remove MDBGN from Annex VI of the EU Cosmetics Directive (*List of Preservatives which Cosmetic Products may Contain*), which was based on the 2006 Scientific Committee on Consumer Products (SCCP) opinion that MDBGN was a skin sensitiser and that no safe use levels in cosmetic leave-on and rinse-off products could be established. Based on the SCCP opinion the EU made a decision to ban MDBGN for use in cosmetics by 23 June 2008. The decision to give industry 24 months phase out by the EU suggested that the EU considered a transition from using MDBGN was warranted.

  Members noted that the SCCP recommendations were addressed by a EU Commission Directive (2007/17/EC) of 22 March 2007 that agreed to delete MDBGN from Annex VI. However, numerous other changes to the Cosmetics Directive were also agreed to, all with an implementation date of 23 June 2008 i.e. it appeared that

the ~24 months was not a specific 'phase out' period for MDBGN but rather the standard implementation time. XXXXX clarified that it wished the Committee to particularly note that MDBGN was not of immediate concern to the EU as it did allow the usual implementation period.

- Regulations in the USA still permit cosmetic use of MDBGN at up to 0.025 per cent in leave on products and 0.06 per cent for rinse-off products. This submission asserted that the USFDA had a rigorous post-market surveillance program which provided equivalent safety to the EU system. The US had yet to make any decisions to reduce the level of MDBGN or ban it completely as a cosmetic ingredient.
- Advised that it was not aware of any specific adverse events reporting linking products with MDBGN as a preservative to sensitisation in Australia.
- This submission requested that the Committee adopt the same risk management strategy used by the EU for MDBGN and vary the decision to ban MDBGN from an effective date of 1 January 2009 to 1 June 2010. An effective date of 1 June 2010 would give industry a 24 month phase out period from June 2008.

Members also noted that a letter was received from XXXXX describing the impact of a 1 January 2009 implementation for the MDBGN ban. This letter, while not a valid post-meeting comment, was tabled as separate information to assist the Committee's consideration of XXXXX post-meeting comment. Members particularly noted:

- This submission advised that it produces XXXXX sunscreen products for the Australian market. For many years, MDBGN has been included as a preservative in sunscreens and as of 12 December 2007 was an approved ingredient in Listed Medicines.
- A June 2008 pre-meeting comment was not submitted because use of this preservative was restricted to Listed Medicines (sunscreens) and so the understanding from the pre-meeting gazette notice that the consideration was referring only to cosmetics.
- Members noted that the Gazette Notice was a broad "consideration of scheduling" with the "including a possible ban for cosmetic use" reflecting the main proposal in the submission before the Committee (which in no way limited the scope of the consideration). This extra detail in the Gazette Notice has been a feature for several years following Committee support for numerous industry requests for such detail.
- Noted a factual error in the June 2008 Record of Reasons where it stated that "*a search of the ARTG located 45 products containing MDBGN (44 sunscreens and 1 antibacterial liquid handwash). However, all products were tagged as export only medicines*". Investigations indicate that there are 41 products containing MDBGN of which only 4 are Export Only.
- Noted the international movement away from MDBGN for products that involve skin contact and did not contest the proposed scheduling of MDBGN. XXXXX

- Advised that, to ensure stocks of sunscreens are available for the 2008/2009 summer season, many of the sunscreens had already been manufactured and dispatched to warehouses and distribution centres. XXXXX. Asserted that withdrawal / disposal of these sunscreens and un-used packaging would have a severe commercial effect.
- These sunscreens have an expiry of three years so product produced in 2007 and not sold for the 2007/2008 summer will contain MDBGN and will be available in the retail market for the 2008/2009 summer.
- Therefore requested an extension to the implementation date until 1 June 2011 to allow product produced for the 2008/2009 summer to be exhausted at retail level.

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

XXXXX

- XXXXX had undertaken a hazard assessment for MDBGN which recommended that, due to oral toxicity, skin and eye irritation and skin sensitising potential, the following:
  - To include MDBGN in Appendix C for cosmetic use and products intended to be in contact with the skin.
  - For uses other than cosmetics and products intended to be in contact with the skin, the Committee may consider it appropriate to include MDBGN in Schedule 6 with specified warning statements and safety directions, or to consider a Schedule 6 entry unless such specified statements and safety directions are used.

Recommended Warning Statement

- 28 Repeated exposure may cause sensitisation.

Recommended Safety Directions

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

International controls

- Detailed the EU ban on MDBGN in all cosmetic products and contrasted this with the USA regulations permitting some use (as set out in the post-meeting comment above).

Absorption

- Readily absorbed following oral, dermal and intravenous administration in animals. ~12-22 per cent was absorbed within 3 to 4 days following application of 5 - 25 mg/kg bw to skin.

Acute toxicity

- Moderate oral toxicity (LD_{50} 770 mg/kg for males, 515 mg/kg for females) and low acute toxicity by dermal ($LD_{50} > 5$ g/kg) and inhalation ($LC_{50} > 13$ mg/L) routes.

Irritancy

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

Sensitisation

- Skin sensitising potential has been extensively investigated in numerous animal and human studies. Based upon positive LLNA results, available animal data suggested that MDBGN is a skin sensitiser.
- In humans, the prevalence of MDBGN sensitivity has been monitored in numerous countries and over an extended period by the routine patch testing of contact dermatitis patients. The rate varies significantly between countries, as expected since the use of MDBGN as a preservative is more widespread in some countries than others. Across all available patch test surveys (0.03-0.5 per cent) the prevalence rate of positive reaction ranged from 0-11.7 per cent with a median prevalence rate of 2 per cent. The prevalence rate increased up to 19.6 per cent when 0.3 per cent MDBGN was tested in patients sensitised to their own cosmetics.
- A number of studies were carried out on individuals pre-sensitised to MDBGN, and apart from a single contradictory study, these individuals developed dermatitis upon re-exposure to lotions or ointments containing MDBGN. The prevalence rate of positive reaction ranged from 7.7-92 per cent when patients were patch tested with MDBGN at concentrations of 0.0001-1 per cent.
- There have been multiple case reports of MDBGN contact sensitivity, rarely in the 1980s but with a greater frequency from 1990 onwards. Most case reports were attributed to cosmetics or toiletries. In contrast, human repeat insult patch tests carried out in the early 1980s on naïve individuals indicated that MDBGN was not a sensitising agent.
- Overall, despite negative results from repeat insult patch tests, available human data from diagnostic patch test surveys, individual case reports and elicitation studies in MDBGN sensitised individuals indicate that MDBGN is a human skin sensitiser.

Repeat dose toxicity

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

ulcers; dermal chronic active inflammation and sebaceous gland hyperplasia were also reported.

Genotoxicity and carcinogenicity

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

Reproduction

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

Exposure

- MDBGN is used as a preservative and biocide in a range of products. Following a NICNAS call for information from Industry in 2007, MDBGN was reported in products such as adhesives and coatings, and personal care products, including sunscreens (at 0.04 per cent), shampoos and shower gels (between 0.003 and 0.004 per cent) and wet wipe hand towels. A recent Australian case noted use in adhesives in a female sanitary pad led to an individual reporting dermal sensitisation.
- Consumer exposure to MDBGN is likely to be widespread because of its use in cosmetics and a variety of other consumer products. The main route of consumer exposure is through dermal contact.
- In Australia, allergy clinics have reported cases of allergy (prevalence of 0.7 per cent) associated with the use of MDBGN as a preservative, mostly in hand cleaners.

XXXXX discussion

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

- XXXXX recommendation to include MDBGN in Appendix C for cosmetic use and products intended to be in contact with the skin was based on the expected widespread public exposure from use of cosmetics containing MDBGN, the acute oral toxicity, the skin sensitisation potential, the eye and skin irritation potential, and the lack of an established safe use-level in leave-on and rinse-off products and the current prohibition of MDBGN for use in cosmetics within the EU.

June 2008 Members Discussion

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

DISCUSSION – RELEVANT MATTERS UNDER 52E

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

Members noted that none of the comments received expressed concern with the June 2008 decision to ban the use of MDBGN (for cosmetic use and for products intended to be in contact with the skin) and agreed that the implementation date was the only aspect of the June decision which might require variation. It was agreed that, as it had not been made aware of sunscreens containing MDBGN currently being supplied in Australia at the time of the June 2008 Meeting, such reconsideration was appropriate.

A Member suggested an implementation delay to 1 May 2009, to allow existing supplies to be used for the 2008-09 summer (noting that the current implementation date of 1 January 2009 would coincide with the middle of this peak). A Member noted, however, that some regions in the north of Australia used sunscreens all year round. Another Member asserted that a 1 May 2009 implementation would also be in line with similar action in New Zealand.

A Member noted that previously the Committee has been mindful of the impact of scheduling decisions on industry and has been sympathetic to requests for delaying implementation unless urgent restrictions are required. Members therefore generally agreed that, as there was not a pressing safety issue for MDBGN requiring immediate action, it would be appropriate to consider a phase out period for MDBGN that would adequately accommodate existing stocks and minimise industry impact. Members generally agreed that extending the implementation date to 1 January 2010 reasonably balanced the benefit of a phase-out period with the need to withdraw this known skin sensitiser from use in skin preparations.

RESOLUTION 2008/54 – 9 (Variation of Decision 2008/53-20)

The Committee decided to vary the June 2008 methyldibromo glutaronitile (MDBGN) Resolution (2008/53–20) by:

- including MDBGN in Appendix C for cosmetic use and for products intended to be in contact with the skin;
- including a parent MDBGN entry in Schedule 6 to capture any uses not caught by the Appendix C entry;
- including MDBGN in Appendix F Part 3 (Warning Statement 28 –"Repeated exposure may cause sensitisation" and Safety Directions 1,4 and 7 – "Avoid contact with eyes", "Avoid contact with skin" and "Wash hands thoroughly after use"); and
- varying the implementation date for this decision from 1 January 2009 to 1 January 2010.

Schedule 6 – New entry

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

Appendix C – New entry

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

Appendix F, Part 3 – New entry

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

3.2 CYANOGEN (ETHANEDINITRILE)

PURPOSE

The Committee considered a post-meeting comment on the June 2008 cyanogen Resolution (2008/53 - 18) regarding the naming of N≡C–C≡N.

BACKGROUND

Cyanogen, also known as ethanedinitrile, has the structure: N≡C–C≡N .

In animals, humans and the environment cyanogen hydrolyses to cyanide, which is responsible for the toxicity effects observed. Cyanogen and cyanide are readily absorbed

by inhalation, distributed to all organs and tissues, detoxified to thiocyanate and other compounds and eliminated mainly through the urine.

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

At the June 2008 NDPSC meeting the Committee decided to create new Schedule 7 and Appendix J (condition 1 – Not to be available except to authorised or licensed persons) entries for cyanogen. The Committee also decided to cross-reference ethanedinitrile to cyanogen in the SUSDP index.

DISCUSSION - SUBMISSIONS

Members were advised of a post-meeting comment from XXXXX requesting reconsideration of the use of "cyanogen" for the entries, disputing that the term cyanogen should be used for the sake of clarity and instead argued that the term "ethanedinitrile" provided better clarity.

The post-meeting comment accepted that the term "cyanogen" was commonly defined in text books and chemical dictionaries as the compound N≡C–C≡N and also that this compound has been referred to as "cyanogen" in written reports. However, it was asserted that internet searches were now more commonly relied on and results of internet searches should not be ignored when considering terms to use for the purpose of "clarity" of substance identification. The post-meeting comment advised that:

- A Google search for "cyanogen" gave 572,000 hits while "ethanedinitrile" gave 4,280 hits.
- A search in ChemIDplus on "cyanogen" gave two options (a) ethanedinitrile and (b) cyanogen radical.
- A search of the website ChemIndustry.com for "cyanogen" gave 2,205 references including cyanogen radicals.
- A search of NCBI PubChem database for "cyanogen" as substance yielded 48 item compared with five for ethanedinitrile. A similar search on "oxalonitrile" (another name listed in ChemIDplus website for cyanogen yielded 25 items.
- In the NCBI PubChem searches:
  - cyanogen includes cyanogen compounds and the cyanogen radical,
  - oxalonitrile includes references to oxalonitrile and the oxalonitrile radical, and
  - ethanedinitrile only references N≡C–C≡N.

The post-meeting comment asserted that there was much broader use of the term "cyanogen" than just referencing N≡C–C≡N. Further, the term "ethanedinitrile" only referred to one compound (N≡C–C≡N) and hence it was suggested that the term "ethanedinitrile" was more specific and provided greater clarity as to the identity of the substance. The Committee recalled that the October 2008 NDPSC Meeting noted that a draft International Union of Pure and Applied Chemistry (IUPAC) provisional recommendation (October 2004) gave oxalonitrile as the preferred name for the compound N≡C–C≡C, that the name "ethanedinitrile" was also in strict compliance with IUPAC rules for the nomenclature of organic compounds and that "Cyanogen" was the common name for this compound (which the XXXXX advised, at the June 2008 NDPSC Meeting, was in wide use by industry).

The Committee also recalled the following points from June 2008 Meeting:

- XXXXX applied to the APVMA for approval of a new active constituent, "ethanedinitrile", and XXXXX.
- XXXXX undertook an evaluation and recommended that:
  - Cyanogen should be included in Schedule 7 based on its toxicology and metabolism profile, consistent with the existing scheduling for cyanides and hydrocyanic acid. XXXXX also recommended inclusion in Appendix J with condition 1 "not to be available except to authorised or licensed persons".
  - Two genotoxicity studies on cyanogen were submitted. These studies, together with toxicology information on cyanide from published papers, from international reports (WHO) and other national reports (US ATSDR and Netherlands) were used by XXXXX to assess the potential human health risks.
  - The XXXXX report, while entitled "ethanedinitrile", referred throughout to "cyanogen".
- Members considered whether to schedule as "ethanedinitrile" or as "cyanogen". The Committee generally agreed that cyanogen better communicated what the substance was and therefore, for the sake of clarity, agreed that cyanogen be used for the SUSDP entries.

Members also noted the following consolidated summary of hazard profile from the evaluation report:

Absorption, distribution, metabolism and excretion in mammals

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

Acute toxicity

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

Short-term toxicity

Target/critical effect	Changes in male reproductive organs and functions; Pulmonary, liver and kidney effects
Lowest relevant oral NOEL	0.5 mg/kg bw/day (cyanide)
Lowest relevant dermal NOEL	No data
Lowest relevant inhalation NOEC	24 mg/m^3 (cyanogen)

Genotoxicity	XXXXX

Long-term toxicity and carcinogenicity

Target/critical effect	Decreased thyroid function

Lowest relevant NOEL	No adequate data
Carcinogenicity	A conclusion on carcinogenicity cannot be made due to small group size and limited exposure time in two long term studies.
Reproductive toxicity	
Reproduction target/critical effect	Reduction in sperm motility and in the weight of cauda epididymidis.
Lowest relevant reproductive NOEL	0.5 mg/kg bw/day (30 mg sodium cyanide/L drinking water)
Developmental toxicity	
Developmental target/critical effect	Vertebral and rib anomalies and encephaloceles and skeletal malformations in hamster.
Lowest relevant developmental NOEL	7.4 mg/kg bw (cyanide), single dose
Delayed neurotoxicity	Delayed neurotoxicity signs including Parkinsonism-like signs, dystonic and apraxia, apathetic, agitation, involuntary movements, akinetic mutism, loss of muscle strength, damage to centra axonal auditory and somatosensory signal propagation,etc.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The following matter under 52E (1) was considered particularly relevant to this consideration: (i) any other matters that the Committee considers necessary to protect public health, i.e. nomenclature clarity may enhance compliance with scheduling.

A Member noted that the post-meeting submission was only concerned with nomenclature and that no other issues had been raised.

The Member suggested that since all three possible names (cyanogen, ethanedinitrile and oxalonitrile) appeared to be equally valid for the substance N≡C–C≡N, ensuring appropriate cross-referencing in the SUSDP index was the most important consideration. Another Member suggested that the index should cross-reference both oxalonitrile (the IUPAC preferred name) and ethanedinitrile to cyanogen.

RESOLUTION 2008/54 – 10 (Variation of Resolution 2008/53 – 18)

The Committee decided to vary the June 2008 NDPSC Resolution (2008/53-18), namely to create new Schedule 7 and Appendix J (condition 1 - Not to be available except to authorized or licensed persons) entries for cyanogen and the cross-reference of ethanedinitrile to cyanogen in the SUSDP index, to include a further cross-reference of oxalonitrile to cyanogen.

Schedule 7 – New entry

CYANOGEN.

Appendix J, Part 2 – New entry

POISON	**CONDITIONS**
Cyanogen	1

SUSDP Index – New entries for inclusion in SUSDP 24 consolidation

ETHANEDINITRILE
See CYANOGEN

OXALONITRILE
See CYANOGEN

4. OTHER OUTSTANDING MATTERS FROM PREVIOUS MEETINGS

4.1 LEAD IN PAINTS OR TINTERS

PURPOSE

The Committee considered the scheduling of lead when in paints or tinters as foreshadowed by the June 2008 NDPSC Meeting.

BACKGROUND

The February 2004 NDPSC Meeting, following a request from XXXXX, endorsed an industry initiative of reducing lead in industrial paints and recommended that the matter be referred to NOHSC (now the Australian Safety and Compensation Council – ASCC) as the agency with responsibility for occupational health and safety including the development of standards for the safe use of lead in the workplace.

Prior to the October 2007 NDPSC meeting, the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) published a Priority Existing Chemical (PEC) assessment report "Lead in Industrial Surface Coatings and Inks" (http://www.nicnas.gov.au/Publications/CAR/PEC/PEC29.asp) which recommended that the Committee consider (a) including lead compounds for use in inks in Appendix C and (b) reviewing the Uniform Paint Standard (Appendix I) in relation to the declared lead compounds for surface coatings. The Committee decided:

- that XXXXX to write to ASCC encouraging consideration of the NICNAS report's recommendations as soon as practicable given the high priority that the NDPSC has placed on removing lead from domestic settings;
- that, as industrial use of paint fell within the ASCC jurisdiction, the various references to industrial use in Appendix I were in need of review. The Committee agreed to foreshadow a review of Appendix I for the February 2008 NDPSC Meeting; and
- to foreshadow inclusion of lead compounds in inks in Appendix C with a consequential amendment to the Appendix A entry for "PRINTING INKS or INK ADDITIVES".

The February 2008 NDPSC Meeting noted progress to date on a review of Appendix I. The Committee also considered the foreshadowed inclusion of lead compounds in inks in Appendix C and decided:

- to include lead compounds in inks (or ink additives) in Appendix C (with a low level cut-off for inks containing ≤ 0.1 per cent lead, calculated on the non-volatile content of the ink or ink additive) with consequential amendments to Schedule 4, 5 and 6; and
- to amend the Appendix A general exemption for "PRINTING INKS or INK ADDITIVES" to no longer apply to preparations containing lead compounds.

The June 2008 NDPSC Meeting considered a review of Appendix I including a proposal to ban lead in paints and tinters at > 0.1 per cent lead, and decided to foreshadow:

- replacing the current Appendix I Clause 3 with "A person must not manufacture, sell, supply or use paint containing more than 0.1 per cent lead calculated on the non-volatile content of the paint";
- deleting Clause 1 of Appendix I (i.e. remove the exemption which allows use of lead carbonate in mirror backing);
- deleting the Third Schedule and amend Part 2, paragraph 16 and Appendix F to remove reference to the Third Schedule or controls on lead;
- amending the Schedule 6 lead compounds entry by deleting the zinc based paints exemption (≤ 0.2 per cent) and to amend the other paints exemption to exclude all paints, tinters, inks or ink additives (i.e. > 0.1 per cent will be captured instead by the Appendix C entry);
- amending the Appendix C entry for lead compounds in inks or ink additives (as per the February 2008 NDPSC Resolution 2008/52 – 8) to also include paints or tinters, maintaining an exception for ≤ 0.1 per cent lead; and
- amending Clause 4 of Appendix I to include reference to Part 3 of the current Australian/New Zealand Standard for safety of toys (AS/NZS ISO 8124.3:2003) and add "as specified or amended from time to time".

DISCUSSION - SUBMISSIONS

Following the June 2008 NDPSC Meeting, the Secretariat wrote to XXXXX regarding the foreshadowed decision. Members noted the following from the responses:

- XXXXX asserted that the foreshadowed changes appeared to be sufficient to give effect to the recommendations the paint industry has put to government and are, therefore, supported.
- XXXXX was pleased with the proposed revisions to Appendix I and prohibition of lead compounds in paint through Appendix C as these were in line with XXXXX recommendations. XXXXX also advised that it had no concerns on the proposed inclusion of tinters in the Appendix C entry, as this was consistent with the recommendations of the NICNAS PEC report.

A Member also advised that the recent scheduling changes to ban lead in inks (included in SUSDP 23/1) appeared to have an inadvertent error. Inks containing < 0.1 per cent lead were captured by Schedule 6, when the Committee's intention was that they be unscheduled. Additionally, as there was no inks exemption from Schedule 6, lead in inks at ≥ 0.1 per cent would be captured by both Appendix C and Schedule 6. The Member suggested that this could be overcome by:

- Changing part (a) of the Schedule 6 entry to "when included in Schedule 4 or 5 or Appendix C". Members noted that there was no precedent for a schedule entry referring to Appendix C except through inclusion of "†".
- Adding a new paragraph to the Schedule 6 entry "in printing inks or ink additives containing 0.1 per cent or less of lead calculated on the non-volatile content of the ink or ink additive".

The Committee generally agreed that the June 2008 foreshadowed change to exception (b) of the Schedule 6 entry "in paints, tinters, inks or ink additives" appeared to have already resolved the above issue.

With regard to the foreshadowed proposal to amend Clause 4 of Appendix I (to change the reference for paint specifications for toys to AS/NZS ISO 8124.3:2003 including "as specified or amended from time to time"), the Members noted that:

- Legal advice was received (following the June 2008 NDPSC Meeting) that references in a legislative instrument registered on the Federal Register of Legislative Instruments (FRLI) (such as the SUSDP) must be specific to a particular version (unless it is a reference to an Act). As such, inclusion of "as specified or amended from time to time" was not appropriate for the proposed reference.
- The following table sets out the relevant differences between the existing reference (AS 1647) and AS/NZS ISO 8124.3:2003:

Relevant Differences	Proposal
• AS/NZS ISO 8124.3:2003 *Safety of toys Part 3: Migration of certain elements* has the same maximum migration from toy materials for tin, arsenic, cadmium, chromium, lead, mercury and selenium. • Barium (except modelling clay and finger paint) in AS/NZS ISO 8124.3:2003 is 1000 mg/kg rather than the 500 mg/kg in AS 1647. • AS/NZS ISO 8124.3:2003 allows an analytical correction of 30 to 60 per cent, depending on element i.e. allowed level is in fact > than AS 1647. • Testing procedures in AS/NZS ISO 8124.3:2003 are similar to, but more comprehensive than, AS 1647.	Replace reference to AS 1647 in Appendix I with "the paint complies with the specification for coating materials contained in Australian/New Zealand Standard AS/NZS ISO 8124.3:2003 entitled *Safety of Toys Part 3: Migration of certain elements*.

Members recalled that Appendix I is currently applied in 2 ways:

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

Members also recalled the following from the June 2008 Minutes:

The NICNAS PEC Report

- NICNAS did not support the use of lead compounds in industrial surface coatings and inks. Inks containing lead compounds are currently not sold for consumer use.
- Lead compounds were not essential in industrial surface coatings and inks and a number of substitutes were available. Use of surface coatings and inks that do not contain lead will avoid the risks associated with the use of industrial surface coatings and inks that contain lead compounds.
- There were no voluntary controls implemented by the paint/surface coatings and inks industries regarding lead-based compounds. A number of companies had phased out or were currently phasing out the use of lead compounds in their products. Members of the APMF had embarked on a phase out of all lead compounds in industrial surface coatings and inks over the next three years.

XXXXX

- Lead-containing paints should be excluded from Appendix I and, instead, be captured by an entry in Appendix C in a similar manner to lead-containing inks. Consequential amendments would need to address the references to the Third Schedule in Part 2, paragraph 16 and Appendix F, and the entry for zinc based paints in Schedule 6.
- The Appendix I exemption allowing use of lead carbonate in mirror backing should be removed as industry has indicated that this use has been phased out (from April 2008 surface coatings containing > 0.1 per cent lead carbonate cannot be imported or manufactured for industrial application to mirror backings).
- Clause 4 of Appendix I should be amended to reference AS/NZS ISO 8124.3:2003 and adding 'or its successor" to avoid inconsistencies in case of future updates.

XXXXX

- XXXXX was of the view that it was preferable to keep all references to paint within Appendix I. This would make it easier for users of the SUSDP to access the paint section and for authorities and other stakeholders to reference the paint restrictions through their own legislation, codes of practice, etc. The June 2008 NDPSC Meeting noted that XXXXX, in asserting the above, did not comment on jurisdictional divergence in adopting Appendix I regulations.

Discussion at the June 2008 NDPSC Meeting

- XXXXX recommendation only made allowance for the continued availability of ≤ 0.1 per cent lead in paints due to public health concerns. Confirmation was sought, and received, that XXXXX was specifically recommending discontinuation of the ≤ 0.2 per cent limit for lead when in zinc based paints.
- Members noted that a move of > 0.1 per cent lead based paints / tinters to Appendix C should have no great impact as voluntary moves to limit lead in these products by the Australian industry had been quite successful.
- The Committee generally supported a ban of > 0.1 per cent lead based paints / tinters because of public health concerns from exposure to lead, but noted that this could be achieved either through Appendix C or Appendix I:

  Appendix I

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

  Appendix C

  – The February 2008 NDPSC Meeting's decision to included lead containing ink and ink additives (> 0.1 per cent) in Appendix C could be expanded to encompass paints and tinters. Additionally it was noted that there was precedent for

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

- In light of the benefits arising from each of these options, Members agreed that both could be done. The Committee felt that the increased clarity justified the duplicative nature of this approach, particularly as this may increase compliance in reducing public exposure to lead. An alternative, of inclusion in Appendix C with a cross-reference to Appendix C from Appendix I, was not generally supported by the Committee.
- Members also noted that by banning > 0.1 per cent lead in paints / tinters there was no longer a need for the Appendix I Third Schedule or the references to this schedule in Part 2, Paragraph 16 and Appendix F. The Committee therefore agreed to remove these superfluous entries, which would have the added benefit of simplifying those sections of the SUSDP.
- However, given the complexity of the proposed changes and that this issue had not been included in the pre-meeting Gazette Notice, it was agreed that these decisions should be foreshadowed for consideration at the October 2008 NDPSC Meeting. This would also allow time for public comments to address any inadvertent impacts, particularly given the size and diversity of the paint / tinter sector in Australia.

DISCUSSION – RELEVANT MATTERS UNDER 52E

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

Members agreed that the intent of the changes foreshadowed by the June 2008 NDPSC Meeting remained appropriate i.e. banning lead in paints or tinters at > 0.1 per cent. It was noted that all pre-meeting comment had also supported this intent. The Committee did note, however, that some minor adjustments were required:

- A Member advised that the lead ban through Appendix I would only be effective under the current Western Australian regulations if the Third Schedule continued to exist (but amended to only include lead or lead compounds containing > 0.1 per cent i.e. delete the entry for > 0.2 per cent when an impurity in a zinc based paint). Consequently, the Committee agreed that the proposed change to Clause 3 ("A person must not manufacture, sell, supply or use paint containing more than 0.1 per cent lead calculated on …") would instead be worded "A person must not manufacture, sell, supply or use a Third Schedule paint".
- As detailed above, the exact wording of the reference being added to Clause 4 of Appendix I could no longer include "as specified or amended from time to time".

RESOLUTION 2008/54 - 11

The Committee decided to:

- replace the current Appendix I Clause 3 with "A person must not manufacture, sell, supply or use a Third Schedule paint.";
- delete Clause 1 of Appendix I (i.e. remove the exemption which allows use of lead carbonate in mirror backing);
- delete the lead in zinc based paint entry from the Third Schedule.
- amend Part 2, paragraph 16 and Appendix F by removing reference to the Third Schedule or controls on lead;
- amend the Schedule 6 lead compounds entry by deleting the exemption for use in zinc based paints and to amend the other paints exemption to exclude all paints, tinters, inks or ink additives (i.e. > 0.1 per cent will be captured instead by the Appendix C entry);
- amend the Appendix C entry for lead compounds in inks or ink additives to also include paints or tinters, maintaining an exception for ≤ 0.1 per cent lead; and
- amend Clause 4 of Appendix I to include reference to the specification for coating materials in Australian/New Zealand AS/NZS ISO 8124.3:2003 entitled *Safety of toys Part 3: Migration of certain elements*.

Part 2 Labels and Containers – Amendment

Paragraph 16 – Amend entry to read:

Paints

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

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

(a) contains only Schedule 5 poisons; or

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

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

(ii) the expression "KEEP OUT OF REACH OF CHILDREN", written in bold-face sanserif capital letters, the height of which is not less than 2.5 mm,

on a separate line immediately below the word "WARNING"; and

(iii) the appropriate warnings specified for the paint in Appendix F, written immediately below the expression "KEEP OUT OF REACH OF CHILDREN"; and

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

(2) a tinter which contains:

(a) only Schedule 5 poisons; or

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

Schedule 6 – Amendment

LEAD COMPOUNDS – Amend entry to read:

† LEAD COMPOUNDS **except**:

(a) when included in Schedule 4 or 5;

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

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

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

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

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

written in letters not less than 1.5 mm in height.

Appendix C – Amendment

LEAD COMPOUNDS – Amend entry to read:

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

Appendix F, Part 3 – Amendment

Paint – Amend entry to read:

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

Appendix I – Amendment

Amend Appendix I to read:

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

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

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

   (2) furniture; or

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

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

2. A person must not manufacture, sell, supply or use a Third Schedule paint.

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

in Australian/New Zealand Standard AS/NZS ISO 8124.3:2003 entitled *Safety of toys Part 3: Migration of certain elements*.

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

The First Schedule

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

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

The Second Schedule

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

The Third Schedule

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

Substance	**Proportion**
LEAD or lead compounds	more than 0.1 per cent

4.2 PROTHIOCONAZOLE

PURPOSE

The Committee considered the scheduling of prothioconazole including a foreshadowed proposal (2008/53 – 11) to reschedule prothioconazole from Appendix B to Schedule 5.

BACKGROUND

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

The June 2005 NDPSC Meeting considered an evaluation of an application to XXXXX for approval of the active prothioconazole. The Committee noted that the acute toxicological profile of prothioconazole was similar to most other triazole fungicides in this class (20 triazole fungicides previously scheduled, with 16 classified as Schedule 5 and 4 classified as Schedule 6). The Committee noted, however, that prothioconazole had low oral, dermal and inhalation toxicity, with only slight skin irritation, and was not a skin sensitiser. Based on low oral and inhalation toxicity the Committee agreed to include prothioconazole in Appendix B. The June 2005 NDPSC Minutes did not discuss by-products, just the low toxicity of prothioconazole itself.

The June 2008 NDPSC Meeting was advised that XXXXX had provided data to amend the particulars and conditions of the APVMA approved active constituent prothioconazole. XXXXX had modified its manufacturing process in order to eliminate a by-product, prothioconazole-desthio, which had been identified as a significantly more potent developmental toxin than prothioconazole itself. However, the new manufacturing process resulted in the generation of three by-products, (i) prothioconazole-triazolidine thione XXXXX, (ii) prothioconazole dimer XXXXX, and (iii) an increased level of the previously present prothioconazole-deschloro XXXXX.

XXXXX evaluation report on the new technical grade active constituent (TGAC) prothioconazole highlighted that two of the by-products, prothioconazole-deschloro and prothioconazole-triazolidinethione, were skin sensitisers in XXXXX. No additional skin sensitisation studies were provided on the new-TGAC produced by the modified manufacturing process which may contain up to XXXXX of these two by-products.

Due to concerns that the by-products had the potential to cause skin sensitisation, the Committee agreed that prothioconazole would need to be upscheduled to Schedule 5 unless sensitization data on the TGAC (such as a Local Lymph Node Assay-LLNA) was provided which supported an Appendix B listing. Members agreed to foreshadow inclusion of prothioconazole in Schedule 5 for the October 2008 NDPSC Meeting, noting that this intent could be reviewed, should sensitisation information become available.

DISCUSSION - SUBMISSIONS

Members recalled the following from the June 2008 NDPSC discussion:

- XXXXX sensitisation concern arose from the by-products of a particular manufacturing process, not from prothioconazole itself. Members considered whether this was a scheduling issue, or whether impurities are a manufacturing quality issue for the APVMA regulator. It was noted that if the Committee were to schedule based on an impurity profile this may require reconsideration of scheduling whenever the impurity profile changed (e.g. a change in manufacturing process, or if new suppliers of prothioconazole came into the market).
- Members considered foreshadowing separate specific scheduling for prothioconazole-triazolidinethione and prothioconazole-deschloro on the basis of sensitisation potential. APVMA could then address the prothioconazole-triazolidinethione and prothioconazole-deschloro impurity issue through the listing of prothioconazole in the APVMA Standards for Active Constituents as part of the registration process for the active.
- Members noted that a Schedule 7 parent entry for these two compounds may add enforcement strength to the allowable impurity levels of these substances in products, however Schedule 7 was considered inconsistent with concerns arising from skin sensitisation potential. A Member suggested that the option of scheduling the impurities should not be pursued at that time.
- A Member noted that while the impurities were sensitisers, it had not been determined that the TGAC itself was a sensitiser. The Member suggested that a LLNA using the TGAC would settle the issue of skin sensitisation.
- Another Member noted that sensitisation need not be linearly related to concentration and that the TGAC had the potential to be a sensitiser. Without data to address this concern the Committee would need to be cautious, even though the known sensitiser impurities made up only XXXXX of the TGAC.

Members also recalled the following particular points from XXXXX evaluation:

Recommendations to APVMA

- No objections on public health grounds to the continued approval of prothioconazole TGAC sourced from XXXXX.

Public Health Standards

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

Toxicity

<u>Prothioconazole (TGAC)</u>

- The TGAC produced using the modified manufacturing specification had the potential to cause skin sensitisation. The acute and reproductive toxicity profile of prothioconazole was not expected to be affected by the presence of the three by-products at the specified maximum concentrations. Apart from this, the toxicological profile of the TGAC was unchanged from the 2005 evaluation. The following toxicology data was obtained from a previous evaluation of prothioconazole (TGAC) produced using the old manufacturing process:
  - *Low oral XXXXX, dermal XXXXX and inhalational XXXXX toxicity in XXXXX.*
  - *No skin or eye irritation in XXXXX and not a skin sensitiser in XXXXX.*
  - *The liver and kidney were target organs in XXXXX. XXXXX. Liver toxicity was characterised by XXXXX, suggesting that the effect appear to be a class effect. The changes were in accord with extensive metabolism and the presence of high levels of the parent compound in the liver.*
  - *Prothioconazole was not associated with selective effects on the reproductive system or developing offspring in the absence of toxicity in parental animals. The test substance was not genotoxic. There was no evidence of carcinogenic potential.*
- No studies were provided regarding the toxicokinetics or metabolism of the new by-products. The major metabolic reactions that were observed in the original TGAC were conjugation with glucuronic acid, desulfuration to produce prothioconazole-desthio, and oxidative hydroxylation of the phenyl moiety. It was not expected that the new by-products would significantly change the identity or relative fraction of the metabolites as determined in the original TGAC evaluation.

- Prothioconazole was not listed on the ASCC Hazardous Substances Information System Database. XXXXX has classified prothioconazole as a hazardous substance according to National Occupational Health and Safety Commission (NOHSC) Approved Criteria for Classifying Hazardous Substances (R43, ≥ 1 per cent, "May cause sensitisation by skin contact").

Prothioconazole-deschloro

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

Prothioconazole-triazolidinethione

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

Prothioconazole-asymmetric disulfide

- Prothioconazole-asymmetric disulfide has low acute oral toxicity XXXXX. There was no evidence of genotoxicity in an XXXXX. There is no mention in XXXXX report of sensitisation data for this by-product.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The following matters under 52E(1) were considered particularly relevant to this consideration: (a) the toxicity and safety of a substance; (c) the potential hazards associated with the use of a substance; and (e) the dosage and formulation of a substance.

A Member noted that since there had been no response from the applicant regarding additional sensitisation data, the Committee should proceed with the foreshadowed rescheduling.

A Member maintained that the current Appendix B scheduling of prothioconazole was appropriate based on its low toxicity and suggested that the deschloro and triazolidinethione impurities, responsible for the skin sensitisation, should instead be separately listed in Schedule 5 with a cut-off to unscheduled in amounts less than 0.5 per cent. Another Member supported this argument by suggesting that it was illogical to

upschedule prothioconazole when it was only the impurities that have clear data demonstrating skin sensitiser characteristics and the Committee was yet to ascertain that the TGAC is not a skin sensitiser.

A Member questioned whether there was sufficient information on hand to schedule these two impurities. The Committee generally agreed that the data available was supportive of the deschloro and triazolidinethione impurities being captured by Schedule 5. The Member noted, however, that these substances had not been included in the pre-meeting gazette notice so instead the Committee agreed to foreshadow a proposal to schedule these two substances in Schedule 5.

RESOLUTION 2008/54 - 12

The Committee decided:

- that the current Appendix B scheduling of prothioconazole remained appropriate; and
- to foreshadow capturing prothioconazole-deschloro and prothioconazole-triazolidinethione in Schedule 5 at the February 2009 NDPSC meeting.

FORESHADOWED DECISION (for consideration at the February 2009 Meeting)

Schedule 5 – New entries

PROTHIOCONAZOLE-DESCHLORO **except** in preparations containing 0.5 per cent or less of prothioconazole-deschloro.

PROTHIOCONAZOLE-TRIAZOLIDINETHIONE **except** in preparations containing 0.5 per cent or less of prothioconazole-triazolidinethione.

4.3 OVERLAP BETWEEN APPENDIX C AND THE SCHEDULES

PURPOSE

The Committee considered the foreshadowed Resolution (2008/53 – 64) to remove the overlap between the Appendix C and schedule entries for ethylhexanediol, Basic Orange 31, methyl methacrylate, formaldehyde and paraformaldehyde.

BACKGROUND

The June 2008 NDPSC Meeting considered the issue of overlaps between entries in the schedules and in Appendix C (specifically the Schedule 4 entry for ethylhexanediol and the Schedule 6 entries for Basic Orange 31, methyl methacrylate, formaldehyde and paraformaldehyde) and decided to foreshadow proposed amendments to the Schedule 4 ethylhexanediol entry and Schedule 6 entries for Basic Orange 31, methyl methacrylate, formaldehyde and paraformaldehyde to clarify that anything captured under Appendix C was not also captured in a schedule entry.

DISCUSSION - SUBMISSIONS

Members recalled the following points from the June 2008 NDPSC Meeting:

- The standard practice had been to word entries in Appendix C in such a way that they do not overlap with entries for the same substance in any of the schedules, just as entries in two schedules were not written to overlap with each other.
- A Member advised that in recent times, there appeared to have been a departure from the practice of avoiding overlaps between the schedules and Appendix C and that this presented a practical problem in NSW where control of Appendix C substances was achieved by including them in Schedule 7 of the NSW Poisons List. The NSW Poisons List adopted the SUSDP schedule entries by reference. If overlaps continued between the schedules and Appendix C, NSW could be forced to depart from referencing the SUSDP for such substances to avoid overlaps between the schedules in the NSW Poisons List.
- The October 2006 NDPSC Meeting included ethylhexanediol in Schedule 4 to harmonise with New Zealand and that the February 2007 NDPSC Meeting confirmed that the Schedule 4 entry was intended to capture animal therapeutic use only.

The Secretariat advised that the foreshadowed amendments to the Schedule 6 entries for formaldehyde/paraformaldehyde did not fully eliminate overlap with Appendix C in respect of:

- aerosol sprays for cosmetic use containing ≥ 0.005 per cent of free formaldehyde.
- all other cosmetic preparations containing > 0.05 per cent of free formaldehyde.

This overlap arose because the foreshadowed amendment to the formaldehyde and paraformaldehyde entries still captured cosmetics containing > 0.05 per cent free formaldehyde in Schedule 6 even though all cosmetic use (apart from nail hardener cosmetic preparations containing < 5 per cent and cosmetic preparations containing ≤ 0.2 per cent when labelled with the appropriate warning statement) were captured by the Appendix C entry. It was therefore suggested that Members consider exempting all cosmetic use (apart from nail hardener cosmetic preparations) from Schedule 6.

The Committee also noted that the current Schedule 6 entries for formaldehyde and paraformaldehyde captured preparations containing 0.05 per cent or more of free formaldehyde but the proposed foreshadowed amendments to the Schedule 6 entries exempted preparations containing 0.05 per cent or less free formaldehyde and hence the proposed new Schedule 6 entries would no longer capture preparations containing exactly 0.05 per cent free formaldehyde. Members therefore considered amending the exemption to preparations containing less than 0.05 per cent free formaldehyde from Schedule 6.

The Appendix C entry for ethylhexanediol captured all human use and the foreshadowed Schedule 4 entry captured animal therapeutic use only, thus leaving other animal uses unscheduled. The Committee considered amending the foreshadowed Schedule 4 entry

to capture all animal use which would result in capture of all animal and human uses of this substance without leaving any gaps in coverage by the SUSDP.

The Committee also noted a pre-meeting submission from XXXXX. XXXXX asserted that, based on their current knowledge of these substances and the risks and benefits associated with the use and extent and patterns of use previously considered, they did not believe that further changes to the scheduled entries other than addressing the issue of overlap was warranted.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The following matters under 52E(1) were considered particularly relevant to this consideration: (h) the purpose for which a substance is to be used; (i) any other matters the Committee considers necessary to protect public health, i.e. to remove any impediment for inclusion of the schedules and appendices in the relevant legislation of the States and Territories.

A Member noted that currently the only mechanism to ban a substance is by placing it in Appendix C (unless the substance may be abused or misused, in which case it could be listed in Schedule 9).

The Committee was advised that in Western Australia (WA) the only mechanism to prohibit the sale, supply and use of a substance was to include it in a proclamation by the Governor under Section 22 of their *Poisons Act 1964*. Variation of the proclamation to include new substances added to Appendix C usually required a minimum of three months to implement. As a consequence, any new entries in Appendix C would not be prohibited in WA until such time as the proclamation could be varied. It was generally agreed that this was an issue for WA to address and that Appendix C, as a part of the current SUSDP, should not overlap with schedule entries.

RESOLUTION 2008/54 - 13

The Committee agreed to amend the:

- Schedule 4 entry for ethylhexanediol to capture animal use only in order to remove overlap with Appendix C;
- Schedule 6 entry for Basic Orange 31 to also exempt preparations for skin colouration and dyeing of eyelashes or eyebrows in order to remove overlap with Appendix C;
- Schedule 6 entry for methyl methacrylate to also exempt cosmetic use in order to remove overlap with Appendix C; and
- Schedule 6 entries for formaldehyde and paraformaldehyde to also include an exemption for all other cosmetic preparations and for nail hardener cosmetic preparations containing 5 per cent or more free formaldehyde in order to remove overlap with Appendix C.

Schedule 4 – Amendment

ETHYLHEXANEDIOL – Amend entry to read:

† ETHYLHEXANEDIOL for animal use only.

Schedule 6 – Amendments

BASIC ORANGE 31 – Amend entry to read:

† BASIC ORANGE 31 (2-[(4-aminophenyl) azo]-1,3-dimethyl-1H-imidazolium chloride) **except**:

(a) in preparations for skin colouration and dyeing of eyelashes or eyebrows; or

(b) in hair dye preparations containing 1 per cent or less of Basic Orange 31 when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN;

If in eyes wash out immediately with water; and

WARNING - This product contains ingredients which may cause skin irritation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye.

written in letters not less than 1.5 mm in height.

FORMALDEHYDE – Amend entry to read:

† FORMALDEHYDE (excluding its derivatives) **except**:

(a) for human therapeutic use;

(b) in oral hygiene preparations;

(c) in nail hardener cosmetic preparations containing 5 per cent or more of free formaldehyde;

(d) in nail hardener cosmetic preparations containing 0.2 per cent or less of free formaldehyde when labelled with the statement:

PROTECT CUTICLES WITH GREASE OR OIL;

(e) in all other cosmetic preparations;

(f) in other preparations containing 0.2 per cent or less of free formaldehyde when labelled with the warning statement:

CONTAINS FORMALDEHYDE; or

(g) in preparations containing less than 0.05 per cent of free formaldehyde.

METHYL METHACRYLATE – Amend entry to read:

† METHYL METHACRYLATE (excluding its derivatives) **except**:

(a) for cosmetic use; or

(b) in preparations containing 1 per cent or less of methyl methacrylate as residual monomer in a polymer.

PARAFORMALDEHYDE – Amend entry to read:

† PARAFORMALDEHYDE (excluding its derivatives) **except**:

(a) for human therapeutic use;

(b) in oral hygiene preparations;

(c) in nail hardener cosmetic preparations containing 5 per cent or more of free formaldehyde;

(d) in nail hardener cosmetic preparations containing 0.2 per cent or less of free formaldehyde when labelled with the statement:

PROTECT CUTICLES WITH GREASE OR OIL;

(e) in all other cosmetic preparations;

(f) in other preparations containing 0.2 per cent or less of free formaldehyde when labelled with the warning statement:

CONTAINS FORMALDEHYDE; or

(g) in preparations containing less than 0.05 per cent of free formaldehyde.

4.4 2,4-D

The Committee noted the inclusion of 2,4-D as a standing item on the agenda to remind the Committee that the implementation date for the February 2008 Resolution (2008/52-6, Schedule 6 with a ≤ 20 per cent cut-off to Schedule 5) was 1 January 2009.

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

5.1 SUSDP, PART 4

5.1.1 PYRITHIONE ZINC

PURPOSE

The Committee considered the scheduling of pyrithione zinc including a proposal to exempt ≤ 0.1 per cent when in construction materials such as jointing compounds and sealing materials.

BACKGROUND

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

The December 1965 Meeting first scheduled pyrithione zinc in Schedule 2. The February 1967 Meeting subsequently agreed to a ≤ 2 per cent Schedule 2 to Schedule 5 cut-off. The August 1985 Meeting deleted the Schedule 5 entry and amended the Schedule 2 entry so that it applied to human therapeutic use only.

The August 2000 Meeting agreed to a Schedule 6 pyrithione zinc entry following consideration of the toxicology of a marine antifouling paint. The Committee also agreed that pyrithione zinc veterinary hair products should be exempt from scheduling.

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

The February 2007 Meeting considered the harmonisation of pyrithione zinc and amended the Schedule 2 entry by referring to “for treatment of the scalp” rather than specifying “semi-solid” or “shampoo”. The Members similarly amended the Schedule 6 entry for non human therapeutic shampoos.

The February 2008 Meeting decided to include a Schedule 6 to Schedule 5 cut-off for paints containing ≤ 0.5 per cent. The Committee also corrected an erratum from the

February 2007 decision which inadvertently omitted animal hair products from the Schedule 6 exemption.

The June 2008 Meeting, while considering a comment regarding use on the human scalp, was advised that a submission for the October 2008 Meeting had been received that was very similar to the carbendazim and octhilinone considerations from the June 2008 Meeting.

DISCUSSION - SUBMISSIONS

Members noted that XXXXX had submitted an application seeking an exemption for pyrithione zinc when used in paint and construction materials at ≤ 0.1 per cent. The applicant proposed the following Schedule 6 amendment: "PYRITHIONE ZINC when used in paint and construction materials at 0.1 per cent or less".

The Committee was advised that no toxicology data was provided with the submission. XXXXX addressed this by asserting that pyrithione zinc had previously been examined and scheduled.

Members noted the following from XXXXX submission:

- Pyrithione zinc has been used extensively in surface coatings, particularly in the USA, but not previously in Australia. Changes to technology in protecting the pyrithione zinc in coatings from UV degradation and loss by leaching have shown potential for use in Australia.
- The applicant asserted that manufacturers of wall board jointing compounds needed to provide protection to these products to prevent fungal growth on plaster compounds between application and drying. Fungicides may also be added to other plaster products, such as skim coats and sealing compounds that were used to coat surfaces and in joints such as baths, sinks and showers to stop the ingress and/or escape of moisture.
- The applicant stated that jointing compounds and sealants were commonly referred to as construction products within the industry.

Members also recalled the following toxicology data for pyrithione zinc considered at the June 2008 NDPSC Meeting:

SCCNFP Review

- Noted the following from a review by the EU's Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers (SCCNFP) European Cosmetic, Toiletry and Perfumery Association (COLIPA) (http://ec.europa.eu/food/fs/sc/sccp/out225_en.pdf) on the safe used of ≤ 2 per cent for preservative and non-preservative purposes (in hair products).

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

<u>2004 US EPA review</u>

- Moderate acute oral toxicity (LD_{50} 267 mg/kg). No significant acute dermal toxicity (LD_{50} > 2000 mg/kg).
- Was a severe eye irritant but did not appear to demonstrate significant dermal irritation. Did not demonstrate dermal sensitization potential.
- Repeat dose:

  - Dermal – relatively non-toxic (decreased food consumption, decreased body weight gain, decreased food efficiency at the limit dose of 1000 mg/kg/day).
  - Oral – significantly greater toxicity (increased relative organ weights, clinical toxicity, and hind limb weakness at 3.75 mg/kg/day).

- Negative for mutagenic effects. Caused adverse developmental effects. Two dietary acute reference doses: females of child bearing age (0.0016 mg/kg/day); and general population (0.0025 mg/kg/day).
- Very high acute toxicity (low ppb) to fish and invertebrates, as well as to aquatic plant species. Causes adverse chronic impacts on freshwater and marine invertebrate reproduction and growth at very low concentrations, which indicate that pyrithione zinc may be a potential human endocrine disrupter. However, pyrithione zinc degrades fairly quickly in water and was not expected to persist for long periods in water or microbial soils and sediments. The reported octanol / water partition coefficient was < 1000 and was therefore not expected to bioaccumulate in aquatic organisms.
- There was concern that the neurotoxic effects of pyrithione zinc had not been completely characterized by the available toxicology data.

<u>August 2000 NDPSC Meeting</u>

XXXXX

- Almost no dermal irritation occurred even after daily exposure to approximately XXXXX. However, pyrithione zinc was particularly active against mucous membranes, with oral administration resulting in corrosion to the mucous membranes of the gastro-intestinal tract.
- Ocular test for a XXXXX – severe to corrosive eye irritation. However, in a low volume eye irritation assay, the effect was moderate to severe eye irritancy. The evaluator concluded that corrosive eye irritancy would be likely to occur down to concentration as low as 0.3 per cent.
- The Committee's Schedule 6 decision was based on the acute toxicological profile, in particular pyrithione zinc's acute oral toxicity and severe eye irritancy / corrosivity.

<u>August 2001 NDPSC Meeting</u>

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

Members also recalled the following from the June 2008 NDPSC considerations of carbendazim and octhilinone:

- A Member asserted that the issue surrounding this item was whether the risk at ≤ 0.5 per cent carbendazim / ≤ 1 per cent octhilinone was greater from materials identified in the application compared to paint. Another Member noted that given the broad general use of paint, the exposure risk was likely to be lower. The Committee

generally agreed, therefore, that the Schedule 6 exemptions could be broadened to cover some construction materials.

- Members noted, however, that the wording proposed by the applicant to amend the entry, i.e. "construction materials" was difficult to define and would have a broader meaning given the range of materials used in the construction industry. The Committee agreed that the wording "sealants and jointing compounds" was appropriate.
- For octhilinone only, a Member stated that because octhilinone concentration in a paint was usually calculated based on the levels present in the non-volatile content, it would be appropriate to also calculate the octhilinone content in jointing compounds and sealants on the non-volatile content. The Committee agreed.
- The following Schedule 6 amendments were therefore agreed to:

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

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

Members also noted that a pre-meeting comment from XXXXX advised that XXXXX had not raised any issues with the proposal to exempt ≤ 0.1 per cent or less of pyrithione zinc when in construction material such as jointing compounds and sealing materials. If scheduling consideration should go beyond construction materials such as jointing compounds and sealing materials, XXXXX would be able to provide additional information with regard to the risks and benefits associated with the additional uses and/or other matters under section 52E.

DISCUSSION – RELEVANT MATTERS UNDER 52E

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

A Member asserted that there was a low risk of exposure to the eye from jointing compounds and sealants containing ≤ 0.1 per cent pyrithione zinc, certainly less that the 2 per cent pyrithione zinc shampoos currently exempted from scheduling. Members generally agreed that there was minimal risk and therefore an exemption for jointing compounds and sealants containing ≤ 0.1 per cent pyrithione zinc was appropriate.

RESOLUTION 2008/54 - 14

The Committee decided to exempt pyrithione zinc from scheduling when in paints, jointing materials and sealants at 0.1 per cent or less, calculated on the non-volatile content.

Schedule 5 – Amendment

PYRITHIONE ZINC – Amend entry to read:

PYRITHIONE ZINC in paints containing 0.5 per cent or less of pyrithione zinc calculated on the non-volatile content of the paint **except** in paints containing 0.1 per cent or less of pyrithione zinc calculated on the non-volatile content of the paint.

Schedule 6 – Amendment

PYRITHIONE ZINC – Amend entry to read:

PYRITHIONE ZINC **except**:

(a) when included in Schedule 2 or 5;

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

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

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

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

(f) in paints, jointing materials or sealants containing 0.1 per cent or less of pyrithione zinc calculated on the non-volatile content.

5.2 SUSDP, PART 5

Nil.

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

6.1 BENOMYL

PURPOSE

The Committee considered the scheduling of benomyl including a proposal to upschedule from Schedule 6 to Schedule 7.

BACKGROUND

Benomyl is a broad spectrum systemic fungicide belonging to the benzimidazole class of compounds, which includes carbendazim. Its mode of action allegedly involves the disruption of the mitotic spindle apparatus leading to cellular mitotic arrest. Benomyl was first registered for use in Australia in 1968 and has been widely used as a broad-spectrum fungicide. In addition to its agricultural applications, benomyl is also used as a fungicide in paint at concentrations of up to 0.5 per cent.

The November 1982 Poisons Schedule (Standing) Committee (PSC) Meeting originally placed benomyl in Schedule 6, based on low acute toxicity, and recommended that benomyl products be withdrawn from the home-garden market through registration action, principally because of concerns over the potential for testicular atrophy and the need to minimise exposure to pregnant women (developmental toxicity) and the risk to users unlikely to take precautions, e.g. home gardeners. The recommendation for withdrawal of home garden products through registration action was reaffirmed by the August 1993 DPSSC Meeting. Separately, the August 1990 Drugs and Poisons Schedule Committee (DPSC) Meeting agreed to an exemption for paint containing 0.5 per cent or less of benomyl.

In October 2003, the APVMA suspended approvals of benomyl and registrations of products containing benomyl. Currently there are no benomyl-based products registered in Australia.

DISCUSSION - SUBMISSIONS

In 1993, benomyl attracted media attention in a number of countries, including Australia, following the publication of a British newspaper article alleging an association between benomyl exposure and the occurrence of eye defects in infants born in Britain. These allegations led to a review of benomyl in Australia, with particular emphasis on its potential for causing developmental effects. This review re-affirmed previous conclusions reported by Australian regulatory authorities between 1983-85 that teratogenicity induced by benomyl was only seen after oral gavage and not when admixed in the diet. The teratogenic response associated with bolus doses of benomyl was thought to result from a saturated excretion pathway, leading to transient high maternal systemic concentrations that crossed the placental barrier, causing malformations in the developing foetus.

Sustained exposure to benomyl in the diet only produced a teratogenic response at significantly higher doses and effects did not include microphthalmia/anophthalmia. However, during a 1993 review XXXXX noted that there were several studies, including more recent developmental studies, that had not been evaluated and therefore benomyl was nominated and subsequently accepted into the APVMA's Chemical Review Program, so that these additional studies could be reviewed and Australia's position with respect to the health concerns relating to benomyl exposure could be consolidated.

XXXXX has prepared a review on benomyl as part of the APVMA Chemical Review Program. This review is a consolidation of all data reviewed by the Department of Health and Ageing between 1983-2002, evaluations by the Joint Food and Agriculture Organization/World Health Organization Meeting on Pesticide Residues, additional data submitted by a sponsor in 2000, supplementary data and position papers submitted by sponsors in 2003 in response to the February 2003 draft version of the review, and a further data submission from a sponsor in 2004.

Members noted the following from XXXXX review:

Summary of Recommendations relevant to scheduling

- No changes were warranted to the First Aid Instructions for benomyl, or to the Safety Directions based on hazard alone. Any products containing benomyl registered in Australia should bear the following warning statement: "Contains benomyl which causes birth defects in laboratory animals. Women of child bearing age should avoid contact with benomyl".
- The toxicity profile of benomyl, in particular its developmental toxicity, appeared incompatible with its current Schedule 6 status. It was recommended that the schedule for benomyl be revised from Schedule 6 to Schedule 7 on the grounds that the chemical is a developmental toxicant in laboratory animals in the absence of maternal toxicity and that the mechanism of toxicity may be relevant to humans.
- XXXXX had no objection to the approval of benomyl technical or registration of products containing the chemical, provided that the consequent risks were managed appropriately and therefore, it was possible that benomyl products may again be registered in Australia, which would lead to occupational exposure and exposure from consumption of treated food commodities.
- There were no objections on toxicological grounds to retention of the existing exemption for paint containing 0.5 per cent or less of benomyl.

Other XXXXX conclusions

- The review found that the toxicological database on benomyl was uneven in its coverage and quality. Many of the constituent studies date back to the 1960s, and did not conform to current test guidelines or standards of reporting. Data gaps included a lack of dermal and inhalational acute toxicity studies and the absence of short-term repeat-dose studies via the oral route (with the exception of special purpose studies on

testicular toxicity). However there was extensive data on reproductive and developmental toxicity, the end points of greatest concern. Apart from skin and eye irritation and dermal sensitisation studies, there was a sufficient range of acute toxicity studies available for benomyl formulations. However, there were no suitable eye irritation studies available for benomyl active constituent. Taken as a whole, there was sufficient data to enable regulatory standards to be set for benomyl although the database was incomplete.

- At comparatively moderate doses benomyl was a reproductive toxin in males, and was a teratogen that could potentially cause severe and irreversible malformations in the foetus without concomitant maternal toxicity. Developmental toxicity was demonstrated following administration of single doses of benomyl. These effects probably arose from interference with cellular division and differentiation, which has been demonstrated in cultured cells at physiologically relevant concentrations of benomyl.

Members also noted the following from XXXXX review:

Toxicology

- Benomyl had very low acute oral toxicity, with a LD_{50} of >10000 mg/kg bw in rats. There are no experimental data on acute toxicity via the dermal and inhalation routes. Although benomyl is a skin irritant, the severity of dermal irritation is unknown, and studies on eye irritation and skin sensitisation gave no interpretable results. However, there are clinical reports of dermal sensitisation in agricultural workers.
- Until the product registrations were suspended in October 2003, benomyl was used as an agricultural fungicide in a wide variety of crops, to which it was applied by ground or aerial spray. These included fruit and vegetables, grapes, sugarcane seedpieces, tobacco, cereals, peanuts and subterranean clover. However, there were no home garden products. The products for which data was available were of very low acute oral, dermal and inhalation toxicity, caused no or slight dermal irritation, but were moderate or severe eye irritants. One product was a strong skin sensitiser in guinea pigs.
- In repeat-dose studies with benomyl by oral administration, the principal target organs were the liver and male reproductive system. Benomyl caused liver injury and testicular degeneration, atrophy, and reduced or abolished sperm production in XXXXX. XXXXX were especially sensitive to reproductive toxicity, which occurred at doses down to XXXXX. The ADI for benomyl (0.02 mg/kg bw/d) is based on a pivotal NOEL of XXXXX for testicular injury in XXXXX. In XXXXX, benomyl was carcinogenic, producing hepatocellular adenomas and lung tumours in males at dietary doses of XXXXX No treatment-related effects were detected in a chronic XXXXX study at doses of up to XXXXX, but interpretation of the results was hindered by a high incidence of testicular degeneration among controls.
- Adverse effects on male reproduction were confirmed in a two-generation reproduction study in XXXXX a reproductive toxicity screening test XXXXX and in

numerous mechanistic studies in XXXXX. Spermatogenesis was reduced at doses ranging down to XXXXX, and irreversible effects were noted in some studies at doses of XXXXX and above. Administration of benomyl to XXXXX at XXXXX during gestation and the first two weeks of lactation induced permanent reductions in the testis and accessory male sex gland weights of XXXXX.

- When administered by gavage to XXXXX, benomyl was a developmental toxin capable of inducing severe malformations in the absence of maternal toxicity. Abnormalities including anophthalmia, microphthalmia, hydrocephaly and skeletal deformities consistently occurred in studies in XXXXX. The NOEL for these effects in XXXXX was XXXXX, but in some studies XXXXX have shown greater sensitivity, with the LOEL by repeat-dose gavage administration being XXXXX. Even a single gavage dose of benomyl can cause cranial, eye and brain malformations in XXXXX foetuses. The ARfD for benomyl (0.06 mg/kg bw) is based on a pivotal NOEL of XXXXX for foetal malformation in XXXXX.
- Benomyl's effects on the male reproductive system and foetal development are probably related to its inhibition of tubulin association, which interrupts spindle formation during cell division. There is substantial evidence that benomyl induces numerical chromosomal aberrations (aneuploidy and polyploidy) in cultured cells (including human lymphocytes) at concentrations similar to those present in the blood of maternal XXXXX and their foetuses following gavage administration of a teratogenic dose. Furthermore, benomyl interferes with the differentiation of XXXXX *in vitro* by disrupting the outgrowth of neurites, an effect which may be detrimental to nerve development. Benomyl does not, however, cause structural chromosomal damage or gene mutations.
- Benomyl may present a developmental hazard to the foetuses of pregnant female agricultural workers using products containing it.
- A summary of the toxicology hazard profile of benomyl is tabulated below:

Acute toxicity

Rat oral LD_{50}	> 10,000 mg/kg bw
Worst oral LD_{50} in other species	XXXXX
Rat dermal LD_{50}	No data
Worst dermal LD_{50} in other species	No data
Rat inhalation LC_{50}	No data
Worst inhalation LC_{50} in other species	No data
Skin irritation	Contact dermatitis in XXXXX
Eye irritation	No data
Skin sensitisation	Contact dermatitis and dermal sensitisation in humans

Short-term toxicity

Target/critical effect	Hepatotoxicity XXXXX
Lowest relevant oral NOEL	Can not be reliably established
Lowest relevant dermal NOEL	XXXXX
Lowest relevant inhalation NOEC	XXXXX

Genotoxicity	Not genotoxic, however induces numerical chromosomal aberrations by disrupting mitotic spindle formation. Some clastogenic effects were noted at cytotoxic concentrations.
Long-term toxicity and carcinogenicity	
Target/critical effect	Liver cirrhosis and perturbations in hepatic biochemistry. Testicular degeneration.
Lowest relevant NOEL	XXXXX
Carcinogenicity	Induces hepatic cell proliferation leading to hepatocellular adenomas in XXXXX (not considered to be an appropriate model for the formation of hepatic tumours in humans). No evidence of interaction with DNA in genotoxicity testing.
Reproductive toxicity	
Reproduction target/critical effect	Depression in XXXXX bodyweight gain, oligospermia, seminiferous tubule atrophy/dilation
Lowest relevant reproductive NOEL	XXXXX
Developmental toxicity	
Developmental target/critical effect	Exencephaly, hydrocephaly and cleft palate in XXXXX. Micro-/anophthalmia, hydrocephalus, encephalocele in XXXXX and small kidney papillae in XXXXX.
Lowest relevant developmental NOEL	XXXXX (rats)
Delayed neurotoxicity	No evidence of delayed neurotoxicity in XXXXX
Immunotoxicity	No data

Summary	NOEL (mg/kg bw/d)	Study	Safety factor
ADI (0.02 mg/kg bw/d) [testicular degeneration]	XXXXX	Chronic feeding study in XXXXX	XXXXX
ARfD (0.06 mg/kg/bw) [micro-/anophthalmia]	XXXXX	Teratogenicity studies in XXXXX	XXXXX
NOEL for OHS assessment (women of child bearing age) [micro-/anophthalmia]	XXXXX	Teratogenicity studies in XXXXX	-

Estimates of occupational exposure from paint:

- Exposure for persons mixing and applying paint containing 0.5 per cent benomyl is estimated to be 0.0009 mg/kg bw (based on a 0.01 cm film of paint covering 25 cm^2 of skin, an absorption factor of 4.5 per cent over 4 h working day and a body weight of 60 kg), this equates to approximately 4.5 per cent of the ADI and 1.5 per cent of the ARfD. Therefore, the toxicological hazard from applying paint containing benomyl is not considered to be significant. Nor is any hazard anticipated from dried paint, given that the vapour pressure of benomyl is low and the chemical will be encapsulated within the paint film.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The following matters under 52E(1) were particularly relevant: (a) the toxicity and safety of a substance; (c) the potential hazards associated with the use of a substance; (d) the extent and patterns of use of a substance.

It was noted that in the past there had been several cases of birth defects in infants born in NZ that were potentially associated with benomyl exposure.

A Member advised that at the time of benomyl's original scheduling in the early 1980s, the scheduling committee's membership did not include the same expert members that is now set down in legislation. This point was raised in the context of reasons why the substance was scheduled as it was then, despite the awareness of the potential developmental effects and testicular atrophy. The Member also noted that the proposed mode of action (involving binding to tubulin) did not accord well with its low acute toxicity profile but noted benomyl's dramatic effect on testicular tissue at relatively low dose and suggested that "true" teratogens must be appropriately restricted.

The point was raised that the case with benomyl highlighted the need for a pro-active formal review program of existing substances. The Committee noted that the APVMA did have such a program in place and that XXXXX has input to prioritisation of that program.

A Member noted that agricultural and veterinary products containing benomyl are required to be labelled with a warning statement indicating that benomyl causes birth defects in laboratory animals and that women of child bearing age should avoid contact with this substance through requirements set down in FAISD handbook. Creating an entry for benomyl in Appendix F would require paints (which are usually not agricultural or veterinary products) containing benomyl to display the same warning statement.

XXXXX confirmed that currently there were no benomyl containing products registered with the APVMA.

RESOLUTION 2008/54 - 15

The Committee decided to:

- upschedule benomyl from Schedule 6 to Schedule 7 with a ≤ 0.5 per cent exemption for paint; and
- include benomyl in Appendix F Part 3 with Warning Statement 46: "WARNING – Contains (name of substance) which causes birth defects in laboratory animals. Women of child bearing age should avoid contact with (name of substance)."

SCHEDULE 6 – Amendment

BENOMYL – Delete entry.

SCHEDULE 7 - New entry

BENOMYL **except** in paint containing 0.5 per cent or less benomyl.

APPENDIX F, Part 3 – New entry

POISON	**WARNING STATEMENTS**	**SAFETY DIRECTIONS**
Benomyl	46	

6.2 DIDECYLDIMETHYLAMMONIUM CARBONATE / BICARBONATE

PURPOSE

The Committee considered the scheduling of didecyldimethylammonium (DDA) carbonate/bicarbonate.

BACKGROUND

DDA-carbonate/bicarbonate is not a single compound but rather is a mixture of two compounds, each with its own chemical abstracts registry number. These are quaternary ammonium compounds and may therefore currently be captured under the general schedule entries for quaternary ammonium compounds. Alternatively, DDA-carbonate/bicarbonate may currently be captured as salts of the specifically scheduled DDA-chloride (Schedule 6 with an exemption at ≤ 1 per cent when labelled "Avoid contact with eyes"). DDA-chloride has been used as a manufacturing concentrate for disinfection, wood preservation and swimming pool water treatment.

Scheduling history of DDA-chloride

The February 1979 Meeting considered the scheduling of DDA-chloride and agreed that there was no reason why DDA-chloride should not be captured by the Schedule 5 general entry for quaternary ammonium compounds.

The November 1993 Meeting again considered the scheduling of DDA-chloride following a submission for scheduling a wood preservative product containing 5.5 per cent DDA-chloride. The Committee recommended that the product be classified as Schedule 6 on the basis of acute toxicity XXXXX, moderate inhalational toxicity, eye corrosivity and severe skin irritancy properties. The Committee appeared not to have contemplated a group or class entry for DDA as the chloride salt was the only substance before them.

The August 2000 NDPSC Meeting considered the scheduling of a fabric deodoriser containing 0.125 per cent DDA-chloride. The main hazard with DDA-chloride appeared to be eye irritation and the Committee decided to exempt from scheduling preparations containing ≤ 1 per cent DDA-chloride on the basis of reduced toxicity of low concentration preparations and the ability of the label "Avoid contact with eyes" to adequately warn of any hazard.

DISCUSSION - SUBMISSIONS

XXXXX was seeking APVMA approval of DDA-carbonate/bicarbonate as a technical active. The application stated that DDA-carbonate/bicarbonate had similar toxicological properties to its analogue DDA-chloride, which had been previously assessed and approved. The applicant also stated that DDA-carbonate/bicarbonate would be a replacement raw material for the existing technical active, DDA-chloride.

XXXXX has undertaken an evaluation of XXXXX application and recommended:

XXXXX

Scheduling

- The scheduling of DDA-chloride (Schedule 6 with an unscheduled cut-off at ≤ 1 per cent when appropriately labelled, together with an Appendix E entry) was also considered appropriate for DDA-carbonate/bicarbonate for the following reasons:
  - The acute oral toxicity was the same for both compounds;
  - Both compounds are corrosive to the eyes and skin;
  - The toxicity of DDA-carbonate/bicarbonate had been bridged to the toxicity of DDA chloride, since both dissociated to a common bioactive antimicrobial cation (the quaternary didecyldimethylammonium ion); and

- The impurities found in DDA-carbonate/bicarbonate were not expected to add significantly to the toxicity of the parent compound.

- The Committee should also consider the need for warning statements, similar to those for DDA-chloride, to address the risks associated with the corrosive properties of this compound.

Public health standards

- DDA-carbonate/bicarbonate was not being considered for food producing use and no residues of this product were expected in food from its proposed use. Therefore an ADI and an ARfD were not established for DDA-carbonate/bicarbonate.

Product label statements

- **First Aid Instructions**
  - If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 131126; New Zealand 0800 764 766.
  - If swallowed, do NOT induce vomiting. Give a glass of water.
  - If skin contact occurs, remove contaminated clothing and wash skin thoroughly.
  - If in eyes, hold eyes open, flood with water for at least 15 minutes and see a doctor.

Members noted the following from the evaluation report:

- The data package provided in support of the submission comprised four acute toxicology studies on DDA-carbonate/bicarbonate manufacturing concentrate XXXXX, three acute toxicology studies on DDA-chloride and a justification for using data on the analogue compound DDA-chloride as a bridge to support the approval of DDA carbonate/bicarbonate.
- The applicants justification for why DDA-chloride data would be appropriate for use as bridging data in support of DDA-carbonate/bicarbonate included:
  - At concentrations not exceeding the water solubility and at potential exposure concentrations, the quaternary ammonium compound would be completely dissociated in aqueous solution, and therefore the cation active in the case of DDA-carbonate/bicarbonate would be just as readily available for biological effects as that of DDA-chloride.
  - In the body, the anion associated with the positively charged DDA^+ will change many times depending upon the type and concentration of anions that are present in body compartments in which the DDA^+ resides at any given time. For example, following an oral dose, essentially all of the DDA^+ molecules would be associated

with Cl^- (whether dosed with DDA-chloride or DDA carbonate) because of the high concentration of Cl^- (from HCl) in the stomach of most mammals.

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

DDA-chloride

- The acute oral LD_{50} of DDA-chloride in XXXXX was XXXXX and in XXXXX was XXXXX, these values both in the moderate range. The acute dermal toxicity was low, the LD_{50} for abraded skin XXXXX and that for intact skin XXXXX. DDA-chloride was a severe eye and skin irritant in XXXXX. DDA-chloride was not found to be a skin sensitiser in XXXXX.

A No Observable Effects Limit (NOEL) of XXXXX DDA-chloride XXXXX was established following XXXXX.

DDA-carbonate/bicarbonate

- Based on the findings of the four acute toxicological studies evaluated, DDA-carbonate/bicarbonate was considered to have moderate acute oral toxicity. The acute dermal toxicity of DDA-carbonate/bicarbonate could not be established due to its corrosive nature. The table below summarises the submitted acute toxicity studies involving DDA-carbonate/bicarbonate (conducted with XXXXX active in a mixture):

Study type	Species	Result
Oral	XXXXX	XXXXX
Dermal	XXXXX	N/A
Skin irritation	XXXXX	Corrosive
Photoallergy	XXXXX	Not a photosensitiser

- Subchronic toxicity, developmental toxicity, two-generations XXXXX, chronic toxicity, carcinogenicity, ADME XXXXX and *in vitro* skin penetration-human skin have been bridged to data on DDA-chloride.

The Committee additionally noted the following pre-meeting submissions:

- XXXXX who marketed cleaning/disinfectant products containing DDA-chloride, indicated that they were not aware of the specific aspects triggering the consideration of scheduling, nor were they aware of any particular issues with the regulation of DDA-chloride locally or internationally and may have information which would be useful in considering the scheduling.
- XXXXX, whose interest lay mainly with DDA-chloride which was used by XXXXX in disinfectant products below 1per cent. Based on their current knowledge of DDA-chloride and its toxicity and safety, the risks and benefits associated with the use and the extent and patterns of use, did not believe that further changes to the scheduled entry for DDA-chloride are warranted.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The following matters under 52E(1) were considered particularly relevant to this consideration: (a) the toxicity and safety of a substance; (c) the potential hazards associated with the use of a substance; (i) any other matters that the Committee considers necessary to protect public health.

A Member suggested that each substance should be individually listed in the SUSDP, i.e. separate entries for both DDA carbonate and DDA bicarbonate. Members noted that separate entries would have a minor effect on the cut-off to unscheduled as differences in the molecular weights of the salts would alter the amount of DDA in a 1 per cent preparation. Additionally, separate entries would allow cumulative mixtures of different DDA salts to increase DDA content.

Another Member noted that since DDA chloride is, toxicologically, essentially the same as DDA carbonate and DDA bicarbonate, the schedule entry should be a general entry for DDA ion plus its salts. Another Member questioned whether the Committee was satisfied that all salts would have the same toxicity profile. In response it was noted that the salts under consideration contained different anions but toxicologically they were no different, which supported the introduction of a class or group entry for DDA compounds. A Member noted that the anions were not relevant to scheduling considerations as they do not contribute to the toxicity profile.

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The Committee agreed to broaden the Schedule 6 and Appendix E Part 2 DDA-chloride entries to "didecyldimethylammonium salts", creating a broad parent entry which clearly captures all salts including chloride, carbonate and bicarbonate.

SCHEDULE 6 – Amendment

DIDECYLDIMETHYLAMMONIUM CHLORIDE – Amend entry to read:

DIDECYLDIMETHYLAMMONIUM SALTS **except** in preparations containing 1 per cent or less of didecyldimethylammonium salts labelled with the statement:

Avoid contact with eyes.

APPENDIX E, Part 2 – Amendment

Didecyldimethylammonium chloride – Amend entry to read:

POISON	**STANDARD STATEMENTS**
Didecyldimethylammonium salts	A,G3

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

Nil.

8. OTHER MATTERS FOR CONSIDERATION

Nil.

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

Nil.

PHARMACEUTICALS

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

Nil.

11. OTHER OUTSTANDING MATTERS FROM PREVIOUS MEETINGS

11.1 ATROPINE

PURPOSE

The Committee considered the scheduling of atropine, including the foreshadowed decision from the June 2008 NDPSC Meeting.

BACKGROUND

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

Currently OP and carbamate pesticide products registered in Australia must display a label statement directing the user to obtain an emergency antidote supply of atropine tablets in case of poisoning. Compliance is mandatory under the Workplace Health and Safety Act.

XXXXX, in October 2007, received confirmation that the manufacturing of atropine tablets had been discontinued as of February 2006. Future manufacturing was not likely due to the restricted and small market of consumers. Because atropine tablets were also required under a First Aid Instruction (statement “m” - “give atropine if instructed”) in case of poisoning, its lack of availability in tablet form suggested that current and future users of OP and carbamate pesticides would be in breach of workplace health and safety legislation.

The October 2007 Meeting considered this issue and agreed to form a Working Group to investigate options for alternative product presentations and treatment methods. The June

2008 NDPSC Meeting considered a report from the Working Group and agreed that it was not necessary to require OP and carbamate users to have a supply of atropine at hand. It was further agreed that use of atropine requires a doctor's advice and, as workers could obtain prescriptions for Schedule 4 atropine prior to pesticide use, there was no reason to retain part (b) of the Schedule 2 atropine entry (which was therefore foreshadowed for deletion).

The Working Group report was made publicly available on the OCS website: http://www.health.gov.au/internet/main/Publishing.nsf/Content/ohp-ocs-anticholinesterase-cnt.htm.

DISCUSSION - SUBMISSIONS

A pre-meeting comment was received from XXXXX which noted that the foreshadowed decision should not impact on current cut-off levels under Schedule 2, 4 and Appendix G.

Members recalled the following from the June 2008 NDPSC Meeting:

- Requirements for atropine-related First Aid Instructions were reviewed in 2000 and at that time the clinicians recommended to retain relevant statements in the SUSDP supporting atropine use. A Member asserted that conditions have changed since then due to reduction of OP and carbamate use, increased training programs, and switch over to less toxic alternatives. During this time atropine tablets were also withdrawn from the market, yet there was no evidence of increased incidence in reported poisoning. The Committee was in general agreement that, due to the above reasons, it was no longer necessary to require OP and carbamate users to have a supply of atropine tablets at hand.
- A Member highlighted that the data on incidence of reported poisonings in no way suggested that OPs and carbamates were less toxic substances than had been previously established.
- A Member asserted that there was no need to remove the current Schedule 2 Part (b) entry as proposed, given that there were some occupations where access to atropine product was still required. This would also mean that remote area nurses would have access to such products. Another Member, however, expressed concerns on whether the availability through Schedule 2 would be the safest way to make such products available and suggested that Schedule 4 availability would be more appropriate. A Member also advised that there were mechanisms under jurisdictional legislation to allow remote area nurses to have access to Schedule 4 products. The Committee therefore agreed that proper use of atropine required a doctor's advice and, as pesticide users could obtain prescriptions for Schedule 4 atropine products prior to pesticide use, there was no reason to retain Part (b) of current Schedule 2 entry. The October 2008 NDPSC Meeting noted that the new Schedule 2 atropine entry would still allow low strength atropine tablets but these were unlikely to be appropriate for treating OP or carbamate poisoning.

- Whilst noting that there was no need to remove the existing Standard Statement SP1 in Part 1 of Appendix E (regarding use of atropine) as it was still the most effective and appropriate first aid measure available for OP and carbamate poisoning, the Members recognised that the registration requirements for atropine availability would be addressed via APVMA processes.
- A Member stated that follow up actions would also be important to advise the medical professionals regarding these developments. The Committee agreed that the Working Group report should be made publicly available on the OCS website.

Members additionally recalled the following from the Working Group report:

- The Working Group considered a contemporary position required for providing an antidote for self administration by non-medical professionals in the event of carbamate or OP poisoning, with a primary focus on the agricultural work place setting. All uses of OPs and carbamates were considered, including veterinary products.
- The conclusions of the report included:
  - Atropine was still the best treatment for OP poisoning, when administered under the supervision of a health professional.
  - Available evidence indicated a decreasing incidence of OP exposure reporting and severity of poisoning cases in an environment where atropine tablets were no longer available.
  - Atropine, in tablet form, would be difficult to administer to an unconscious patient. Atropine treatment may not be crucial for mild to moderate cases but diagnosis and treatment by a health professional was still be necessary. Therefore, the retention of the requirement for readily available atropine sulfate tablets as a first-aid treatment was difficult to justify.
  - While evidence pointed to some non-compliance in sub-groups of remote farmers, increased access to training and rural health networks would have contributed to compliance and reduced the need for a first-aid atropine antidote.
  - Warning statements and safety directions on OP and carbamate product labels instructing users to obtain atropine were no longer warranted. Therefore, FAISD and SUSDP entries pertaining to the requirement of atropine for the treatment of carbamate and OP poisonings should be amended.
- The decreased reporting rates and the severity of accidental poisonings were thought to be consequences of regulatory initiatives (e.g. stricter implementation of the legislative requirements for Schedule 7 chemicals, which had lead to the improved training of chemical operators, promotion of alternative and less toxic chemicals by regulatory agencies and integrated management practices).
- The literature on treatments for OP poisoning was equivocal in regard to the ability of alternative antidotes to atropine (oximes, benzodiazepines and combination treatment)

to reduce morbidity and mortality in humans. The injectable form of atropine was considered to be most effective.

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

DISCUSSION – RELEVANT MATTERS UNDER 52E

The relevant matters under section 52E (1), to this item, included: (b) risks and benefits; (d) extent and patterns of use; (e) the dosage and formulation; and (f) the need for access.

Members noted that no objections to the foreshadowed proposal were raised in pre-meeting comment.

Members also noted the Working Group report's recommendation that various stakeholders be advised of these developments. Members were advised that XXXXX was undertaking to notify manufactures of these developments but was not disseminating information to medical professionals etc. It was suggested that the Secretariat could write to rural and remote medical practitioners via relevant peak bodies regarding these developments (e.g., that there may be a need for remote/rural medical professionals to consider their access to atropine should a poisoning present).

RESOLUTION 2008/54 - 17

The Committee decided to amend the Schedule 2 atropine entry by deleting part (b), i.e. removing the specific entry for atropine sulfate when for the treatment of organophosphorus poisoning.

Schedule 2 – Amendment

ATROPINE – Amend entry to read:

ATROPINE (excluding atropine methonitrate) for oral use:

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

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

11.2 HYDROQUINONE

PURPOSE

The Committee considered the scheduling of hydroquinone, as foreshadowed at the June 2008 NDPSC Meeting.

BACKGROUND

Hydroquinone is a reducing agent which oxidizes to form quinone in air. Hydroquinone increases melanin excretion from melanocytes and may also prevent its production. It is used topically as a depigmenting agent for the skin in hyperpigmentation conditions such as chloasma (melasma), freckles, and lentigines (small macules that resemble freckles). Concentrations of 2 to 4 per cent are commonly used; higher concentrations may be irritants and increase the risk of ochronosis.

Hydroquinone was first included in Schedule 4 of the SUSDP in 1969 due to concerns being raised about the promotion and free availability of skin lightening creams which were being targeted to the PNG and indigenous Australian populations. The Committee agreed that, due to the highly toxic nature of this substance and the potential for ADRs, free availability was not warranted and, therefore, it should be included in Schedule 4.

The February 1971 Meeting agreed to amend the Schedule 4 entry for hydroquinone to allow an exemption from scheduling for preparations of hydroquinone containing 2 per

cent or less. At the May 1986 Meeting, a recommendation to delete the exemption from scheduling for 2 per cent preparations was made which would result in all preparations of hydroquinone for human use becoming Schedule 4. This decision was based on concerns raised regarding the potential for skin lightening creams to be used unknowingly on melanomas and, thus, delay treatment and worsen the prognosis for such patients. The Committee also considered the overall ADR profile for hydroquinone warranted inclusion in Schedule 4; however, this recommendation was not implemented.

Further discussion was undertaken at the May 1987 Meeting, where it was agreed to foreshadow creation of a new Schedule 2 entry for preparations of 2 per cent or less of hydroquinone for human therapeutic or cosmetic use. An evaluation of data addressed the concerns raised by the Committee previously about the potential for use on melanomas. It was noted that there was only one case report of this and that both dermatologists and oncologists felt that the likelihood of hydroquinone use disguising a melanoma was remote. Members agreed that the safety profile of preparations of 2 per cent or less hydroquinone warranted inclusion in Schedule 2 with an accompanying Appendix F warning statement entry. This was confirmed at the July 1987 Meeting.

At the June 2008 Meeting, the Committee noted concerns raised about possible carcinogenic properties of hydroquinone as a result of prolonged usage, following a request that the Committee give consideration as to whether hydroquinone was appropriately scheduled.

The Committee noted that the USFDA announced a review of the safety of hydroquinone products because of concerns about carcinogenicity with regard to topical use. The USFDA ruling on hydroquinone is not expected to be finalised before the end of 2008.

DISCUSSION - SUBMISSIONS

Members recalled the following points from the June 2008 NDPSC Meeting:

- XXXXX, received a letter from XXXXX regarding a February 2008 media article on the dangers of using hydroquinone cream for skin lightening. XXXXX responded and has forwarded a copy of said response to the Committee along with a request that the Committee give consideration as to whether this substance is still appropriately scheduled.
- Hydroquinone was been banned from use as a skin lightening agent in the UK and the EU as of January 2001 (although France appears to have banned its use in 1998). It also appears to have been banned from use for cosmetic purposes in Japan and South Africa (in 1998).
- On 29August 2006 the USFDA withdrew the previous ruling on the current *Skin Bleaching Drug Products For Over The Counter Human Use* (1982) products in favour of a new proposed rule.

- The USFDA proposed to issue a ruling that OTC skin bleaching drug products are not generally safe and effective (GRASE) and are misbranded. The 3 September 1982 proposed rule was withdrawn, as of 29 August 2006. In summary:
    - The USFDA has issued a notice of proposed rulemaking that OTC skin bleaching drug products are not generally recognized as safe and effective (GRASE) and are misbranded.
    - The USFDA has withdrawn the previous proposed rule on skin bleaching drug products for OTC human use, which was issued in the form of a tentative final monograph (TFM). The USFDA is issuing this proposed rule after considering new data and information on the safety of hydroquinone, the only active ingredient that had been proposed for inclusion in a monograph for these products.
    - Upon issuance of a final rule, the USFDA intends to consider all skin bleaching drug products, whether currently marketed on a prescription or OTC basis, to be new drugs requiring an approved new drug application (NDA) for continued marketing.
    - The 3 September 1982 proposed rule (47 FR 39108) was withdrawn on 29 August 2006. The new proposed rule classifies hydroquinone as nonmonograph and has withdrawn the tentative final monograph.

Members noted the following "Tentative Conclusions on Skin Bleaching Drug Products" contained in the USFDA draft report ("Proposed Rule"):

Toxicokinetic Studies

- Hydroquinone (2-per cent) in an alcoholic vehicle was found to penetrate readily in human forehead skin following a single topical exposure *in vivo* for 24-hour duration. The average percutaneous absorption of hydroquinone was 57 per cent. The addition of a penetration enhancer increased the absorption to 66 per cent. Addition of a sunscreen, with and without a penetration enhancer, decreased the absorption of hydroquinone (35 and 26 per cent, respectively).

Carcinogenicity Studies

- Carcinogenesis studies on orally administered hydroquinone have indicated "some evidence" of carcinogenicity in male and female rats and in female mice. A Carcinogenicity Assessment Committee agreed that the available data are insufficient to rule out the potential carcinogenic risk from topically applied hydroquinone and recommended that additional studies be performed to assess the safety of skin bleaching drug products containing 2-per cent hydroquinone.

The USFDA's Tentative Conclusions

- The actual risk to humans from the use of hydroquinone has yet to be fully determined. There is, however, evidence of carcinogenicity related to hydroquinone in animals and disfiguring effects (ochronosis) in humans. Under these circumstances,

the use of hydroquinone as an active ingredient in OTC skin bleaching drug products cannot be justified. The USFDA finds that because of the carcinogenic and ochronotic potential of hydroquinone, its use in skin bleaching drug products should not be available OTC but should be restricted to prescription use only, and users of such products should be closely monitored under medical supervision.

- The USFDA tentatively concludes that the benefits of OTC skin bleaching drug products are insignificant when compared to the potential risks and that this proposed rule would benefit society because it would eliminate a potentially unsafe drug product. The benefit of removing OTC skin bleaching drug products from the market will be a reduction in the number of cases of ochronosis that would otherwise occur each year.

XXXXX put forward the following comments:

- In addition to the OTC 2 per cent hydroquinone preparations, dermatologists have prescribed higher strength preparations prepared by compounding pharmacists.

- Over many years there have been very few adverse events associated with hydroquinone use in Australia.

- Problems associated with hydroquinone use in the United States may not be relevant to Australia because of the larger proportion of dark skinned individuals who often apply high concentrations over extensive body surfaces. In Australia, high concentrations are more commonly used to treat localised melasma hyperpigmentation or post-inflammatory hyperpigmentation.

- Evidence for carcinogenicity was based on animal studies (mice and rats) using dosages far exceeding human dosages that are delivered systemically or dermally and not topically. The Committee noted that, in order to elicit clear evidence of carcinogenicity (or, indeed any toxicological) effect, **all** pre-clinical (animal) studies require doses that far exceed standard human therapeutic doses.

- The submitter stated that it would "object to the delisting of hydroquinone, but would consider it not unreasonable to list it as a schedule (3 or) 4 substance for all strengths".

- Dermatologists throughout Australia find hydroquinone a useful therapeutic substance (without readily available, affordable, acceptable and safe alternatives) and its absence would significantly compromise their ability to care for patients.

XXXXX suggested that the present scheduling should remain until the USFDA review has been considered by the TGA, having regard to the absence of a graded scheduling regime in that country.

A submission from XXXXX stated:

- There is good scientific basis for retaining the current exemption for hydroquinone used in hair dyes based on an opinion of the Scientific Committee on Cosmetic Products and Non-Food Products (SCCNFP) on 17 February 1999.

- Separate schedule entries for hydroquinone and its derivatives be considered for any further scheduling decisions in order to prevent potential confusion surrounding the schedule entry for hydroquinone applying to derivatives of hydroquinone such as arbutin (a glycosylated hydroquinone derivative found in pears and the leaves of blueberry, cranberry and mulberry shrubs). A plant extract containing arbutin is currently used in a number of cosmetic products at low concentration.

In response to the NDPSC Secretariat enquiry as to the current status of the 'new rule' proposal on hydroquinone, the USFDA responded with the following points;

- The public submissions have been read and have raised many issues that are being addressed as the final rule is being written.
- To resolve the issues raised, the USFDA will expend considerable resources in terms of numerous USFDA scientists collaborating on the final rule, in the interests of making decisions in the best interest of public health.
- Updates on the progress of regulatory actions can be found under the Unified Agenda of Federal Regulatory and Deregulatory Actions. The most recent updates are at: http://www.fda.gov/cder/otcmonographs/category_sort/skin_bleaching.htm .

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed the following provisions of 52E were particularly relevant to this matter: (b) the risks and benefits associated with the use of a substance; (c) the potential hazards associated with the use of a substance and (i) matters that the Committee considers necessary to protect public health, including risks i.e. possible carcinogenicity.

On the issue of carcinogenicity, the Committee noted the USFDA's tentative conclusions were that the actual risk to humans from the use of hydroquinone was yet to be fully determined (further noting that animal studies pointing to *some evidence* of carcinogenicity in male and female rats and female mice was with orally administered hydroquinone). By comparison, the Committee noted that the International Agency for Research on Cancer (IARC) has the position that there is inadequate evidence in humans for the carcinogenicity of hydroquinone and limited evidence in experimental animals, the overall assessment of IARC being that hydroquinone is not classifiable as to its carcinogenicity in humans.

The Committee discussed the EU cut-offs for hydroquinone as an approved cosmetic ingredient: 0.3 per cent or less for use in hair dyes and 0.02 per cent or less in professional-use artificial nail systems. As noted in pre-meeting submissions, these cut-offs were as per the 1999 recommendations of the Scientific Committee on Consumer Products and Non-Food Products (SCCPNFP). The point was raised that hair dyes

imported from Europe would be likely to meet the EU cut-off of 0.3 per cent, rather than the Australian cut-off of 1 per cent. Given that the SCCPNFP recommendation was based on available evidence of safety, the Committee agreed that it should re-examine the 1 per cent cut-off for hair preparations by foreshadowing consideration of aligning with the EU cut-off of 0.3 per cent.

The Committee discussed the USFDA's tentative conclusions. As stated in the Proposed Rule, there is evidence of carcinogenicity related to hydroquinone in animals and disfiguring effects (ochronosis) in humans. The Committee noted that the USFDA had taken the position that, because of the carcinogenic and ochronotic potential of hydroquinone, it should not be available OTC but should be restricted to prescription use only so that its use is only under medical supervision. It was further noted that the US drug classification system does not include a pharmacist-only schedule and the use patterns in the US are not necessarily comparable to use patterns in Australia.

In summary, hydroquinone is known to carry some risk and is of limited benefit. Further, the point was made that chloasma and other hyperpigmentation conditions should not be self-diagnosed by consumers. The Committee believed that use of hydroquinone on the skin at least requires a pharmacist's supervision and so agreed to foreshadow up-scheduling hydroquinone in preparations for human external use (excluding hair dyes) to Schedule 3.

RESOLUTION 2008/54 – 18

The Committee decided to foreshadow up-scheduling hydroquinone in preparations for human external use (excluding hair dyes) and to re-examine the 1 per cent cut-off for hair preparations by foreshadowing consideration of aligning with the EU cut-off of 0.3 per cent.

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

12.1 SUSDP, PART 4

12.1.1 LIGNOCAINE

PURPOSE

The Committee considered the scheduling of lignocaine, including a proposal to broaden the current Schedule 2 exemption for dermal use (≤ 2 per cent) to also exempt use on gums.

BACKGROUND

Lignocaine is a local anaesthetic of the amide type which acts by reversible inhibition of nerve impulse generation and transmission. It is used in local, surface and topical

anaesthetics. The uses of the low dose topical formula are in the management of teething in infants, in the treatment of transient mouth ulcers, minor oral injury, new dentures and inflammation of the gums, palate and tongue.

Erythema may occur after topical use of some lignocaine formulations while transient blanching of the skin is frequent after application of eutectic lidocaine/prilocaine mixtures to the skin. True hypersensitivity reactions, including dermatitis, may rarely occur. Methaemoglobinaemia has occurred after the topical application of a eutectic preparation of prilocaine and lignocaine. After the use of this mixture in infants and children, some infants may be particularly susceptible to induced methaemoglobinaemia during the first 3 months of life probably due to their limited enzyme capacity.

In February 1998 the Committee considered a submission for rescheduling of dermal preparations containing 1 per cent or less of lignocaine in packs of 30 g or less, from Schedule 2 to unscheduled. The Committee decided that based on the use pattern at that time, it did not wish to amend the scheduling of lignocaine.

At the May 1998 Meeting, following its reconsideration of the applicant's argument, and subsequent examination of public comments, the Committee decided that it did not wish to change the decision of the February 1998 Meeting and that lignocaine would remain a scheduled substance.

The Trans Tasman Harmonisation Working Party recommended that 2 per cent lignocaine or less in dermal preparations should be exempted from scheduling. This recommendation was adopted at the February 2001 NDPSC Meeting.

DISCUSSIONS – SUBMISSIONS

XXXXX made a submission to amend the scheduling of topical preparations of 0.5 per cent lignocaine for use in the mouth, from Schedule 2 to unscheduled. Members noted that the SUSDP terminology means that topical oral use does not include internal use i.e. ingestion. The applicant made the following points:

- Lignocaine is indicated for temporary pain relief treatment of infant teething, transient mouth ulcers, new dentures and inflammation of the gums, palate and tongue. The applicant asserted that these are self-limiting conditions readily identified by the consumer and amenable to the short-term relief of pain.
- That there are several unscheduled infant teething products and products formulated as complimentary medicines available in grocery stores and that lignocaine is widely available as an unscheduled medicine in lozenges containing up to 30 mg and in dermal preparations containing up to 2 per cent lignocaine.
- The preparation in question contained 2 per cent choline salicylate which is less than half the amount found in another preparation for use in the mouth (containing 8.7 per cent choline salicylate), currently sold in grocery stores. The Committee confirmed that scheduling is per substance, not per product.

- The applicant argued that the lignocaine based product would provide an alternative for consumers seeking products containing less salicylate, as well as an alterative to the homeopathic and complementary medicine products.
- The argument was that the medicine *per se* already meets the criteria for unscheduled access and that safe and proper use of the medicine does not rely on access to a pharmacist's advice. The safe and established precedent of self selection of teething products for over 35 years in Australia was used as evidence.
- The applicant asserted that the availability of a 0.5 per cent lignocaine preparation specifically designed and packaged for use in the mouth would provide a useful alternative to more concentrated lignocaine preparations and thus help avoid potential administration or dosing errors associated with use.
- The applicant described the changes to packaging as a result of rescheduling (Appendix D), as minor. Members noted matters which may be considered under 52E (2) including "…and may take into account the labelling, packaging and presentation of a substance". The applicant had not described the safety measures for dosage that would be put into practice if the product is rescheduled.
- Throughout the submission the applicant stated that serious adverse reactions to lignocaine are uncommon but are mainly attributed to over dosage, rare hypersensitivity (characterised by skin lesions, urticaria, oedema and anaphylactoid reactions) and side effects of oral administration (including nausea, vomiting and abdominal discomfort). The following dosage information was given:
  - A 10 g tube of the product contains 50 mg lignocaine at 0.5 per cent. If the gel was to be applied every hour for 24 hours, contrary to the instructions, the total daily dose of lignocaine would be 12 to 24 mg, which is below the safe maximum daily dose for use in children under 3 years of 3 mg/kg or 25 mg every 3 hours (200 mg per 24 hours) applied topically and/or given orally.
- The following points were made in relation to pharmacokinetics:
  - Neonates and infants (up to 8 months) exhibit increased volume of distribution and delayed clearance of amide local anaesthetics compared with older children and adults and thus there is the potential to develop toxic blood concentrations during continuous infusion of local anaesthetics in this population.
  - Lignocaine is readily absorbed from mucous membranes and through damaged skin.
  - Oral bioavailability of lignocaine is around 35 per cent.
  - In general terms, there are few differences in the pharmacokinetics of local anaesthetics between children and adults.

The applicant addressed the claims under 52E (1) as follows:

(a) Toxicity and safety of the substance

- Due to the very low potential for adverse effects and lack of contraindications lignocaine is unscheduled in lozenges containing up to 30 mg and in dermal preparations containing less than 2 per cent.
- Lignocaine is also safe to use in pregnancy (Category A) and lactation.
- XXXXX, containing lignocaine 0.5 per cent for use in the mouth, has been available for 35 years with no evidence of toxicity or unacceptable risk associated with the product.
- Topical administration of lignocaine is not associated with any food or drug interactions.

(b) The risks and benefits associated with the use of the product.

- Down-scheduling would allow access to products which provide symptomatic relief from teething pain and mouth ulcers should be widely available.
- The convenience of wider access to a greater choice of preparations is of benefit to the consumer.
- There are also no risks of drug interactions, contraindications or precautions associated with topical use of lignocaine.
- The temporary relief of pain caused by teething irritation is established as a suitable indication for self-diagnosis and treatment by products with unscheduled status.
- Ingestion of up to 15 mg/kg results in only minor effects.

(c) Potential hazards with the use of the substance

- The applicant argued that potential hazards associated with use of lignocaine in an unscheduled setting have been assessed as low for lozenges containing up to 30 mg and for dermal preparations containing up to 2 per cent.
- Lignocaine plasma concentrations greater than 5 mcg/mL have been reported to result in toxic symptoms, while ingestion of 100 to 500 mg lignocaine has resulted in seizures in children. This equates to between 2 and 10 tubes of XXXXX and is most unlikely to arise.
- Reports of incorrect dosage of orally administered lignocaine preparations or accidental overdose included:
  - in 19 children, the product was given as therapeutic errors (median age: 11 months, range: 7 months–4 years). The mean ingested dose for lignocaine was 2.7 mg/kg (SD 1.3 mg) and the largest ingested lidocaine dose was 5.9 mg/kg. Two children developed minor symptoms. One child vomited twice following ingestion of 3.3 mg/kg lidocaine. The second was reported to have increased salivation and difficulty with solid food for 20 min following ingestion of 4.1 mg/kg. No other adverse effects occurred;

– a 5-month old infant was given lignocaine 2 per cent solution at a dose of 7.5 mg/kg/dose for 5 days and developed status epilepticus. A similar overdose occurred in a 15month child who developed generalised seizures.

(d) The dosage and formulation of a substance/Adverse effects and toxicity

The applicant stated that there has been only one reported adverse event to XXXXX. The applicant presented a report on published cases involving topical use and/or oral ingestion of more concentrated lignocaine preparations. The following points were to support the argument.

- In paediatric dental practice, lignocaine 5 per cent ointment is rubbed into gums, and lignocaine 4 per cent solution is also used in doses of up to 3 mg/kg.
- A 2 per cent lignocaine viscous solution is approved for use in children less than 3 years of age in doses up to 25 mg every 3 hours, with a maximum of 8 doses (200 mg) in 24 hours.
- XXXXX contains 0.5 per cent lignocaine. When used in accordance with directions, the maximum lignocaine exposure is 4 to 8 mg per day.
- Lignocaine 0.5 per cent for use in the mouth may also be used safely in unsupervised settings. Excessive use of lignocaine 2 per cent viscous for teething in an 11-month infant has resulted in seizures. The product was applied to the infant's gums 5-6 times daily for one week, with a total of 80 mL of solution used (1600 mg lignocaine), resulting in blood levels of 10 mcg/mL and seizure activity. EEG was normal 4 days after hospitalisation. This level of exposure equates to 32 packs of XXXXX.

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

- Products with similar formulations to the applicants own product have been available on the UK Market since 2003.
- Unscheduled products for topical use in the mouth are already available in Australia. XXXXX, containing 8.7 per cent choline salicylate, has been an unscheduled product for many years and primarily indicated for infant teething.
- The main products currently sold in supermarkets all contain choline salicylate.

Members noted the following from the evaluation report.

- One case was described whereby a 2 per cent lignocaine gel was applied excessively over a week, resulting in a total dose of 1600mg of lignocaine being applied to the gums of an infant. This dose induced seizures. Oral doses of up to 6mg/ kg of lignocaine in infants and small children have resulted in only minor side effects.

When used in accordance with directions, the maximum lignocaine exposure of 4-8 mg/day of lignocaine is safe.

- There is only one ADRAC report of syncope with a link to lignocaine (the term lidocaine is used in the TGA Case line listing). On 25 October 2007, a 52 year old female experienced loss of consciousness in which lignocaine was the suspected cause.
- The conclusion drawn by the evaluator was that, based on past patterns of use and toxicity profiles post-marketing, the product does not appear to have any major safety concerns over many years as a Schedule 2 item.
- The evaluator therefore recommended that the Schedule 2 entry for lignocaine be amended so that < 2 per cent lignocaine for use on the gums be exempt from scheduling.

The applicant confirmed that it had no comments to make on the evaluator's recommendations.

XXXXX made the following points.

- That the exemption applying to lignocaine for dermal use not be broadened to include gums.
- The assertion was made that data on systemic absorption is limited.
- The fatal ingestion by a young child was cited, following the use of oral viscous preparations containing lignocaine. The assumption was made that these oral preparations would not be captured by the request for extension of the schedule 2 exemption.
- A literature review conducted by the NSW Poisons Information Centre found that oral doses under 6mg/ kg of lignocaine ingestion are unlikely to cause adverse symptoms but require observation, and that severe toxicity is unlikely unless doses of more than 15mg/ kg are ingested. Ingestion of 1.5mL of a 2 per cent lignocaine preparation could pose a potential risk to children under 5 kg.
- The pleasant flavourings used in topical preparations should be taken into account in rescheduling decisions.
- Restriction to pharmacy sales provides easy access to professional advice on safe use, including potential risks associated with overuse and storage to avoid accidental ingestion.

XXXXX made the following points.

- Reservations about down scheduling, because of the possibility that some parents may use teething gels too frequently.
- Advice of the Medicines Evaluation Committee (MEC) should be sought.

XXXXX submission included the following points.

- That this product is safe, effective and has little potential for abuse or misuse and so has no objection to the proposal *per se*.
- There is potentially only one product (a teething gel) that this rescheduling would affect.
- MIMS product information contraindicates gel for children less than 6 months of age, and suggests an advisory statement be required on the packaging of this and any other product.
- Therefore, does not support making any product for the treatment of mouth ulcers exempt from scheduling.

DISCUSSION – RELEVANT MATTERS UNDER 52E

It was noted that, while the Gazette notice referred to 2 per cent lignocaine, the data presented in the rescheduling submission related to 0.5 per cent lignocaine.

The point was made that the intended indication was for use as a teething gel (i.e. in infants) and consideration of use in this particular patient population was a critical issue. A member raised the fact that post-marketing data probably related to all presentations for use on the gums and the majority of such products containing lignocaine are actually indicated for adults. Thus, these data may not truly reflect the safety profile in the intended population. Further, the applicant compared the safety of lignocaine in lozenges to the gel preparation stating that gel would be no more hazardous than a lozenge. The Committee noted that lozenges are only indicated for persons aged 6 years and older.

A Member stated that treating the clinical symptoms of a teething infant is more complex than simply providing a teething gel alone. The infant may be febrile, may have an associated nappy rash or suffering other typical symptoms associated with teething. With this in mind, a pharmacy provides the appropriate setting to ensure adequate health care advice is given, addressing the matter *in toto*. This consideration is relevant to 52E (1) (h), the purpose for which a substance is to be used, as well as (i) other matters considered necessary to protect public health.

While the applicant quoted an oral bioavailability for lignocaine of approximately 35 per cent, the Committee noted that bioavailability via oral mucosa is close to one hundred per cent. The Committee therefore contested the applicant's claims that lignocaine has a wide therapeutic index for this presentation and indication. Specifically, of the 28 reported cases, two children developed adverse effects, although no seizures or arrhythmia were reported ("*Lignocaine and chlorhexidine toxicity in children resulting from mouth paint ingestion: A bottling problem*." Journal of Paediatrics & Child Health. 42(6):350-353, June 2006.). The doses which caused these ADRs were quoted as 3.3 mg/ kg and 4.1 mg/kg respectively. This would translate, for a six kilogram infant, to 19.8 mg and 24.6 mg total dose respectively. Given that these overdoses involved oral administration

of a paint and lignocaine's oral bioavailability is approximately 35 per cent, administration of seven milligrams as a single dose via the oral mucosa in the infant could potentially result in such adverse effects. This would equate to only 1.4 mL of a 0.5 per cent oral gel preparation. This weighed heavily on the Committee's consideration, given that mucosal membrane is the intended route of administration.

The Committee agreed that there tended to be a public perception that products which are available on a supermarket shelf are of low risk. Further to this point, a situation might arise whereby a concerned parent may use more of the product than dosing instructions recommend, in an attempt to alleviate an infant's discomfort more quickly. Given the concerns raised by the Committee about potential for ADRs at doses only slightly greater than the therapeutic dose range, the use of this substance for the intended indication is not without risk, and therefore not suitable to be made available without any scheduling restriction.

In order to mitigate this risk, the Committee considered a possible reduction in pack sizes with a view to reducing the risk of accidental overdose in an infant. On balance, it was the Committee's view that while a pack size restriction might go some way towards reducing risk, the intended use patterns and concerns relating to the potential for ADRs in this patient population were such that down-scheduling could not be justified.

RESOLUTION 2008/54 – 19

The Committee decided that the current scheduling of lignocaine remained appropriate.

12.1.2 KETOTIFEN

PURPOSE

The Committee considered a proposal to reschedule ketotifen 0.025 per cent or less for ophthalmic use from Schedule 3 to Schedule 2.

BACKGROUND

Ketotifen is a tricyclic benzocycloheptathiophene derivative which has been shown to inhibit passive cutaneous anaphylaxis by antagonism of slow reacting substance of anaphylaxis (SRS-A). Ketotifen shows little anticholinergic activity but has specificity for H1 receptors. It also raises intracellular cyclic AMP levels by inhibiting phosphodiesterase. Ketotifen is a selective non-competitive inhibitor of H1-receptors. Furthermore, it is a mast cell stabilizer and works by inhibiting the release of mediators involved in hypersensitivity reactions. Ketotifen has been shown to inhibit chemotaxis and activate eosinophils.

The November 1998 NDPSC Meeting agreed to include ketotifen in Schedule 4 of the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP). This decision

came from recommendations of the July 1998 Trans Tasman Harmonisation Working Party (TTHWP) Meeting.

The April 2004 Australian Drug Evaluation Committee (ADEC) Meeting recommended the approval of an application by Novartis Pharmaceuticals Australian Pty Ltd to register Zaditen; containing the new substance ketotifen (present as ketotifen hydrogen fumarate) 250 μg/ mL ophthalmic solution, in bottles, for use in the symptomatic short term treatment of seasonal allergic conjunctivitis (SAC) in adults and children 3 years or older.

At the February 2006 NDPSC Meeting, the Committee considered an application for a Schedule 3 classification (and Appendix H listing) for ketotifen 0.025 per cent or less for ophthalmic use. The Committee agreed to reschedule ketotifen in topical eye preparations containing 0.025 per cent or less of ketotifen from Schedule 4 to Schedule 3 on the basis that the product fulfilled criteria for Schedule 3 listing. It was noted that such an approach would also result in harmonisation with New Zealand. The Committee further agreed on the basis of potential public health benefit to include ketotifen in Appendix H.

Members recalled the following from the February 2006 submission:

- Ketotifen eye drops were well tolerated and safe in all populations and age groups, with no clinically significant changes in blood pressure or heart rate and no significant findings noted on visual acuity, pupil size and reactivity or slit-lamp examination. Adverse events were usually mild or moderate in intensity. These include burning or stinging of the eyes, blurring of vision, dry eyes, dry mouth, skin rash, eczema, urticaria or other allergic reactions and headache and somnolence, all occurring in less than 1-2 per cent of cases and appropriately listed in the approved Product Information (P.I.).
- There were over two million patient-years exposure for ketotifen 0.025 per cent and 0.05 per cent. Six Periodic Safety Update Reports (PSURs) had been conducted with no new safety issues identified. The majority of reported Adverse Drug Reactions (ADRs) related to symptoms and signs which were expected, i.e. ocular irritation such as itching, burning, increased tearing and conjunctival oedema.
- SAC was not life threatening, generally self-limiting over several days to months and can be treated by self-management of the symptoms. There was low potential for abuse or harm from inappropriate use.

DISCUSSION - SUBMISSION

A submission was received from XXXXX to amend the scheduling of ketotifen 0.025 per cent or less for ophthalmic use to Schedule 2 (Pharmacy Medicine) which claimed the following:

- Ketotifen 0.025 per cent eye drops met the assessment factors for a Schedule 2 medicine.

- Ketotifen had a well established safety profile with significant post marketing data. The substance has relatively minor side effects often associated with the underlying condition.
- Patient exposure to ketotifen (0.025 per cent and 0.05 per cent) eye drops is estimated to be more than 2.4 million patient years. Ketotifen 0.025 per cent eye drops have been supplied in Australia since September 2004; in USA since October 2006; in Canada and the European Union for approximately 7 to 8 years; in Sweden, Norway, Denmark and Iceland (OTC) from August 2003 through to March 2004 and in New Zealand since March 2005.
- With the availability of ketotifen eye drops as a Schedule 3 medicine since September 2006, consumers should be familiar enough with the medicine for it to be rescheduled under Schedule 2.
- Data show that topical eye preparations containing 0.025 per cent or less ketotifen have at least comparable safety to other Schedule 2 medicines used for the treatment of SAC.

The submission addressed the following matters under 52 E:

(a) Toxicity and safety

- The maximum recommended total daily dose of ketotifen for ophthalmic use corresponds to approximately 30μg/ day or 0.6μg/kg/day for a 50 kg patient. The total amount of ketotifen in a 5 mL bottle of eye drops is 1.25 mg. Safety studies showed that IV doses of ketotifen (15mg/ kg) were necessary to induce cardiovascular effects (hypotension) in cats and dogs. Repeated oral doses of up to 25 mg/kg/day for five weeks in rats and 5 mg/kg/day for 52 weeks in monkeys did not result in changes in the ECGs. Very large oral doses (50-80mg/ kg) were necessary to induce cardiac changes in dogs. Tachycardia was not proved to be a safety concern in humans after more than 25 years of clinical use of oral ketotifen.

- Long-term toxicity studies, including reproduction, genotoxicity, mutagenicity and life-span rodent carcinogenicity testing, reinforced the low risk of any potential long term ill-effects associated with ketotifen. Local tolerance and ocular toxicity studies (including repeat instillations of high concentrations of ketotifen and chronic exposure to the commercial formulation for up to 26 weeks) did not reveal any potential for ocular or systemic toxicity.
- The applicant stated that it has been established, through clinical studies, that ketotifen 0.025 per cent eye drops were well tolerated and safe in all clinical populations and age groups. No clinically significant changes in blood pressure or heart rate, visual acuity, pupil size and reactivity or slit-lamp examination were found.

- It was reported that adverse events were usually mild or moderate in intensity and resolved on discontinuing therapy. The safety of ketotifen 0.025 per cent eye drops were further supported by cumulative experience with ketotifen 0.05 per cent eye drops in Japan and with oral formulations available world-wide that are administered at much higher doses than the eye drops.
- The applicant supported the claim with post-marketing safety evidence of ketotifen eye drops in seven PSURs, where no new safety findings were identified since the product was first registered in Australia.

(b) Risks and benefits

- It was asserted that the clinical efficacy of ketotifen has been established in seven placebo controlled trials involving 1,552 subjects (814 treated with ketotifen) with ocular pollen allergy. Ketotifen 0.025 per cent eye drops were shown to have a rapid onset of action, providing almost immediate relief from the symptoms of SAC.
- The applicant reported that topical ocular formulations of ketotifen fumarate showed little systemic drug exposure, no evidence of interference with the metabolism of other drugs due to the inhibition or induction of drug metabolising enzymes by ketotifen was found, and that no interactions with food were expected.
- The report claimed that unlike the majority of other eye drops used to treat allergic conjunctivitis, ketotifen 0.025 per cent eye drops does not contain a vasoconstrictor. The assertion that the potential for masking a serious disease was lower than with some Schedule 2 products indicated for use in the symptomatic treatment of SAC, was repeated.
- It was stated that dilated ophthalmoscopy and measurements of intra-ocular pressure did not reveal any abnormalities as adverse events where usually of mild or moderate intensity, resolving on discontinuation of therapy.

(c) Potential hazards of use associated with the use of a substance

- The applicant reported that studies conducted to support the registration of ketotifen 0.025 per cent eye drops included safety data for a total of 1,256 subjects. According to the Australian Product Information (PI) document, the most frequently reported ocular adverse effects at the recommended dose were burning/stinging and punctate corneal epithelial erosion (1-2 per cent); all other reactions were reported at a frequency of less than 1 per cent. Non-ocular adverse effects included headache, skin rash and somnolence.

(d) Potential for abuse

- The applicant affirmed that instructions on the use of the product, including the Consumer Medicine Information (CMI) leaflet, would continue to accompany the product, if ketotifen 0.025 per cent eye drops were

rescheduled to Schedule 2. They also stated that clinical results have shown no serious signs or symptoms after oral ingestion of up to 20mg of ketotifen. There had been no reported cases of overdoses with ocular formulations of ketotifen.

(e) Need for access taking into account comparative toxicity with other substances available for a similar purpose.

- Through comparative clinical studies, the applicant asserted it had demonstrated ketotifen 0.025 per cent is as effective as, or more effective than, currently available OTC treatments for SAC.
- In a pivotal registration study conducted in Australia , ketotifen 0.025 per cent eye drops were found to produce a significantly better outcome than levocabastine 0.05 per cent eye drops for the relief of symptoms of SAC (Kidd M et al., 2003 '*Efficacy and Safety of Ketotifen Eye Drops in the Treatment of Seasonal Allergic Conjunctivitis'*, http://www.bjo.bmjjournals.com).
- The applicant also pointed to a comparative study using ketotifen 0.025 per cent and sodium cromoglycate 4 per cent in the conjunctival allergen-challenge model. It confirmed that a single dose of ketotifen was superior to a 2-week regimen of cromoglycate four times daily in alleviating symptoms of allergic conjunctivitis (Greiner JV et al. 2002, '*Single Dose Ketotifen Fumarate .025% vs 2 weeks of Cromolyn Sodium 4% for Allergic Conjunctivitis*' Advances In Therapy Vol 19. No 4.). It was further stated that ketotifen 0.025 per cent eye drops do not contain a vasoconstrictor and that they have less potential than some of the fixed combination eye drops for masking a serious concomitant disease. The applicant reiterated that, unlike some antihistamines (H1-receptor antagonists), ketotifen does not adversely influence the ECG (including QT time).
- The applicant referred to the PIs of two other eye drops containing lodoxamide and levocabastine respectively. Their adverse event profiles compare favourably to that of ketotifen eye drops. Both of these products are Schedule 2 medicines.

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

- The submission asserted that there are no potential public health issues arising from Schedule 2 availability of ketotifen 0.025 per cent eye drops due to the favourable safety profile of the drug and the lack of potential drug interactions. The applicant further stated that self assessment of SAC by the patient and use of ketotifen without direct supervision of a pharmacist has been found, through clinical testing, to be safe.

The applicant also gave the following summary of marketing experience:

- The applicant described new international marketing experience gained in Japan where ketotifen 0.05 pre cent eye drops have been available since 1991. The post-marketing safety of ketotifen 0.025 per cent and 0.05 per cent eye drops had been monitored and evaluated in multiple PSURs.
- The applicant repeated the statement that no change in the safety profile of ketotifen eye drops had been observed and no new safety findings identified in their report. The majority of reported adverse events have been related to signs and symptoms of ocular irritation such as itching, burning, increased tearing and conjunctival oedema. It was also put forward that some of these events may be associated with the underlying condition.

Members noted the evaluation report which suggested that ketotifen should be available as a Schedule 2 medicine, given that other comparable histamine products for SAC are available in Schedule 2. The evaluator supported the applicant's arguments: that there is substantial local and overseas post marketing experience, consumers should be familiar with the use of the product and rescheduling would bring ketotifen into line with the majority of other preparations indicated for the treatment of SAC. The evaluator cited the lack of any new PSURs safety findings since the product was first registered. The evaluator specifically supported the applicant's assertions regarding safety, stating that ketotifen:

- is suitable for self-treatment of a minor ailment which a consumer can self-monitor;
- has extremely low potential for abuse or for potential harm from inappropriate use;
- has low potential for harm from inappropriate use;
- has low or well characterised incidence of ADRs;
- has a wide therapeutic index;
- has low risk of masking serious disease; and
- has a low risk of compromising medical management as the condition it treats (SAC) does not require ongoing or close medical management as it is easily recognised by the consumer and requires short term treatment.

The applicant submitted a pre-meeting comment on the evaluation report. The applicant welcomed the evaluators' suggestion that the request for down-scheduling from Schedule 3 to Schedule2 be accepted. The applicant provided the following comments regarding the report;

- The evaluation report was clear and concise and provided a summary of the noteworthy features of the substance.
- The applicant welcomed the evaluator's recommendations and believed that the availability of this product as a Schedule 2 medicine would provide a significant

benefit to consumers by allowing more ready access to treatment with a favourable safety profile.

XXXXX made a submission stating that ketotifen eye drops should remain Schedule 3 on the grounds of safety and to encourage appropriate use which is more likely to occur via a pharmacist consultation at the time of purchase. The following points were made.

- Retaining Schedule 3 status means that a pharmacist is able to advise customers as to when they need to see a doctor if the condition does not improve and to give storage and disposal information. The pharmacist is also able to advise the customer on adverse reactions that may occur.

- Consultation with a pharmacist supports the preferred approach of overall caution in the treatment of all eye conditions.

XXXXX made a submission expressing no objection to this proposal.

DISCUSSION – RELEVANT MATTERS UNDER 52E

XXXXX

It was agreed that the systemic side-effects for ketotifen was commensurate with the condition (i.e. seasonal allergic conjunctivitis). In particular, the incidence of corneal epithelial erosion was discussed (listed in the PI as common adverse reaction i.e. one to two per cent occurrence). The Committee agreed that the occurrence of this adverse reaction may actually be related to the condition itself, rather than the ketotifen *per se*.

The Committee concurred that the safety data presented demonstrated ketotifen to have comparable safety to other treatments for seasonal allergic conjunctivitis which are already Schedule 2. Further, it was noted that there is little systemic absorption and that ketotifen has a wide therapeutic index. It was concluded that it was appropriate to down-schedule ketotifen 0.025 per cent or less for opthalmic use to Schedule 2.

RESOLUTION 2008/54 - 20

The Committee decided to reschedule ketotifen 0.025 per cent to Schedule 2 and remove it from Appendix H.

Schedule 2 – New entry

KETOTIFEN for ophthalmic use in preparations containing 0.025 per cent or less of ketotifen.

Schedule 3 – Amendment

KETOTIFEN – Delete entry.

Schedule 4 –Amendment

KETOTIFEN – Amend entry to read:

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

Appendix H – Amendment

KETOTIFEN – Delete entry.

12.1.3 ELECTRONIC CIGARETTES CONTAINING NICOTINE

PURPOSE

The Committee considered a proposal to amend the scheduling of nicotine in relation to use in electronic cigarettes or e-cigarettes.

BACKGROUND

Nicotine is a highly toxic substance and in acute poisoning, death may occur within minutes due to respiratory failure arising from paralysis of the muscles of respiration. The fatal oral dose of nicotine for an adult is from 40 to 60 mg. Less severe poisoning causes initial stimulation followed by depression of the autonomic nervous system. Nicotine is rapidly absorbed through the skin, by inhalation and by ingestion. Typical symptoms of nicotine absorption include burning of the mouth and throat, nausea and salivation, abdominal pain, vomiting, diarrhoea, dizziness, weakness, hypertension followed by hypotension, mental confusion, headache, hearing and visual disturbances, dyspnoea, faintness, convulsions, sweating, and prostration. Transient cardiac standstill or paroxysmal atrial fibrillation may occur.

In June 1991, the Schedule 4 entry for nicotine was amended to include all preparations which could be used as an aid in stopping smoking e.g. transdermal patches. At the August 1993 meeting, the Committee considered a submission to have 2 mg sublingual tablets rescheduled from Schedule 3 to Schedule 2 and the 4 mg rescheduled from Schedule 4 to Schedule 3. This submission was unsuccessful. At the November 1993 Meeting, after receiving advice from ADEC, the Committee agreed that Schedule 4 remained appropriate for the patch formulations. At the November 1987 Meeting, it was decided that nicotine (in chewable tablets containing 2mg or less) was to be placed in Schedule 3. The entry was, “Schedule 3 new entry - Nicotine in chewable tablets containing 2 mg or less of nicotine per tablet for use as an aid in withdrawal from tobacco smoking.”

The first reference to sublingual use of nicotine appears to be at the February 1999 Meeting. The decision was that the nicotine entry in Schedule 3 should be changed to, “Nicotine as an aid in withdrawal from tobacco smoking in preparations for inhalation or sublingual use.”

At the February 1997 Meeting, the Committee agreed that the 2 mg nicotine chewing tablet could be rescheduled to Schedule 2. However, the Committee did not agree to place the 4 mg tablet into Schedule 2 because it was considered that it was more advantageous to put this preparation into Schedule 3 to enable heavy smokers to be counselled in a clinical setting, which had been seen as particularly beneficial for this group of smokers.

The issue of advertising of nicotine gum as part of a nicotine replacement therapy (NRT) program was canvassed at length at the February 1997 Meeting. While the Minutes of this meeting do not indicate whether the Committee expressed a specific opinion on the issue of advertising, the information presented a strongly positive view of the benefits of advertising NRT as part of smoking cessation programs. However, the effect of the NDPSC decision to retain the 4 mg nicotine gum in Schedule 3 precluded the complementary advertising for the higher-strength product. The Committee recalled that Appendix H came into being after May 1998.

At the May 1997 Meeting, the Committee considered a submission requesting that nicotine in herbal cigarettes be exempted from scheduling. Herbal cigarettes containing nicotine are captured by the Schedule 7 entry for nicotine. The Committee noted comment from XXXXX advising that, from a public health perspective, perhaps the greatest concern would be that the market availability of an herbal cigarette may deceive both current and potential smokers into believing that they might be a safe alternative to conventional cigarettes.

At the November 1998 Meeting, the Committee decided that Schedule 3 was appropriate for nicotine in cartridges for oral inhalation and agreed that the arguments in support of advertising of NRT considered at the August 1998 Meeting could be applied to the inhaler formulation and that advertising of the formulation should be permitted. At the August 2001 Meeting the Committee agreed that nicotine lozenges would have a pharmacokinetic and safety profile, as well as toxicological properties to the sublingual tablets, and so was appropriate for inclusion in Schedule 3. The February 2002 NDPSC meeting agreed to the rescheduling of nicotine inhaler for use as an aid in withdrawal from tobacco smoking, from Schedule 3 to Schedule 2. The decision was made on the basis that nicotine inhaler had a safety and side-effect profile consistent with other NRT products including the chewing gum.

At the June 2002 Meeting, in reference to non TGA approved products, the Committee noted an article reporting that the USFDA had issued warning letters to pharmacies selling illegal nicotine lollipops and or nicotine lip balm products over the internet. The products were promoted as an aid for smoking cessation or to treat nicotine addiction. The USFDA was concerned about the health risk because they appeared to be compounded and dispensed without a doctor's prescription. The products were reported to contain a form of nicotine which was not used in USFDA-approved smoking cessation products and because they were candy-like products, they also presented a risk of accidental use by children. The Committee also noted an internet advertisement for a nicotine supplement called NICO Water. The product was promoted as "a convenient

nicotine beverage for when you can't or don't want to smoke … is pharmaceutically formulated and bottled for purity with standardised pharmaceutical grade water and the approved ingredient – nicotine polacrilex to insure efficacy and safety".

At the October 2003 Meeting, the Committee agreed to exempt nicotine in gums, transdermal patches and lozenges from the requirements of scheduling to harmonise with New Zealand. The Committee was of the view that widening the availability of NRT products should encourage more smokers to quit smoking, and as a first step, this approach should improve public health outcomes. This decision was confirmed at the February 2004 NDPSC Meeting following consideration of post-meeting comments. The June 2004 NDPSC Meeting agreed to delete nicotine from Schedule 3 and it was later deleted from Appendix H.

At the June 2005 Meeting, the Committee agreed, in the interests of harmonisation with New Zealand; to exempt sublingual tablets from scheduling. The current nicotine entries therefore exempt chewing gum, lozenges, or preparations for sublingual or transdermal use from scheduling.

At the June 2008 Meeting, a member reported on a company marketing "electronic cigarettes" via the internet. The company's website made a number of claims relating to the "safety" of the product when compared to smoking normal cigarettes. This issue was referred to the TGA by the jurisdiction.

DISCUSSION - SUBMISSIONS

This matter was referred to the Committee by the Victorian jurisdictional member. Under the Therapeutic Goods Regulations 1990 , sub regulation 42CZW(1) states that a submission prepared in relation to a substance by a Committee Member and submitted before or at the meeting, about scheduling of the substance, must be considered by the Committee at the meeting. The following points were made:

- Under Victorian legislative requirements, an individual cannot supply Schedule 7 poisons wholesale without a drugs and poisons licence. However, it should be noted that, under the *Drugs, Poisons and Controlled Substances Act 1981* and associated regulations, retail sale or supply of a Schedule 7 poison cannot be prevented. This is the case even when the wholesale supplier is located in another State or Territory. The only exceptions are substances listed in the Victorian Poisons Code. This Code includes those substances listed in paragraph 41(3) of the SUSDP plus acrylonitrile, benzene, cacodylic acid, 1,2-dibromo-3-chloropronane, 4 dimethylaminoabenzine, 4,4' - methlenebis [2-chloroaniline], ovulatory stimulants, prostaglandins, retinoids, thalidomide, vinyl chloride (when it is a Schedule 7 poison) and all substances listed in Appendix C. The Code is a list of poisons which cannot be retailed (plus a Chinese medicine list.). Further, Victoria has not adopted Appendix J.
- The Committee was informed at the meeting that amendments to the Victorian Poisons Code were a Ministerial decision.

- The Member put forward that an amendment to the Schedule 4 entry for nicotine to cover internal human use (non tobacco), not solely for therapeutic use, could be considered. Such an amendment would mean that electronic cigarettes would be classified as Prescription Only. This would likely require consequential amendments to other schedule entries, but would ensure availability is restricted in a nationally consistent manner.
- The Jurisdictional representative was concerned that electronic cigarettes pose a public health risk on several fronts: that the nicotine may cause addiction in non nicotine addicted users, that websites advertising electronic cigarettes focus on the recreational aspects of the product as a cigarette replacement and that the current scheduling of nicotine might not cover this intended human use.
- The representative argued that it is incongruous with the classification to have an Schedule 7 poison available for human internal use in a recreational consumer product; as most of the substances included in Schedule 7 are agricultural products and industrial chemicals which have certain controls on use. Further, given that these products are currently not considered therapeutic goods, there is yet to be Australian evaluation on their quality and safety.

A summary of State and Territory legislation in relation to licensing requirements and supply for Schedule 7 poisons follows:

- VIC - Drugs, Poisons and Controlled Substances Act 1981 or Regulations 2006:
  - *The sale or supply of a Schedule 7 poison in Victoria by retail cannot be prevented. This applies even when the wholesale supplier may be located in another State or Territory.*
  - *Supply by wholesale is with a Drugs and Poisons Licence, or by retail adhering to legislative provisions relating to records of retail supply, restricting retail supply to those eighteen years and over, and supervised retail storage.*
- NSW - Clause 19 of the Poisons and Therapeutic Goods Regulation 2002 NSW requires written authority from NSW Health by both the supplier and the person supplied a Schedule 7 poison (except for non domestic purposes).
- TAS - Adopts Appendix J and paragraph 41 of the SUSDP. Schedule 7 poisons are banned from domestic and domestic garden use. Authorisation is required to manufacture, obtain, use or supply nicotine.
- SA – there are requirements for persons who sell by wholesale or sell by retail or supply a schedule 7 poison to a person to be licensed. [Regulation 13, 14 of the Controlled Substance (Poisons) Regulations 1996]. Regulation 22 of the Poisons Regulations specifies a person must not sell, supply, purchase or use a schedule 7 poison for a domestic or domestic gardening, purpose.
- WA - Poisons Act 1965, Section 24, (which picks up Appendix J) WA Licences Schedule 7 wholesalers but they are restricted to a range of poisons for specific

purposes e.g. veterinary, agricultural or industrial. Nicotine may only be sold by holders of retail licences who are approved persons, and these licence holders are sent a copy of the notice each time they obtain or renew their licence.

- QLD - Health (Drugs & Poison) Regulation 1996. A person cannot sell a Schedule 7 poison in QLD without the relevant licence or written authority.
- NT - A person must have an S 7 authorisation in order to purchase an S 7 product. The NT Department of Health would not issue an S 7 authorisation for consumers wishing to use an electronic cigarette, and have adopted Appendix J.
- ACT -legislation prohibits and regulates the sale of nicotine as a Schedule 7 poison. A licence is required to sell or manufacture the substance. Sale must be through an 'authorised' person only. These restrictions apply to both the community and to individuals.

Table of State and Territory Legislative Provisions on Nicotine.

Requirements and restrictions for a retailer of a Schedule 7 substance.	NSW	ACT	QLD	VIC	SA	TAS	NT	WA
Is the sale of nicotine as a Schedule 7 poison generally prohibited?	✓	✓	✓	*No*	✓	✓	✓	✓
Is the sale of nicotine as a Schedule 7 poison generally regulated?	✓	✓	✓	✓ (7)	✓	✓	✓	✓
Do you need a licence to sell nicotine as a Schedule 7 poison?	*No (w'sale)* Yes (retail)	✓	✓	Yes (w'sale) *No* (retail)	✓	✓	✓	✓
Is there an exemption for authorised persons to sell nicotine as a Schedule 7 poison? (An authorised person generally refers to medical practitioners, dentists, pharmacists, vets.)	*No*	*No (2)*	✓	N/A	✓	*No*	*No*	(4)
Do you need a licence to manufacture nicotine as a Schedule 7 poison?	*No*	✓	✓	*No(* 8)	✓	✓		✓
Who is subject to these restrictions and requirements?	I&C	I&C	I&C	I&C	I&C	I&C(4)	I&C	I&C(6)
Who can obtain a licence to sell or manufacture nicotine as a Schedule 7 poison?	I&C	I&C	I&C	I&C(8)		I&C(4)	I&C	I&C (6)

✓	Yes
No	No
I	Individual
C	Company

Key:
1 In QLD, section 298 (2) of the Health (Drugs & Poison) Regulation 1996 prohibits vaporisers.
2 Exception is for 'possession'.
3 Includes exceptions for 'possession' NT Delete.
4 Exception for possession and supply by authorised persons as part of professional practice only, cannot sell Schedule 7 poison "in an open shop" without a licence.

5 For a person carrying on business as a manufacturing or wholesale chemist.
6 A license may be issued to an individual on behalf of a company, but cannot be granted to a company in WA.
7 In Victoria there are record keeping, storage and age restriction provisions for retail sale or supply of a Schedule 7 poison.
8 Victoria does not issue a licence to manufacture. Victoria may issue a licence to manufacture sell or supply by wholesale a Schedule 7 poison or a licence to manufacture and sell or supply by retail a Schedule 7 poison.

The electronic cigarette is currently being promoted, through various websites, as a recreational product for use in bars and clubs, a fun product, with few restrictions on the period of use, the level of nicotine concentration or the quantity of nicotine inhaled through the apparatus. The intention appears to be to market to those already addicted to smoking, as well as to a new younger market not yet addicted to nicotine or smoking. The apparatus is described as a tobacco-less tool designed to resemble a traditional cigarette and to be "smoked" in the same way. The smoke is in the form of vapour mixed with nicotine from a cartridge inserted into the "cigarette".

The Gamucci website (http://www.gamucci.com.au), describes the device as "a truly healthier alternative!" The website graphics portray a sexy party girl, James Bond style image. Visuals throughout the site are slick and sophisticated. The device is described as using "state of the art sophisticated micro-electronic technology to provide users a real smoking experience without the tobacco and tar found in real cigarettes. It looks like, feels like and tastes like a real cigarette. It is truly a healthier and satisfying alternative. Join the Revolution today!" The company includes the statement that "product testing has been carried out over the last 12 months". The health statement says, "Gamucci does not include any carcinogenic substances. It looks like, feels like and tastes like a real cigarette, yet it is so much more".

Selling points included that the device is "just like a real cigarette", that it gives a nicotine hit, that it contains no tar, no tobacco, is non-flammable, non carcinogenic, reusable, that the vapour is diluted nicotine, and that the device is sophisticated, but cheap and "beat the smoking ban" legally, save up to 80 per cent on your smoking costs.

This site also listed the following claims: 1 cartridge is equivalent to 20 cigarettes, no butts, no smoke, non flammable, can be smoked everywhere, cool & sophisticated design, different flavours and strengths, rechargeable, cheaper than cigarettes and a healthier option. It includes testimonials from UK users of the product. One user says "I recommend it to everyone looking to give up." Another says "I have been smoking Gamucci for three months and I have not smoked a real cigarette since."

Some questions answered in the FAQ section included:

- *What is nicotine? "……The carcinogenic properties of nicotine in a stand-alone form have not been evaluated by the International Agency for Research on Cancer (IARC). [Secretariat note: the International Agency for Research on Cancer (IARC) is part of the World Health Organization. IARC's mission is to coordinate and*

conduct research on the causes of human cancer, the mechanisms of carcinogenesis, and to develop scientific strategies for cancer control.] Current available literature indicated that nicotine in stand alone form does not promote the development of cancer in healthy tissue and has no mutagenic properties."

- *Can I get nicotine poisoning if I continue to smoke? "…....No you will not get nicotine poisoning from using Gamucci. Gamucci has a built in electronic security system which stops automatically if too many inhalations occur within a shot space of time or you take an inhalation over 8 seconds long. The nicotine levels per inhalation are considerably lower than traditional cigarettes."*

Of note, the disclaimer at the bottom of webpage states "Gamucci is intended for use by adults and not intended for pregnant women or those who are sensitive to nicotine. Nicotine is highly addictive. Gamucci is not intended as a smoking cessation device. Gamucci is simply a healthier alternative to traditional smoking." Further, compliance or endorsement logos which might appear (to a customer) to relate to endorsement from some type of health authority actually relate to the compliance of the device to European Economic Area (EEA) regulations. (The contracting parties to the EEA Agreement are three of the four EFTA states—Iceland, Liechtenstein and Norway—and the 27 EU Member States along with the European Community. The non EU members of the EEA (Iceland, Liechtenstein and Norway) have agreed to enact legislation similar to that passed in the EU in the areas of social policy, consumer protection, environment, company law and statistics.) The CE Mark is a mandatory conformation mark; the Waste Electrical and Electronic Equipment (WEEE) and Restriction of Hazardous Substances (RoHS) relate to disposal of product and of production associated waste.

The Egar website (http://www.egar.com.au) was to have been modified on advice from the TGA; it was to no longer be claimed that electronic cigarette are designed to aid withdrawal from smoking. It is claimed to be "a healthier alternative" to smoking. The Egar site is largely based on information and format of the Gamucci Electronic Cigarette webpage. The device is also described as "A truly healthier alternative!" The website graphics portray a downmarket version of glamorous sexy party images, of attractive, young people in casual gear. The site map contains *Home*, *What is it? Benefits*, Products, FAQs, How *to Buy*, *Press* and *Contact Us* pages.

- Selling points included the following: that 1 cartridge is equivalent to 300 puffs, that the device is "just like a real cigarette", that it gives a nicotine hit, that it is non-flammable, non carcinogenic, cheap, that it can be smoked everywhere, that it has different flavours and strengths of nicotine, that it is rechargeable and a healthier option. Similar to the Gamucci site, under the heading of *Testing* the claim is made that the electronic cigarette has been extensively tested, that the cartridges are "toxicologically approved" and producted [sic] in a laboratory which is European Economic Community (EC) certified.
- FAQ Section: *What is nicotine?* "… The carcinogenic properties of nicotine in a stand alone form have not been evaluated by the International Agency for Research on

Cancer (IARC). Current available literature indicates that nicotine on its own does not promote the development of cancer in healthy tissue and has no mutagenic properties. Its' teratogenic properties have not yet been adequately researched. Nicotine replacement manufacturers recommend consultation with a physician before using a nicotine patch or nicotine gum while pregnant or nursing. However, nicotine and the increased cholinergic activity it causes have been shown to impede apoptosis which is one of the methods by which the body destroys unwanted cells. Since apoptosis helps to remove unwanted or damaged cells that may become cancerous, the inhibitory actions of nicotine may create a more favourable environment for cancer to develop, though this also remains unproven."

- This advice is followed by two disclaimers which state that the product should not be used by anyone who has a health problem or who may be pregnant or is lactating: "Egar does not claim to alleviate or cure the disease of smoking dependence nor is it designed to influence, inhibit or modify a physiological process associated with nicotine dependency and craving. In fact this product can be used to deliver nicotine, and it can be used as a smoking device where smoking is prohibited! Egar should NOT be used by people under the age of 18 years, pregnant or lactating women. It is not recommended for people with health problems. Egar is less harmful than smoking cigarettes".
- Further warnings on the website state that "Ava Tech Pty Ltd T/A EGAR Australia does NOT encourage smoking and does not recommend the act of smoking. We believe that Egar is less harmful than conventional cigarettes as it does NOT contain many of the chemicals that are associated with cigarettes. Our product may contain nicotine depending on the cartridges used, nicotine is highly addictive. Our product should not be used by people with health problems, pregnant or lactating women. This product should not be used by anyone under the age of 18."
- Statements made on either website deliver contradictory messages. While both make clear claims that their products provide a 'healthier alternative" to 'real' cigarettes and that their product will not cause cancer, they both advise (seemingly) anyone with a health problem to avoid the product and give such advice in very strong language. Further, the disclaimer is made on both sites that, according to the IARC, the carcinogenic properties of nicotine in a stand alone form have not been evaluated.

An article appeared in the Western Australian on 19 August 2008 which reported on the Committee's intended consideration of this matter. The article claimed that smokers may soon be able to "beat" smoking bans. It stated that a Government peak advisory body (i.e. the NDPSC) is examining who should be able to buy e-cigarettes and where they should be sold. A would-be distributor was quoted as saying that they do not claim to be a smoking cessation device, but a means of delivering clean nicotine. This individual stated the intention to sell online and through pharmacies. A TGA spokesperson and the President of the Australian Council on Smoking and Health were also quoted.

The Committee noted that under the *Therapeutic Goods Act 1989* it is an offence to import, export, supply or manufacture therapeutic goods in Australia unless included on

the Australian Register of Therapeutic Goods (ARTG). To date, no application has been made to include electronic cigarettes on the ARTG. The Regulatory Compliance Unit (RCU) of the TGA has been monitoring the situation in regards to supply of these products in Australia. The TGA gave the following general advice to various stakeholders who have made inquiries on electronic cigarettes:

- The objective of the *Therapeutic Goods Act 1989* is to provide a national framework for the regulation of therapeutic goods in Australia to ensure the quality, safety and efficacy of medicines and ensure the quality, safety and performance of medical devices.
- Therapeutic goods must be entered on the ARTG before they can be supplied for human use approved for supply in or exported from, Australia.
- A 'therapeutic good' is broadly defined as a good which is represented in any way to be, or is likely to be taken to be, for therapeutic use (unless specifically excluded or included under Section 7 of the Therapeutic Goods Act 1989). Therapeutic use includes use in or in connection with:
  - preventing, diagnosing, curing or alleviating a disease, ailment, defect or injury;
  - influencing inhibiting or modifying a physiological process;
- The regulation of medical devices includes the following features:
  - classifying the medical device based on different levels of risk;
  - assessing compliance with a set of essential principles for their quality, safety and performance;
  - implementing appropriate regulatory controls for the manufacturing processes of medical devices;
  - including the medical device in the ARTG; and
  - implementing a comprehensive post market vigilance and adverse incident reporting program.

In relation to current scheduling, there are two possible classifications for electronic cigarettes. Firstly, if the claim is made that the product is for aiding in the withdrawal from tobacco, Schedule 2 of the SUSDP applies and the nicotine contained within is a medicine. Further, the electronic device is a powered drug delivery system - at least a class II a medical device and needs conformity assessment and entry on the ARTG. However, if the claim is made that the product is not for aiding smoking cessation, Schedule 7 applies.

Interestingly, given that electronic cigarettes claim to aid the user in replacing “real” cigarettes by imitating the taste, smell, feel and action of smoking (as well as delivering nicotine via inhalation), it could be suggested that these devices could be seen to be therapeutic goods, even without the nicotine cartridge. Further claims made on various

Australian websites and claims made in documents lodged with the Australian patent application also add weight to these devices being considered therapeutic goods whether they include the nicotine cartridge or not.

A submission was received from XXXXX. Three copies of the submission have been received, twice from XXXXX, and once from XXXXX on behalf of XXXXX. The following points were raised:

- That the product does not fit any of the current schedule entries of the SUSDP: it does not fit Schedule 7 exemptions because it is not for human therapeutic use, it does not fit Schedule 6 because it is not for animal use, it does not fit Schedule 2 because it is not an aid to withdrawal and it does not fit Schedule 4 because it is not for human therapeutic use. Members noted that the submitter may not have realised that Schedule 7 is the parent entry so, should a product not meet the conditions of any other schedule entry; it therefore falls into Schedule 7.
- An argument was put forward that the product does not meet the definition of therapeutic good. The submission claimed that the product does not achieve its principal intended action by chemical means on the body of a human. Further, it was claimed that the product is not a medical device. That is to say that it claimed that the device does not produce any changes to the pharmacology or neurotransmitters of the human body. Provisions under 52E were addressed as follows:
- Toxicity and safety of the substance. It was stated that the product is currently labelled to comply with the Schedule 7 poison requirements; however the Dangerous Poison labelling will be left in place once the product is made exempt from these requirements. It was asserted that the capsule containing the nicotine was too large to swallow and unpalatable, being made of plastic. It was claimed that the product packaging is extremely safe, and infers that it is impossible for children to open.
- Risks and benefits. It was claimed that no major or minor risks have been identified, and that the product contains no carcinogens, and that the nicotine contained in the product cannot be ingested or applied to the skin.

In an attached report titled “How Safe is An E-Cigarette”, an independent chemical and microbiological analysis conducted by Health New Zealand Ltd (a private research company), several areas requiring further testing were noted, such as the need to measure the vaporised mist by GC-MS after drawback, to allow for the higher temperature during vaporisation; the source of the acetaldehyde in the cartridge liquid should be detected and eliminated if at all possible; a scan of the vaporised mist from the e-cigarette is required to check what else has been vaporised. The conclusion drawn by this study was that e-cigarettes are safer than smoking tobacco. Extent and patterns of use of a substance is addressed, but from the company’s commercial standpoint, not from a public health one, discussing issues of pricing and the ability to use the device to smoke in places where smoking has been banned.

- Potential hazards associated with the use of a substance. It was stated that no real or potential hazards have been identified with this product.
- Extent and patterns of use of a substance. It was asserted that smokers use the product in addition to tobacco products, and repeats that it is not a smoking cessation device. It was affirmed that the advantage of the product is that it can be used in any environment where cigarette smoking has been banned.
- Dosage and formulation of a substance. The cartridges for the EGAR electronic cigarettes are available in 4 strengths that are equivalent in nicotine content as follows:
  - No nicotine - 0 mg
  - Low nicotine - 11 mg
  - Med nicotine - 14 mg
  - High nicotine - 18 mg
- Potential for misuse/abuse of the substance. The point was raised on the "warning factor" on the device which stops the user from inhaling nicotine for 2 minutes, if too many puffs have been taken too quickly. It was claimed that the potential for misuse has been greatly reduced.

The Yunnan Changning Dekang Biotechnology Co. Ltd provided a safety report which has been based on Procedures and Methods for Toxicological Assessment on Food Safety, which states that the results indicate acute peroral toxicity in mice: "that maximal tolerance dose of acute peroral toxicity test in Kunming mice of both sexes, to electronic atomised cigarette fluid (spice) is higher than 10000mg/kg BW, therefore, it belongs to the no toxicity level."

The submission concluded that electronic cigarettes do not fall under any of the schedule listings for nicotine at present. The recommendation is that the Schedule 7 entry for nicotine includes the following exemption:

> (d) in electronic cigarettes prepared and packed as an alternative to traditional smoking.

A submission on behalf of XXXXX has been received from XXXXX. XXXXX has sent the same submission separately, with minor rewording to two sentences. The following points were raised.

- The contrast between *dirty* nicotine in tobacco, and *clean* nicotine in e-cigarettes.
- The provision of an alternative to tobacco smoking, the possibility that use of this product may lead to a reduction in the use of tobacco products, and the addition of a choice for smokers who do not like the currently available products. The letter suggests that a clean nicotine delivery system is better than a dirty one, provided by tobacco.

The submission addressed the following under 52E.

- **Safety and toxicity of a substance**. It was affirmed that the main danger in nicotine is that the substance is delivered through the use of tobacco which exposes consumers to other toxins. It was claimed that nicotine delivered in the electronic cigarette is "clean", while the "tobacco form of delivery is "dirty" and yet freely available.
- **Risks and benefits associated with the use of a substance**. It was suggested that the possibility that the provision of the e cigarette may lower the risks associated with tobacco smoking, and passive smoking.
- **Extent and patterns of use of a substance**. It was claimed that the down scheduling of nicotine in e cigarettes has the potential effect of increasing consumer access to "clean" nicotine and provide an alternative to tobacco smoking. The form of "smoking" may mimic tobacco smoking, be more acceptable to consumers, and therefore may lead to a reduction in tobacco use.
- **The need for access to a substance**, taking into account its toxicity compared with other substances available for a similar purpose. For the reasons stated above.
- **The potential for abuse of a substance**. The potential for abuse would be no more than delivery via tobacco, and would be less subject to abuse.
- **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. It was stated that the down scheduling of nicotine in e cigarettes would be of public health value, whether for the purpose of a tobacco alternative or NRT. It was asserted that the current scheduling does not reflect the logic of making a non tobacco system available to consumers, while tobacco itself is freely available and unscheduled.

A submission was received from XXXXX. The following points were raised.

- It was asserted that electronic cigarettes should be regulated as pharmaceutical products or medical devices because they deliver nicotine, but do not contain tobacco. It was stated that their support is not intended to place undue strain on "regulatory burden" on the marketing of legitimate smoking cessation products, or products that have the potential to offer consumers safer alternatives to cigarettes, but that they are not comfortable with products that deliver nicotine and are marketed without any regulatory oversight. It was not been clearly established which regulatory scheme should apply to electronic cigarettes. Throughout the submission, it was stated that there is confusion about which category the products fall under.
- The information from previously cited media articles was restated and from the web pages of electronic cigarette re-sellers affirming their concern that the range of new products available, including electronic cigarettes, demonstrates the need for regulation which would provide assessment standards for new products and determine the most appropriate regulatory requirements that would apply to them. The main contention was that it is not tenable to allow products which deliver nicotine and are marketed with claims, to be sold without proper regulations.

- While the submission does not categorically address claims under 52E, the submission goes towards (c) potential hazards, (e) dosage and formulation, (f) need for access and (h) purpose for which it is to be used. The submission included a bulk of screen dumps from various websites.

XXXXX did not directly address matters under 52E; however the submission goes towards (f) and (h) (need for access to a substance and the purpose for which a substance is to be used). It was asserted that at this stage e cigarettes are a safer alternative to conventional cigarettes and that Schedule 2 and Schedule 5 are impractical schedules for this product. The conclusion was that electronic cigarettes should not be the subject of therapeutic goods or poisons legislation and if any controls are necessary, they are best applied through tobacco and related laws.

XXXXX recommended that nicotine, in relation to its use in electronic cigarettes, should not be captured in any schedule that would allow for sale in a pharmacy setting. Opposition to any amendment to nicotine scheduling which would allow the sale of electronic cigarettes in pharmacies is stated. Disclaimers used on the websites previously described in this paper, which state that the products are not intended for use as a means of smoking cessation, contrasting this with Nicotine Replacement Therapy (NRT), which aims for withdrawal from tobacco smoking by reducing the amount of nicotine delivered over a period of time.

The submission states that electronic cigarettes are designed as recreational products which assist and perpetuate nicotine addition. In regards to 52E, the following matters are addressed.

- **Toxicity and safety of a substance**. Nicotine is a toxic and addictive substance; so long term use must raise safety concerns. The issue of the product being made attractive to children and young people was also raised. The absence of data about long term effects of nicotine addiction is raised.
- **Risks and benefits**. Any incidental benefit in terms of smoking cessation can be countered by the fact that NRT products for inhalation are captured in Schedule 2. The risk of the product being seen as an attractive novelty by children and young people was raised, as non-smokers or those not yet addicted to nicotine could be drawn into the addiction by the product.
- **Potential hazards associated with the use of a substance**. It was asserted that while the product may be of use to existing smokers, those not yet attracted to nicotine could also be attracted to the product, increasing the number of people addicted to nicotine. Acknowledgement was made that smokers already addicted to nicotine may find the product useful, however this potential benefit should not be considered in isolation from the associated risks.
- **The purposes for which a substance is used**. The sole purpose of the product is to facilitate and perpetuate nicotine addiction, not the treatment of the addiction.

XXXXX made the following points.

- The promotion of the e cigarette device, purely designed for the delivery of nicotine, with no therapeutic affect, is of concern to the company.
- The product is described as "potentially promoting temporary abstinence or harm reduction at best".
- The submission has not categorically addressed matters under 52E, the following issues were raised and although not stated go towards 52E; (b) (c) and (d).
- Potential to provide harm reduction at best.
- No recognizable therapeutic effects.
- Purely nicotine delivery devices.

XXXXX made the following points in a submission.

- It is essential for the public health benefit of improving access to the e-cigarette to be comprehensively evaluated and that the product be removed from the market until its safety and efficacy has been appropriately evaluated.
- Initiatives which help smokers to quit are encouraged, supported by evidence based science principles that are in line with the National Tobacco Strategy.
- The lack of evidence of a public health benefit associated with the product is raised, coupled with the expectation that a proportion of those choosing the e cigarette will continue to remain addicted to nicotine, with the uncertainty surrounding the long term results of this addiction and of the intended purpose of the e cigarette.
- The National Tobacco Strategy 2004-2009 was described, focussing on its stated aim of the Australian governments resolve to work with non-government agencies on a long term national plan to reduce the negative effects caused by tobacco addiction. The objectives of the strategy are to prevent the uptake of smoking, assisting as many smokers as possible to quit, eliminate harmful exposure to tobacco smoke among non-smokers and to reduce the harm associated with continuing use of dependence on tobacco and nicotine.
- NRT was discussed and the fact that indications for use of OTC NRT products does not extend to long term use as an alternative to cigarettes.
- The point was raised that while the product is now available in the US and China, it has been marketed in those countries as an alternative to smoking, not as an aid to smoking cessation.
- It was argued that the NDPSC "must consider whether purveying of an addictive product for the purpose of establishing or maintaining addiction is consistent with the Quality Use of Medicines National Policy."
- The fact that unregulated recreational nicotine products could divert smokers from using pharmacotherapies designed to assist them with smoking cessation was made.

- Data regarding the efficacy of the product in helping smokers to quit could not be found. The Clinical Trial Research Unit at the University of Auckland is currently trying to determine how effectively and rapidly the e cigarette relieves withdrawal symptoms in smokers, compared to a normal cigarette. No adequate safety data to support the safety of the e cigarette as a smoking cessation aid could be sourced. There were no human trials demonstrating the safety for pulmonary delivery, as well as the potential concerns about acetaldehyde, consequently the risk/benefit could not be determined.
- The lack of efficacy data made it difficult to justify amending the current schedule entry for nicotine use in inhalation products to include the e cigarette.
- It was stated that there is the potential to develop a dependence on the e cigarette, and that this factor needs consideration in determining the public health benefit for a Schedule 2 entry for the product.
- In relation to reclassification no supporting local clinical data or local post marketing experience, over at least two years, exists for this product. The point was stated that in the US this product is marketed as an alternative to smoking traditional cigarettes, not as a smoking cessation aid.
- The argument that adolescents and other non addicted people may take up the e cigarette and develop a dependence on nicotine was also put. A Health NZ Ltd safety report said that smokers who try the e cigarette experimentally will either; revert to tobacco smoking as before, use the e cigarette to quit smoking entirely, switch permanently to the e cigarette or continue to use both the e cigarette and tobacco products.
- An amendment to the current Schedule 2 entry for nicotine product for inhalation was not supported because the intended use of the product is ambiguous, there is a lack of safety and efficacy data to support intended use, there is a lack of post marketing experience and data in comparable overseas markets for the use as a smoking cessation aid and the prospect that users of e cigarettes will be long term users is concerning because OTC is for short term conditions for which self management by the user is a prerequisite.
- While not categorically stated, under the section, the submission also addressed following matters under 52E of the Act:
    - Potential for abuse and of a substance. The submitter could not locate any information regarding the extent and patterns of use of the e cigarette. The potential for misuse was rated as “quite high” based on the indications for use which includes long term/permanent use. The fast delivery of nicotine was rated as a potential contributor to nicotine addiction.
    - Toxicity and safety of a substance. Until the safety and efficacy issues have been addressed the appropriate scheduling will remain an issue.

- Risks and Benefits associated with the use of a substance / Purposes for which a substance is to be used. There is still confusion about the intended use of the product, as an alternative to smoking and not as a smoking cessation aid.
- Dosage and formulation of a substance. A lack of data regarding potential concerns over acetaldehyde exists.
- Potential for abuse of a substance. There was concern over the potential for the product to giver rise to new addictions to nicotine in children and adolescents. The warnings on cigarettes may help to turn young people to e cigarettes and nicotine addiction.

XXXXX made a joint submission. The following points were raised.

- Acknowledgement that the SUSDP may not contain a schedule appropriate for and adapted to protecting consumers from specific risks that may arise from the use of electronic cigarettes and similar products and that a broader regulatory regime may be needed to control and monitor the availability of such products.
- Support for the classification of nicotine contained in electronic cigarettes solely within Schedule 4. Rationale was that given the need for further evidence and investigation into the toxicity and risks associated with using nicotine and other chemicals contained in e cigarettes and the need for strict medical controls over its use. It was suggested that the Schedule 7 classification offers inadequate protection to consumers from the potential risks of toxicity and addiction.
- To avoid the implication that any type of nicotine consumed by humans fall within Schedule 7, the meaning of nicotine in Schedule 7 should be amended to state that it does not include nicotine for human use.
- If the product were to be solely under the Schedule 4 classification, this would require evidence of therapeutic benefit, before the product would be allowed on the Australian market. If the product was then available on prescription only consumers would be protected from broader risks arising from prolonged use or other unrecognised side effects.
- Stricter controls over the safety claims made on e cigarettes websites are argued for. Claims like, “contains no carcinogens” and “healthier smoking alternative” are misleading and demonstrate that the products need stricter safety controls.
- Further investigation into the dosages, safety of nicotine, and other chemicals is needed. There is research to suggest that nicotine may cause cancer or contribute to the progression of tumours already initiated.
- A warning on one website was pointed out. It told users not to engage with the product more than 16 times per minute, to avoid overuse, but no evidence of what the risks of overuse are, was given.

- Extensive testing of the product needs to be undertaken to ascertain its safety, before it can be sold on the Australian market. This view extended to the potential for addiction and increased levels of addiction among confirmed smokers.
- As previously mentioned in this paper the testing of the product and its EC certification is queried, as EC certification in no way attests to the safety of the product, but rather to the manufacturing standards. The claims of safety testing in laboratories in China (Pony Lab for Physical and Chemical Analysis, the Tianjin Centre for Disease Control and Prevention) are contested and it was noted that no further evidence to back these claims was produced.

The submission claimed that there was a real likelihood that these products could issue in a dual use of e cigarettes and tobacco according to the environment the smoker is in. The argument was that the smoker may increase the level of nicotine intake, by using electronic cigarettes at work for example and tobacco outside. The other argument was that the vapour emitted while using the product indoors, may not be harmless, and that this factor is unknown until further testing has been carried out. Matters under 52 E are addressed as follows.

- **Risks and toxicity of a substance**. All chemicals and ingredients contained in these products have not been established, and some additives contained in the scenting and flavouring ingredients are not known. Even though the claim was made that the product is free from carcinogens, the chemical agents remaining in the device have not been through any rigorous testing to prove their not detrimental status. Given the potential toxicity, risks and hazards associated with the electronic cigarette, and the lack of substantial evidence of safety or therapeutic benefit, until these prerequisites are met, the products should not be allowed on the Australian market, and taking all of the factors in to account, the applicant encourages the NDPSC to schedule nicotine solely in Schedule 4.

In a news release dated 19 September 2008, the World Health Organization (WHO) criticised inferences made by some electronic cigarette marketers that the products are legitimate (proven) therapies for smoking cessation. For instance, the Gamucci website made a reference to the IARC. The IARC has been used on these sites to imply that electronic cigarettes have some kind of approval or endorsement from the WHO. However, the WHO stated that they knew of no evidentiary basis for the marketers claim that the electronic cigarette helped people to quit, and they are not aware of any clinical studies that have been conducted. The WHO media release stated that electronic cigarette marketers need to conduct clinical studies and toxicity analyses within a regulatory framework before making claims as to the products qualities. The topic of the electronic cigarette will be addressed by the WHO Study Group on Tobacco Product Regulation on 12-14 November 2008.

Non-smoking tobacco (including snuff) was not specified anywhere in the Schedules and so would be captured by the Schedule 7 entry. In the Review of the Schedule to the Excise Tariff Act, (Chapter 5: Tobacco related items in the Schedule to the Excise Tariff Act 1921), 5.4 Item 9 is the discussion of snuff, or powdered tobacco, used for nasal or

oral ingestion. Here it is stated that the Australian Government banned the sale of oral snuff in 1991 due to the link with oral cancers and to act pre-emptively against the increased demand for non-smoking tobacco. It stated that importation of these products for personal use is permitted if the buyer has a permit from the Parliamentary Secretary to the Treasurer (less than 1.5kg). It further stated that oral snuff is banned in Victoria, the ACT and NSW. This ban does cover personal importation.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee noted that while the Victorian government had the option to refuse to issue a licence for the sale of nicotine in the form of the electronic cigarette, it would be difficult to do so if the applicant could demonstrate that they could comply with Victorian drugs and poisons legislation for Schedule 7 poisons. The Victorian Member was of the view that a product such as the electronic cigarette should not be unregulated. The electronic cigarette had not been safety tested or undergone assessment by any regulator. Additionally, the Member put forward that the product undermines national anti-smoking and tobacco regulation policies. The Member acknowledged that while the NDPSC may not be the most appropriate entity to regulate such products, it was the option favoured by Victoria. The Member therefore proposed that Schedule 4 should be the parent entry for nicotine for all human use.

The Committee agreed that while Schedule 7 was a highly restrictive schedule, it noted that not all of the substances included in it were agvet chemicals. Various substances too dangerous to supply domestically - highly toxic and dangerous poisons, of which nicotine is one - belong in Schedule 7 so that public health can be protected and individuals cannot gain access to them.

The Committee expressed concern that placing nicotine for all human use into Schedule 4 (and thus capturing electronic cigarettes as prescription products) might infer some tacit support for (medically supervised) use of an untested and unproven product. It might give the impression that such products had been tested and deemed to be safe.

The Committee agreed that the most appropriate course of action would be to retain the current scheduling for nicotine so that the parent entry for this poison remained in Schedule 7. The Committee confirmed that nicotine in an electronic cigarette is a Schedule 7 poison and is therefore subject to regulatory control as a dangerous poison.

The Committee resolved that, as a matter of urgency, Victoria should amend its Poisons Code to include nicotine. This action would ensure that electronic cigarettes could not be supplied on the domestic market in any Australian jurisdiction.

RESOLUTION 2008/54 – 21

The Committee agreed that the current scheduling of nicotine remained appropriate.

12.2 SUSDP, PART 5

12.2.1 ISOTRETINOIN

PURPOSE

The Committee considered the scheduling of isotretinoin, including a proposal to amend the Appendix D prescribing restrictions to allow prescribing by general practitioners.

BACKGROUND

Isotretinoin is a retinoid. It is the *cis* configuration of tretinoin which is the acid form of Vitamin A. The main indication for oral isotretinoin therapy is severe forms of acne (such as conglobate or nodulocystic acne or acne at risk of permanent scarring) that is unresponsive to other therapy including systemic antibacterials. It is not indicated for uncomplicated adolescent acne.

Isotretinoin and other oral retinoids are teratogenic and therefore contra-indicated in pregnant patients. It is advisable for female patients to begin using contraceptive measures 1 month before starting isotretinoin treatment. Pregnancy should be excluded before starting therapy and avoided during treatment and for 1 month after stopping treatment. Patients receiving isotretinoin should not donate blood during, or for 1 month after stopping therapy, because of the potential risk to the foetus of a pregnant transfusion recipient. Pregnancy or blood donation must be avoided for much longer periods in patients taking acitretin or etretinate. Isotretinoin should be used with care in patients with a history of depression and patients taking isotretinoin should be monitored for signs of depressive illness.

Intra-uterine exposure to isotretinoin has caused spontaneous abortion and a characteristic pattern of foetal malformations involving craniofacial, cardiac, thymic, and CNS structures. Some infants have also shown subnormal intelligence and other neuropsychological impairments. The risk of malformation appears to be high at all therapeutic doses of isotretinoin even when the duration of exposure is short. Unless contra-indicated, oral combined contraceptives are mostly recommended as the contraceptive method of choice for women undergoing retinoid treatment. Use of an additional form of contraception, such as a barrier method, is also recommended. Use of isotretinoin with vitamin A (including dietary supplements) should be avoided because of additive toxic effects if the patient is taking hormonal contraceptives.

At the August 1984 meeting, ADEC referred the scheduling of isotretinoin to the Committee, given its known teratogenic effects. A recommendation for the warning statement, “WARNING - CAUSES BIRTH DEFECTS” (which was later to become warning statement 7 of Appendix F, Part 1) and scheduling in Schedule 4 and Appendix D was made, pending further information about supply restrictions in the USA. This scheduling was confirmed at the November 1984 Meeting.

In February 1986, the Appendix D restrictions were amended to include "the prescriber should ensure that the possibility of pregnancy has been excluded prior to the commencement of treatment and that the patient is informed that she must not become pregnant for a period of one month after completion of the treatment".

XXXXX

In May 1996, the Committee amended the Appendix D listing for isotretinoin so that only oral treatments for human use were captured. Also, warning label 62 [Do not use if pregnant] and warning label 76 [Do not become pregnant during use or within (Insert number of months as per approved product information) month(s) of stopping treatment] were added the Appendix F, Part 3 requirements for human oral use of isotretinoin, further to warning label 7 [WARNING – Causes Birth Defects].

At the February 1999 Meeting, the Committee discussed the application of the Appendix D requirement that isotretinoin be available only "on the prescription or order of a specialist physician or dermatologist". It was concluded that most jurisdictions allowed prescription by either a dermatologist or by a medical practitioner authorised by the State or Territory authority. This was to allow for equity of access for remotely located patients, taking into account relevant qualifications of the prescriber.

DISCUSSION – SUBMISSIONS

This matter had been referred to the Committee by XXXXX. This referral was triggered from a correspondence received from a pharmacist expressing concern regarding the prescription of isotretinoin to women of child bearing age in Queensland and New South Wales. XXXXX.

The letter from the pharmacist expressed concerns about an observed complacency in dermatologists prescribing oral isotretinoin to females of child-bearing age, without standard warnings regarding teratogenicity and contraceptive counselling. These concerns were based on observations between January 2005 and January 2008 in six pharmacies in Queensland and New South Wales. The pharmacist had observed that most females of this age group had not received concomitant oral contraceptive therapy or documented pregnancy testing. Cases of two females on isotretinoin therapy were cited. These women had to be supplied post-coital emergency contraception, not having been made aware of the teratogenic effects of isotretinoin.

The pharmacist put forward that isotretinoin capsules must only be prescribed for females who provide documented evidence of a negative pregnancy test and also who receive oral contraceptives unless those agents are contraindicated (e.g. positive family history of clotting disorders). It was suggested that females not receiving oral contraceptive co-therapy should provide a series of negative pregnancy tests to ensure appropriate health outcomes.

XXXXX responded to XXXXX having discussed the prescribing of isotretinoin to women of child-bearing age. The response put forward the suggestion that GPs might be well placed to prescribe isotretinoin. The argument was put that a specialist physician (particularly a sub-specialist) may have less familiarity with the patient's history than the GP. It was stated that PBS 'access' rationale for rural and remote communities did not necessarily equate with good scientific medicines regulatory practice. It was acknowledged that current practice was to refer to physicians solely for prescription of isotretinoin and that these referrals may have been treated by physicians with low levels of vigilance, potentially including a lack of concomitant oral contraceptive therapy. More strict requirements before prescribing such as citing of a negative pregnancy test, a signed consent form and mandatory information sheet and data systems tracking isotretinoin to terminations and D&C were put forward. With such a scheme in place, it was suggested that the access could be broader, but the regulation more stringent.

XXXXX also responded to XXXXX letter. The response put forward that many non-eligible medical practitioners have been prescribing isotretinoin, in contravention to the State and Territory laws. The response committed to reminding XXXXX of the need to inform women of child-bearing potential of the drugs side effects.

Once this matter was referred to the NDPSC, the secretariat wrote to XXXXX and XXXXX regarding the issues raised in the letter to XXXXX and seeking their input.

Input was received from XXXXX. In general terms, under Section 52E(1) of the Act, (a) toxicity and safety, (d) extent and patterns of use, (h) purpose for which a substance is to be used and (g) potential for abuse were addressed. The following points were made.

- Over the course of the last decade the numbers of isotretinoin prescriptions had been "fairly static" throughout Australia. It was argued that this was because of the relatively small numbers of practicing dermatologists who are able to prescribe isotretinoin that the high standard of clinical care, which they assert is, from their international colleagues, the 'envy of the rest of the world'. The argument continued that there have been relatively fewer problems with the prescription of isotretinoin and particularly fewer pregnancies. The assertion was made that following a letter from XXXXX regarding the need for vigilance in contraceptive counselling with isotretinoin therapy, this message was reinforced XXXXX.
- The claim that significant "leakage" of isotretinoin prescriptions "to those not authorised to prescribe this medication over recent years" was made but not substantiated. However, the argument continued that it is not plausible that a trained dermatologist could contravene prescribing protocols and that the best way to ensure appropriate prescribing was for this to remain with dermatologists. The rationale was, that following the opening up of prescribing to GPs, "a larger number of pregnancies", a "larger numbers of terminations" and an "increased numbers of children with significant disabilities" would occur, because of lack of dermatological training available to pre-vocational GPs. This was corroborated by the "over prescription of antibiotics and the under prescription of retinoids by GPs, in their

treatment of acne conditions". It was additionally claimed that GPs would be disadvantaged because they would not see acne patients more often than "every month or two" while dermatologists see several acne patients per day.

- The assertion was made that in the last 6 years there have "only been a dozen or so" pregnancies, which have "ended up as miscarriage or therapeutic termination of pregnancy" and that the 4 or 5 live births compare favourably with other countries.
- The issue of being able to fast track patients suffering severe cystic acne, which is truly non-responsive to GP treatments, with a quick telephone call to a specialist dermatologist, was raised as the solution to the concern that patients may not have access to prescribed isotretinoin when they need it.
- Opposition to the suggestion that general practitioners are well placed to initiate isotretinoin therapy, "given their familiarity with the pathophysiology and contemporary clinical management of acne" was stated because of the difficulty of ascertaining the individual dosage requirements; depending on severity and weight of each patient and the mucocutaneous side effects, requiring a dermatologist's care. Dermatologists may only prescribe isotretinoin after completing a 4 year fellowship, under a qualified dermatologist.
- The problems in training GPs in isotretinoin therapy and prescribing, and the pressure that GPs would be under to prescribe isotretinoin, more than it is currently prescribed, at a greater cost to the taxpayer were given as reasons for retaining the status quo. Provisions of 52E(1) were also addressed.

XXXXX provided input. In providing input, acknowledgement was made of the contribution from XXXXX. The submission addresses, in general terms, matters (not categorically referred to) under Section 52E (1) of the Act including; (b) risks and benefits, (c) potential hazards, (d) extent and patterns of use and (h) the purpose for which it is to be used. The following points were made.

- That the trend over recent years has been for women to be prescribed isotretinoin for milder cases of acne, often as first-line oral therapy. It was stated that prescribing now includes people with less severe acne and thus a higher potential exists for inadvertent pregnancy.
- The MIMS prescribing information was quoted: "because of significant adverse effects associated with its use, isotretinoin should be reserved for patients with severe cystic acne who are unresponsive to conventional therapy, including systemic antibiotics".
- The data obtained from XXXXX 2000-2008 showed 58 calls regarding exposure to oral isotretinoin during pregnancy. The average maternal age of the patients was 26.9 years with a range of 16 to 42 years. While some pregnancies occurred due to contraceptive failure, others were due to women or their health care providers ignoring the guidelines for the use of oral contraceptives and pregnancy testing.

- Recommended dosage regimens were explained: up to 0.5 mg/kg/day for 2-4 wks in 1-2 divided doses up to a maximum 1 mg/kg/day; treatment should be continued for 16 weeks with the course repeated but only in persistent acne and after 2 months off therapy. Three repeats are available (on the Pharmaceutical Benefits Scheme) with each prescription. The drug is available in capsules of 10 and 20 mg.
- Cases were described where the clients (contraceptive and pregnancy counselling patients) had "basically flawless skin at the time of their consultation", as evidence that the prescribing guidelines for "the treatment of severe acne unresponsive to conventional therapy" are not always being followed. It was argued that larger numbers of women with minor acne are being exposed to isotretinoin when there are relatively few women who properly fit the approved indication.
- It was postulated that if isotretinoin is dispensed as a prescription of 60 tablets with 3 repeats i.e. up to 4 months supply, a woman may stop taking the medication when the condition improves, then resume after a few weeks, simply filling a repeat prescription, without the appropriate pregnancy testing or contraceptive counselling.
- It was suggested that to a large extent this could be avoided by a) ensuring appropriate prescription to only those women with severe acne and b) enforcing monthly dispensing of the medication, ideally with a urinary pregnancy test so as to avoid these types of situations. The USFDA iPLEDGE system was described. This system requires a prescriber to record the results of two pregnancy tests, electronically and further requires renewed counselling and documentation before renewing the monthly prescription. Female patients are also required to use two forms of contraception throughout the therapy, and for one month before and after. The pharmacist must also obtain authorisation to dispense isotretinoin.
- The issue was not who prescribes, but the fact that inadequate discussion and counselling occurs with regard to pregnancy prevention and teratogenic effects, at the time of consultation is currently sometimes happening. It supported the notion of the GP having an ongoing relationship with the patient and thus being better placed to discuss contraceptive issues. Further, the submission states that "dermatologists may not have the time (nor the skill, nor the rapport) to appropriately address the potentially complex counselling issues surrounding the use of isotretinoin and appropriate contraception. This was particularly relevant if the patient was a young teenager who may be shy with a specialist she has never seen before and whom she may be seeing with her parent and will therefore be even less likely to engage in a discussion about her sexual activity and need for contraception".
- A letter published in the August 2008 issue of Australian Pharmacist was quoted: "... of 15 women of childbearing age prescribed oral isotretinoin, two were also receiving effective contraception. Furthermore, since December 2007, I have prescribed the emergency hormonal contraception to three women currently receiving oral isotretinoin. One of these patients was blissfully unaware of the disastrous ramifications of a pregnancy at this time. Of note, most prescriptions were written by consultant dermatologists…" XXXXX further concern was that

isotretinoin can be obtained from some online pharmacies, without adequate contraceptive counselling.

- In summary, both consumers and health professionals in Australia need to be re-educated about the indications for the use of isotretinoin i.e. severe unresponsive acne not the increasingly trivial blemishes that appear to now be treated with isotretinoin. The suggestion was made that a tracked electronic system, such as the USFDA iPLEDE, could be adapted to manage the prescribing and dispensing of oral isotretinoin in Australia.

XXXXX provided input. Section 52E(1) of the Act; (a) toxicity and safety, (b) risks and benefits, (c) potential hazards, (d) extent and patterns of use, (e) dosage and formulation, (f) need for access, (g) potential for abuse and (h) purpose for use are all addressed in general terms. The following points were made:

- It is important that general practitioners have access to isotretinoin for effective and accessible patient management. The rationale was that the general practice is as the first point of contact for primary health care. Through this longitudinal relationship with patients, general practitioners have significant awareness of the overall clinical circumstances, including gynaecological and sexual history, co-morbid medical conditions, social and psychological history. General practitioners currently treat about 500,000 cases of acne per year.
- General practitioners are experienced prescribers of an array of complex medicines, and their duty of care would not alter if the drug were isotretinoin. Regulation may be required around what needs to occur when prescribing of isotretinoin, however the notion that who prescribes it as a surrogate quality filter is not substantiated. The fact that some patients need to travel long distances to access isotretinoin in not in the best interests of these patients.
- Training similar to that for etonogestrel implants may be warranted for isotretinoin (the USFDA iPLEDGE program is mentioned), to enhance safe, effective and efficient prescribing of isotretinoin.

A submission was received from XXXXX. While not categorically discussing matters under 52E, this submission raises issues relating to (b) risks and benefits, (c) potential hazards and (d) extent and patterns of use. The following points are made.

- Given the serious mental health side effects, the estimated numbers of those suffering and the problems in receiving effective treatment of side effects, the proposal to allow prescribing by general practitioners could have significant health consequences.
- The submission referenced the research article published in the New Zealand Clinical Psychologist Journal, Autumn 2008, Vol.18 (1), pages 8-14, titled, Medicine and Mental Health – The Isotretinoin Issue.

- Treatment providers (mental health), need to be better educated on the potential consequences of isotretinoin use. The argument was put that while specialist dermatologists and (possibly) GPs have been made aware of the potential psychiatric effects of isotretinoin, the failure to recognise clients' psychological symptoms as isotretinoin-related has resulted in failure to share information on treatment successes and failures.
- While the concerns related directly to mental health professionals, they also related to good practice for all practitioners who have contact with patients in the categories who may be prescribed isotretinoin.

XXXXX made a submission. The following points were made.

- That the ACD is mistaken in claiming that allowing GPs to prescribe isotretinoin would lead to a host of foetal exposures, as well as other side effects going unchecked. Members noted that this point was most likely in reference to statements made in the media relating to this matter, summarised later in this paper.
- It was estimated that in "some dermatology practices, 25 to 30 per cent of patients are there for the prescribing of isotretinoin." The restriction of prescribing rights in the early 1980s may have been because of the thalidomide tragedy.
- There had been problems with dermatologists not recommending adequate contraceptive methods, not recommending a contraceptive method at all, or passing the onus for such back to gynaecologists or GPs. It was stated that Dermatologists may need additional training on this. Exact data on isotretinoin pregnancy exposure was not available for Australia.

The assertion was made that all GPs who have received specific training in the prescribing of isotretinoin should be allowed to prescribe the drug. Comparisons were drawn with GP certification to prescribe methadone and other addiction-treatment drugs. It was further argued that a 2 day training course for prescribing isotretinoin should be sufficient, with pre-reading and an oral or written examination at the end of the course with the prescribing certificate number required when each prescription is logged. Matters listed under Section 52E (1) of the Act, were addressed as follows.

- *Toxicity and Safety of the substance.* Isotretinoin has multiple side effects, both temporary and transient, as isotretinoin is eliminated from the body within 72 hours, and side effects will abate within 7 days of stopping the drug, but that the drug is teratogenic.
- *Risks and benefits associated with the use of the substance.* The benefits of isotretinoin therapy are that in 85 per cent of cases, the acne clears and is manageable after that with antibiotics and topical preparations. An additional treatment option is certain oral contraceptive pill (particularly ones containing cyproterone acetate), as part of the anti-acne regime, not a concomitant contraceptive therapy. Isotretinoin has multiple side-effects, ranging from mild lip irritation (cheilitis) through to depression/suicide, liver enzyme changes, cholesterol changes and effect on bones

and the formation of osteophytes. Post marketing surveillance from a private company indicates that only 1.5 to 2 per cent of patients need to discontinue isotretinoin due to inability to handle the side effects.

- *Extent and patterns of use of a substance.* There is a scarcity of dermatologists throughout many jurisdictions and especially in out lying and remote areas. '250 to 300' GPs have completed the University of Cardiff's Diploma in Practical Dermatology, a one year correspondence course, culminating in a written and practical examination and a pool of GPs open to additional training, would monitor and prescribe to patients. There are 9 countries which allow GP prescribing of isotretinoin and which have prescribing guidelines for GPs.
- Foetal exposure to isotretinoin is a continuing problem, despite dermatologist only prescribing. A 2008 Garcia- Bournissen et al three-country study of women achieving pregnancy while on isotretinoin reported that "in spite of the importance of pregnancy prevention whilst on isotretinoin, 47 per cent (7/15) of the Israeli, 50 per cent (14/28) of the Canadian and all of the Italian women failed to report the use of any contraceptive method. Seventeen per cent of the woman (9/53 in total made up of 6/28 Canadian, 2/15 Israeli and 1/10 Italian) claimed not to have been informed at all regarding the risk of isotretinoin use during pregnancy."
- The submission outlined the GPs best practice contraceptive advice method, including blood tests for pregnancy, careful explanation of the alternatives, initiation of the agreed method of contraception etc. It was suggested that dermatologist may rely too heavily on the hand out literature on contraceptive advice and not act proactively enough in this area.
- Need for access to the substance, taking into account its toxicity compared with other substances available for a similar purpose. The example of methotrexate was used, which has an extensive side-effect profile and is listed as a Category X teratogen, to draw a comparison.
- Potential for misuse/abuse of the substance. There seems to be no potential for isotretinoin to be addictive.

A submission was received from XXXXX. The submission addressed, in general terms, matters (not categorically referred to) under Section 52E (1) of the Act including; (c) potential hazards, (e) dosage and formulation as well as other matters. The following points were made.

- That the proposed amendment was not supported.
- Dosing-titration requirements are based on weight, efficacy and side effects. Because of the necessity for individual weight to be taken into account when adjusting the dosage, the medical practitioner needs to constantly monitor the dose and provide constant feedback regarding side effects and progress. Meta analysis data from Haider and Shaw in 2004 was quoted which concluded that best results were seen when treatments were individualised.

- Appropriate patient selection and pregnancy issues, including teratogenicity, effective contraception and counselling issues were mentioned.
- Isotretinoin related precautions, side-effects and contraindications were discussed. The safety profile of the substance requires the practitioner to undergo training continuously.
- Training of GPs. The certification and registration requirements for dermatologists were described.
- Prescribing in jurisdictions other than Australia. In areas where isotretinoin was not prescribed by a dermatologist, appropriate risk-management programs are in place.
- The educational program currently followed by dermatologists should be implemented and mandatory for all GPs, should they be allowed to prescribe isotretinoin.

XXXXX submitted an application. In Victoria, legislation was amended in 2006 to enable a registered medical practitioner holding a warrant issued by the Secretary, Department of Human Services to give instructions to another registered medical practitioner to treat a specific patient in accordance with the warrant. This enabled, for example, a general practitioner to prescribe isotretinoin to a specific patient when acting under the instructions of the specialist dermatologist holding a warrant for that patient. The point was also made that, as well as teratogenicity, there is also the possible link between isotretinoin and suicidal ideation Members noted that a causal link on this issue has not been established. For these reasons, caution should be exercised, with the present Victorian regulation offering a reasonable and workable compromise.

XXXXX had no objection *per se* to the proposal to remove the current restrictions on general practitioners being allowed to prescribe isotretinoin. However, it was stated that if this proposal were to be carried through, it is essential that a comprehensive and broad-reaching education campaign be conducted for all general practitioners reminding them of the safety issues associated with, and their obligations in relation to, the use of this drug in female patients of child bearing age.

The issue of isotretinoin and teratogenesis was most recently discussed by the Adverse Drugs Reactions Advisory Committee (ADRAC). Exposure to oral isotretinoin during pregnancy was raised.

- A female taking oral isotretinoin 0.2 mg/kg/day during weeks 4 to 8 of pregnancy gave birth to a baby boy with multiple congenital abnormalities including cleft palate, anomaly of the external ear, double outlet right ventricle and ventricular septal defect, malformation of the nose, hypertelorism and right facial palsy.
- This was the 5th account ADRAC received of foetal malformation, in a pregnant woman taking isotretinoin. There were 5 babies born with congenital malformations, of women taking isotretinoin during pregnancy. The other 4 reports describe multiple congenital abnormalities including deafness and heart disorder; ear

malformation, movement disorder and developmental delay; premature labour, retroplacental haematoma, placental infarction and foetal death; and congenital musculoskeletal anomaly and limb malformation. A further 66 case reports between 2003 and 2008 described drug exposure in pregnancy.

- Patients prescribed oral isotretinoin are requested to sign forms agreeing to refrain from becoming pregnant during treatment with the drug. The reporter for case 240497 notes that the patient ceased the Pill but continued to take Roaccutane. An association with isotretinoin was considered likely in this case. The extent of isotretinoin related adverse events that have been recorded by the ADEC since 2006.
- A Medicine Summary Report on isotretinoin was received from ADRU. The total number of cases involving isotretinoin was 594. The following report recording exposures during pregnancy and medical reactions was noted by the Committee:

– Drug exposure during pregnancy	66/66
– Abortion	1/1
– Missed abortion	1/1
– Abortion spontaneous	1/1
– Stillbirth	1/1
– Premature labour	1/1
– Retroplacental haematoma	1/1
– Placental infarction	1/1

On 25 August 2008, articles appeared in both the *Melbourne Age* and the *Australian* reporting potential consequences if general practitioners were to be allowed to prescribe isotretinoin. Dr Stephen Shumack, Honorary Secretary of the ACD, was quoted stating the following concerns.

- That there would be a risk that patients would not be informed of the dangers of birth abnormalities among babies born to women taking isotretinoin, forcing them to have abortions.
- That the drug may not be prescribed to the appropriate patients and side-effects not managed appropriately.
- That numbers of people prescribed the drug would rise, elevating the risk of pregnancies due to lack of proper screening and concomitant contraceptive therapy.
- The articles reported that 140,000 prescriptions had been written in the last financial year, under the nations 400 dermatologists and specialist physicians.

Prescribing figures for PBS/ RPBS supplied isotretinoin were noted. Figures were for number of prescriptions for women 12 – 45 years old for the last three financial years. These figures gave total number of prescriptions by prescriber type and jurisdiction. The figures indicated that while the total number of prescriptions was increasing, prescribing by specialist physicians (i.e., non dermatologists) remained low. Numbers of

prescriptions for both recognised (through State and Territory legislation) and non-recognised GPs had also increased.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The relevant matters under section 52E(1), to this item, included; (a) toxicity and safety, (c) potential hazards, (f) the need for access to the substance, taking into account its toxicity compared with other substances available for a similar purpose and (i) any other matter the Committee considered necessary to protect public health.

The Committee discussed the issue of lessening current prescribing restrictions because of a perceived shortage of authorised prescribers in rural and remote areas. The Committee reviewed the arrangements for authorising prescribing of isotretinoin in each of the jurisdictions:

- **VIC** Drugs, Poisons and Controlled Substances Regulations 2006, Division 9 - Warrants for ovulatory stimulants, prostaglandins, retinoids and thalidomide.
  - *Requirement for warrants*
  - *(1) A registered medical practitioner must not purchase, obtain, use, supply or prescribe an ovulatory stimulant, a prostaglandin, a retinoid or thalidomide unless he or she holds a warrant under the Act to do so.*
  - *(2) Despite sub regulation (1), a registered medical practitioner acting in accordance with the instruction of a registered medical practitioner who holds a warrant may use, supply or prescribe an ovulatory stimulant, a prostaglandin, a retinoid or thalidomide with respect to a specific patient in accordance with the authorisation given by the warrant.*
  - *Warrant number to be included in any prescription*
  - *(1) A registered medical practitioner who prescribes an ovulatory stimulant, a prostaglandin, a retinoid or thalidomide must include the warrant number on the prescription.*
  - *(2) A registered medical practitioner who prescribes an ovulatory stimulant, a prostaglandin, a retinoid or thalidomide on the direction of the warrant holder must include on the prescription the name of the registered medical practitioner who holds the warrant.*
  - Prohibition on dentists. A dentist must not purchase, obtain, use, supply or prescribe an ovulatory stimulant, a prostaglandin, a retinoid or thalidomide.
  - Note that in relation to the prescription of oral isotretinoin, one of the conditions of the warrant is that the applicant is a physician who is a Fellow of the

Australasian College of Dermatologists and provides evidence of the qualification.

- **NSW** Health authorisation is required to prescribe isotretinoin for oral use. Specialist dermatologists who hold the qualification "Fellow of the Australasian College of Dermatologists" are authorised as a group. An attending medical officer in a public hospital may be authorised to prescribe to an inpatient, admitted for unrelated treatment, who, immediately prior to admission, was undergoing treatment with isotretinoin prescribed by a specialist dermatologist, for the term of the patient's hospital stay only. Other doctors require individual authority.
  - Non-specialists in rural areas have in the past been authorised to prescribe to a specific male patient for treatment initiated by a dermatologist. The most recent of these authorities was issued in 2001. Since then applications for dermatological treatment from doctors who are not Fellows of the ACD have been referred to the College for advice as to the suitability of their qualifications.
  - A number of authorities have been issued to oncologists for individual patients with stage IV neuroblastoma and to specialist endocrinologists for treatment of thyroid cancer.
  - The legislation requiring authority (clause 37 of the NSW Poisons and Therapeutic *Goods Regulation 2008) exempts "a person who is authorised by the Permanent Head of the Commonwealth Department of Health to issue a prescription for that substance"*.
- **QLD** has discretionary powers to authorize non ACD Fellows such as overseas trained dermatologists, medical officers in public hospitals, and rural and remote GPs.
- **SA** The South Australian Controlled Substances legislation does not adopt Appendix D by reference but does mirror the intent of Appendix D. Dermatologists or other authorised specialist medical practitioners can prescribe isotretinoin.
- **WA** allows only physicians and dermatologists to prescribe and has not been made aware of access issues in rural and remote areas.
- **NT** similarly, was not aware of any instances of applications for secondary prescribing authority. NT legislation allows GPs to co-prescribe on treatment that has been initiated by a specialist, but there is no specific authorisation process required under the legislation.
- **ACT** has new legislation (due to commence in February 2009). This will allow authorisation of dermatologists and dermatologists in training, as well as career medical officers in hospitals. The ACT does not have rural or remote areas.
- **TAS** approves general practitioners where the Chief Health Officer is satisfied regarding the qualifications and experience of the prescriber and that a local need is

established. Tasmania has adopted Appendix D and has authorised 3 practitioners (an overseas trained dermatologist, a hospital-based medical practitioner and a GP with a Diploma of Practical Dermatology from the University of Cardiff) to prescribe isotretinoin. These authorisations have been necessary due to the shortage of dermatologists in Tasmania.

- **NZ** Supply is restricted through funding. The prescription must be written by a dermatologist and dispensed from a hospital pharmacy (or a community pharmacy which has a contract with a hospital to dispense medicines normally only available from a hospital pharmacy). Ongoing prescriptions must also be signed by the dermatologist.

In summary, the Committee was satisfied that each jurisdiction had taken steps to address equity of access issues.

Some Members refuted the argument that dose titration for isotretinoin could only be successfully carried out by medical practitioners who had completed specialist training in dermatology. Indeed, given that jurisdictions currently authorise specialist physicians (i.e. non dermatologists) as well, in some cases, dermatologists in training and medical practitioners without specific dermatology qualifications supports the view that dose titration can be successfully carried by other medical practitioners.

The Committee considered the iPLEDGE system and agreed that such a system is not warranted in Australia. While 66 exposures during pregnancy over a five year period (as per ADRAC data) were noted by the Committee, the Committee did not consider that this demonstrated that the current system was not working. However, it did point to the need for prescribers to be reminded of the importance of adequate contraception in women of child bearing age.

The issue of isotretinoin's current streamlined authority status on the Pharmaceutical Benefits Scheme (PBS) was raised. The PBS prescribing figures for isotretinoin that were provided to the Committee revealed that a significant number of specialists other than dermatologists and physicians have been prescribing isotretinoin as a PBS item (beyond what is being authorised by State and Territory authorities). The Committee questioned whether a streamlined authority was appropriate in the case of isotretinoin.

The Committee was not convinced that widening prescribing rights would alleviate the concerns that were raised about the reported failure by some prescribers to counsel patients adequately. Members agreed that the while the concerns that were referred to the Committee were undoubtedly valid, these were seemingly isolated comments. Additionally, the Committee noted the commitment from the relevant Colleges to remind prescribers of the need for vigilance about counselling and contraception.

In summary, given its approved indication for severe cystic acne unresponsive to other treatments, its side-effect profile and well known teratogenic effects, the Committee was not convinced that medical practitioners other than dermatologists and specialist physicians should be allowed to prescribe isotretinoin. Where access issues did exist, the

Committee was satisfied that jurisdictions had mechanisms in place to address these. The Committee agreed to write to the relevant specialist Colleges to inform them of the outcome of its discussions and to again ask them to remind Fellows of the need for appropriate counselling about the teratogenic effects of isotretinoin as well as the need for adequate measures to avoid isotretinoin exposure during pregnancy.

RESOLUTION 2008/54 – 22

The Committee decided that the current entry for isotretinoin remained appropriate.

13. MATTHERS REFERRED BY THE REGISTRATION PROCESS FOR PRESCRIPTION MEDICINES

13.1 NEW SUBSTANCES (NOT SEEN BEFORE BY NDPSC)

13.1.1 ANIDULAFUNGIN

PURPOSE

The Committee considered the scheduling of the new medicine anidulafungin.

BACKGROUND

Anidulafungin (AN) is an antifungal. It is a non-competitive inhibitor of 1,3-β-D-glucan synthase, an enzyme not present in mammalian cells but crucial to fungi. This enzyme is required for synthesis of β-linked glucan, which comprises a major portion of the cell wall carbohydrate in many pathogenic fungi.

- The April 2008 ADEC Meeting recommended approval of a submission from Pfizer Australia Pty Ltd to register ERAXIS powder for injection, containing the new chemical entity, anidulafungin 100 mg for the indication *the treatment of invasive candidiasis, including candidaemia.* XXXXX

DISCUSSION - SUBMISSIONS

The Committee noted the relevant extract of the minutes of the April 2008 ADEC Meeting XXXXX

XXXXX

The Committee also noted that anidulafungin was not classified in New Zealand.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that toxicity and safety, risk and benefits, extent and patterns of use, need for access as well as the purpose for which it is to be used (52E(1)(a)(b)(d)(f)(h)) were relevant to consideration of scheduling of anidulafungin.

RESOLUTION 2008/54 - 23

The Committee decided to include anidulafungin in Schedule 4 of the SUSDP and to recommend to New Zealand that it consider a similar scheduling outcome.

Schedule 4 - New entry

ANIDULAFUNGIN.

13.1.2 DESVENLAFAXINE

PURPOSE

The Committee considered the scheduling of the new medicine desvenlafaxine.

BACKGROUND

Desvenlafaxine is a member of the antidepressant class of drugs. It is a potent, selective serotonin and norepinephrine reuptake inhibitor (SNRI) that potentiates these neurotransmitters in the central nervous system. Desvenlafaxine is the major active metabolite of venlafaxine, which is also used to treat major depressive disorders.

The June 2008 ADEC Meeting recommended

- approval of a submission from Wyeth Australia Pty Limited to register PRISTIQ modified release tablets containing the new chemical entity desvenlafaxine (as succinate) 50 mg, 100 mg and 200 mg for the indication *for the treatment of major depressive disorder (MDD) including prevention of relapse* XXXXX
- XXXXX

DISCUSSION - SUBMISSIONS

- The Committee noted the relevant extract of the minutes of the June 2008 ADEC Meeting XXXXX
- XXXXX

The Committee considered the following pre-meeting submissions.

XXXXX requested that the NDPSC consider including desvenlafaxine in Schedule 4 in a separate and distinct entry from venlafaxine, as the chemical structures and properties of desvenlafaxine and venlafaxine are distinct. Desvenlafaxine is not an isomer or different salt of venlafaxine; desvenlafaxine (succinate) was the subject of a category 1 application to register a new medicine that was provided to the TGA, with the TGA considering this substance to be a new chemical entity requiring a full evaluation of quality, pre-clinical and clinical data (modules 3, 4 and 5 of the common technical document).

XXXXX submitted that in recent years, active metabolites of some drugs have been marketed concurrently with or as replacements for the active parent substance. Examples are loratadine/desloratadine and terfenadine/ fexofenadine. In the interests of consistency and to remove doubt, desvenlafaxine should be scheduled in its own right.

The Committee noted the following from Micromedex Drugdex:

- a black box warning regarding suicidality and antidepressant drugs;
- concomitant use of desvenlafaxine and ethanol does not increase impairment of mental or motor skills;
- the manufacturer recommended that patients be advised to avoid alcohol while using desvenlafaxine;
- patient instructions included warnings *do not drink alcohol while you are using this medicine, this medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that could be dangerous if you are not alert.*

The Committee noted that there was evidence of somnolence at 200 mg. However, as the common dose is 50 mg, the Committee agreed that inclusion in Appendix K was not warranted and that the prescribing information would provide adequate warnings.

The Committee noted that desvenlafaxine was not scheduled in New Zealand

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that toxicity and safety, risk and benefits, extent and patterns of use, need for access as well as the purpose for which it is to be used (52E(1)(a)(b)(d)(f)(h)) were relevant to consideration of scheduling.

RESOLUTION 2008/54 – 24

The Committee decided to include desvenlafaxine in Schedule 4 of the SUSDP and to recommend to New Zealand that it consider a similar scheduling outcome.

Schedule 4 - New entry

DESVENLAFAXINE.

13.1.3 ROMIPLOSTIM

PURPOSE

The Committee considered the scheduling of the new medicine romiplostim.

BACKGROUND

Romiplostim is a unique ‘peptibody’ (a peptide antibody) that directly stimulates the bone marrow to produce platelets by mimicking the action of thrombopoietin, the natural

regulator of platelet production. Romiplostim is indicated for the treatment of immune thrombocytopenic purpura (ITP), a chronic hematologic disorder in which the immune system destroys platelets (blood cells that help prevent bleeding) and where the bone marrow is often unable to compensate for this loss.

ITP patients may experience increased bruising, serious bleeding and occasionally dangerous hemorrhage. Current available treatments include steroid drugs and removal of the spleen (splenectomy), which are designed to reduce platelet destruction and may be ineffective in many patients.

The June 2008 ADEC Meeting recommended approval of a submission from Amgen Australia Pty Ltd to register NPLATE powder for injection containing the new biological entity romiplostim 375 µg and 625 µg for the indication:

> *For the treatment of thrombocytopaenia in adult patients with chronic immune (idiopathic) thrombocytopaenic purpura (ITP)*
> - *who are non-splenectomised and have had an inadequate response, or are intolerant, to both corticosteroids and immunoglobulins;*
> - *who are splenectomised and have had an inadequate response to splenectomy.*

XXXXX

DISCUSSION - SUBMISSIONS

The Committee noted the relevant extract of the minutes of the June 2008 ADEC Meeting XXXXX.

The Committee also noted that in August 2008, the USFDA approved romiplostim (Nplate) only for patients with chronic ITP who do not respond sufficiently to current treatments.

The Committee noted that romiplostim was not classified in New Zealand.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that toxicity and safety, risk and benefits, extent and patterns of use, need for access as well as the purpose for which it is to be used (52E(1)(a)(b)(d)(f)(h)) were relevant to consideration of scheduling.

RESOLUTION 2008/54 - 25

The Committee decided to include romiplostim in Schedule 4 of the SUSDP and to recommend to New Zealand that it consider a similar scheduling outcome.

Schedule 4 - New entry

ROMIPLOSTIM.

13.1.4 H5N1 INFLUENZA VIRUS HAEMAGGLUTININ

PURPOSE

The Committee considered the scheduling of the new medicine H5N1 influenza virus haemagglutinin.

BACKGROUND

Influenza viruses are members of the viral family *Orthomyxoviridae* and have a segmented, single-stranded and negative-sense RNA genome in an enveloped virion. The genome encodes envelope glycoproteins, matrix proteins, non-structural proteins, nucleoproteins and polymerase proteins. According to the antigenic properties of matrix proteins or nucleoproteins, influenza viruses are classified into types A, B and C.

- Influenza A viruses cause epidemics and pandemics of influenza in mammals and birds and aquatic birds are known to be the natural reservoir of these viruses.
- Influenza B and C viruses are isolated mainly from humans and are less pathogenic than influenza A viruses.

Haemagglutinin is an antigenic glycoprotein found on the surface of the influenza viruses as well as many other bacteria and viruses. It is responsible for binding the virus to the cell that is being infected. The name "haemagglutinin" comes from the protein's ability to cause red blood cells to clump together *in vitro.*

Haemagglutinin is the major envelope glycoprotein of A and B viruses and Haemagglutinin-esterase in C viruses is a protein homologous to HA. There are at least 16 different haemagglutinin antigens labelled H1 through H16.

All known flu epidemics in humans have come from the type A influenza virus, which originates in birds. Birds harbor 15 subtypes of the type A virus, but only 6 subtypes are known to have infected humans. Each strain of the virus contains a different form of the haemagglutinin protein and is named for that protein. For example, the 1918 virus contains the H1 form and is designated as an H1 strain.

Three of the subtypes, called H1, H2, and H3, have adapted to humans causing three pandemics over the past century. This includes the 1918 pandemic, also known as the "Spanish flu." Three other subtypes, called H5, H7 and H9, have caused small outbreaks when the virus was transmitted directly from birds to humans. These subtypes have not been transmitted from human to human and have not yet caused any major epidemics.

The current flu outbreak in Asia is caused by an H5 influenza strain, which has the H5 haemagglutinin protein. It is known as the H5N1 strain.

A highly pathogenic avian flu virus, H5N1 has been found to infect humans at a low rate. It has been reported that single amino acid changes in this avian virus strain's type H5 haemagglutinin have been found in human patients that "can significantly alter receptor specificity of avian H5N1 viruses, providing them with an ability to bind to receptors optimal for human influenza viruses. This finding seems to explain how an H5N1 virus that normally does not infect humans can mutate and become able to efficiently infect human cells. The haemagglutinin of the H5N1 virus has been associated with the high pathogenicity of this flu virus strain, apparently due to its ease of conversion to an active form by proeolysis.

The April 2008 ADEC Meeting recommended

- approval of a submission from CSL Limited (Australia) to register PANVAX VACCINE, suspension for injection, containing the new biological entity influenza virus haemagglutinin [H5N1], for the indication *for the prevention of influenza caused by a pandemic strain of influenza virus.*

XXXXX

- approval of a submission from GlaxoSmithKline Australia Pty Ltd to register PANDEMRIX suspension for injection containing the new biological entity influenza virus haemagglutinin [H5N1] for the indication *prophylaxis of influenza in an officially declared pandemic situation. PANDEMRIX should be used in accordance with official recommendations*.

XXXXX

DISCUSSION - SUBMISSIONS

The Committee noted the relevant extract of the minutes of the April 2008 ADEC Meeting and the approved Australian PI for both products.

XXXXX

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that toxicity and safety, risk and benefits, extent and patterns of use, need for access as well as the purpose for which it is to be used, (52E(1)(a)(b)(d)(f)(h)) were relevant to consideration of scheduling.

RESOLUTION 2008/54 - 26

The Committee agreed that H5N1 influenza virus haemagglutinin would be captured under the Schedule 4 entry for influenza and coryza vaccines.

The Committee also decided that a cross-reference to H5N1 influenza virus haemagglutinin should be included in the SUSDP index.

Index – New entry for inclusion in consolidation of SUSDP No.24

H5N1 INFLUENZA VIRUS HAEMAGGLUTININ
See INFLUENZA AND CORYZA VACCINES

13.1.5 RABBIT ANTI-HUMAN THYMOCYTE IMMUNOGLOBULIN

PURPOSE

The Committee considered the scheduling of the new medicine rabbit anti-human thymocyte immunoglobulin.

BACKGROUND

Rabbit anti-human thymocyte immunoglobulin is a purified IgG with immunosuppressive activity against thymocytes and human peripheral blood lymphocytes.

The June 2008 ADEC Meeting recommended approval of a submission from Genzyme Australasia Pty Ltd to register THYMOGLOBULINE Powder for Injection, containing the new biological entity rabbit anti-human thymocyte immunoglobulin 25 mg for the indications:

> *The prophylaxis of graft rejection in renal transplantation;*
> *Treatment of steroid-resistant or moderate to severe renal transplant rejection;*
> *Treatment of refractory or relapsing aplastic anaemia.*

XXXXX

DISCUSSION - SUBMISSIONS

The Committee noted the relevant extract of the minutes of the June 2008 ADEC Meeting XXXXX.

The Committee noted that:

- the Scottish Medicines Consortium rejected rabbit anti-human thymocyte immunoglobulin in August 2008 for use within Scotland's National Health Service for the prevention of graft rejection in renal transplantation although it is licensed for additional indications;

- the United Kingdom licensed rabbit anti-human thymocyte immunoglobulin in April 2008 for use as immunosuppression in solid organ transplantation.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that toxicity and safety, risk and benefits, extent and patterns of use, need for access as well as the purpose for which it is to be used (52E(1)(a)(b)(d)(f)(h)) were relevant to consideration of scheduling.

RESOLUTION 2008/54 - 27

The Committee decided that rabbit anti-human thymocyte immunoglobulin would be captured under the Schedule 4 entry for immunoglobulins.

The Committee also decided that cross-references to both rabbit and equine anti-human thymocyte immunoglobulins be included in the SUSDP Index

Index – New entries for inclusion in consolidation of SUSDP No.24

EQUINE ANTI-HUMAN THYMOCYTE IMMUNOGLOBULIN
see IMMUNOGLOBULINS

RABBIT ANTI-HUMAN THYMOCYTE IMMUNOGLOBULIN
see IMMUNOGLOBULINS

13.2 FOR INFORMATION (SUBSTANCES ALREADY SCHEDULED)

13.2.1 ALISKIREN

PURPOSE

The Committee noted ADEC's consideration of the new medicine aliskiren.

BACKGROUND

Aliskiren is a new antihypertensive / renin inhibitor. It was included in Schedule 4 by the June 2007 NDPSC Meeting to harmonise with New Zealand.

DISCUSSIONS/SUBMISSIONS

The Committee noted the relevant extract of the minutes of the April 2008 ADEC Meeting and that ADEC had recommended the approval of a submission from Novartis Pharmaceuticals Pty Ltd to register ENVIAGE / RASILEZ tablets containing the new chemical entity aliskiren 150 mg and 300 mg for the indication *treatment of hypertension*.

XXXXX

RESOLUTION 2008/54 - 28

The Committee noted the April 2008 ADEC Meeting's consideration of the new medicine aliskiren.

14. OTHER MATTERS FOR CONSIDERATION

Item Deleted

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

Nil.

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

16.1 MEDICINES FOR HARMONISATION

Nil.

16.2 HARMONISATION OF MEDICINES

16.2.1 IRON

PURPOSE

The Committee noted the June 2008 MCC Meeting's consideration of iron.

BACKGROUND

The February 2007 NDPSC Meeting recommended an upper pack size limit of 750 mg and maximum daily dose of 24 mg for general sale iron products when in undivided dose forms or in solid dose forms containing more than 5 mg per dose form. Oral products which exceeded these limits should be classified as pharmacy-only medicines.

The December 2007 New Zealand Medicines Classification Committee (MCC) Meeting agreed that limiting the dose size to 5 mg for general sale products was not justified, but that limiting the pack size to 750 mg was more relevant. The MCC decided to reclassify iron to general sale when in packs containing not more than 750 mg and not more than 24 mg per recommended daily dose and in parenteral nutrition replacement preparations.

MCC Secretariat had advised the NDPSC Secretariat that the New Zealand recommendation would have resulted in a considerably more restrictive classification than the Australian one. Therefore, it was decided that no change would be made, but deferred to the June 2008 MCC Meeting for further consideration.

The June 2008 NDPSC Meeting noted the MCC's harmonisation consideration of iron, agreeing to bring the matter back after further consideration by MCC.

DISCUSSION - SUBMISSIONS

The Committee noted that the June 2008 MCC Meeting reconsidered the general sale classification recommended by the December 2007 MCC Meeting as to whether it reflected the harmonised position with Australian and the intention of the MCC. It was noted from the minutes of that meeting that the MCC had:

- noted that the general sale status of iron in New Zealand would require a pack size limit of 750 mg only when each dose unit exceeded 5mg;
- noted that the December 2007 MCC recommendation would result in all general sale iron products being limited to packs of not more than 750 mg;
- agreed that the main issue was that of child poisonings and considered whether a child could consume a pack containing 150 tablets, if the pack size limit of 750 mg was applied to 5 mg tablets;
- noted that 40 mg/kg constituted a fatal dose for both adults and children, meaning a 10 kg child would need to consume approximately half of a 5 mg pack containing 150 tablets to ingest a potentially fatal dose;
- considered children's access to iron tablets through prescription or as a dietary supplement, noting that one widely used dietary supplement was particularly tasty and that both that product and those which were normally prescribed bore a close resemblance to sweets;
- agreed that there was insufficient information available about quantity and strength of tablets consumed in cases of child poisons and whether these products had been prescribed or purchased as dietary supplements;
- recognised that very few of the reported cases of child overdose of iron had required medical intervention and agreed that there did not seem to be any evidence to justify classifying iron in a more restrictive manner than in Australia.

It was noted that the MCC had therefore recommended that the upper pack size limit for general sale iron products should apply only to those packs containing more than 5 mg per dose unit, as follows:

> *That iron should be classified as a general sale medicine when:*
> - *in packs containing not more than 24 milligrams per recommended daily dose; and in medicines containing not more than 5 milligrams per dose unit; or*
> - *in medicines containing more than 5 milligrams per dose unit and in packs containing not more than 750 milligrams of iron.*

and that New Zealand had fully harmonised with Australia on the scheduling of iron.

RESOLUTION 2008/54 - 30

The Committee noted that Australia and New Zealand are now fully harmonised on the scheduling/classification of iron

17. MINUTES OF THE ADVERSE DRUG REACTIONS ADVISORY COMMITTEE (ADRAC)

Nil

18. MINUTES OF THE MEDICAL DEVICE EVALUATION COMMITTEE (MDEC)

Nil

19. INFORMATION ITEMS

Item deleted

20. GAZETTAL NOTICES

The Committee noted the post-June 2008 Gazette Notice No. GN 31 dated 6 August 2008.

The Committee noted the pre-October 2008 Gazette Notice No. GN 32 dated 13 August 2008.

21. AMENDMENTS TO THE SUSDP

21.1 EDITORIAL CHANGES AND ERRATA

21.1.1 2-OCTYL-4-ISOTHIAZOLIN-3-ONE (OCTHILINONE)

The Committee noted that the wording in the Schedule 6 entries for carbendazim and octhilinone, as amended at the June 2008 NDPSC Meeting, were inconsistent:

CARBENDAZIM **except** in <u>paints, jointing compounds</u> and sealants containing 0.5 per cent or less of carbendazim.

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

The Committee also noted that the November 2000 NDPSC Meeting had amended the Schedule 6 entry for 2-Octyl-4-isothiazolin-3-one (octhilinone) to read ‘octhilinone, but that the corresponding Appendix E entry had been overlooked.

RESOLUTION 2008/54 – 31

The Committee decided to editorially amend the Schedule 6 entry for octhilinone by amending the wording "in paint, jointing materials and sealants" to read "in paints, jointing compounds and sealants".

The Committee also decided to amend the Appendix E entry for 2-Octyl-4-isothiazolin-3-one (Octhilinone) to read "octhilinone".

Schedule 6 - Amendment

OCTHILINONE – Amend entry to read

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

Appendix E, Part 2 – Amendment

2-Octyl-4-isothiazolin-3-one (Octhilinone) – Amend entry to read:

POISON	**STANDARD STATEMENTS**
Octhilinone	A,G3,E2,S1

21.1.2 SUSDP PART 2, SUBPARAGRAPH 16(1)(B)

The Committee noted an error at subparagraph 16(1)(b) under Part 2, Labels and Containers in that the numbering of subparagraph "(vi)" should read "(iv)".

The Committee noted that this was a typographical error which emanated from the drafting of SUSDP 14/3 and transferred to subsequent editions of the SUSDP.

RESOLUTION 2008/54 - 32

The Committee decided to correct the numbering under Part 2, Labels and Containers subparagraph 16(1)(b) by amending "(vi)" to read "(iv)".

Part 2, Labels and Containers - Amendment

subparagraph 16(1)(b)(vi) - Amend entry to read:

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

21.1.3 DOXYLAMINE

The Committee noted that the amendment to the Schedule 3 doxylamine entry published in SUSDP 23/1 was incomplete in that it did not include subparagraph "(b) for the treatment of children under 2 years of age" in line with the decision of the February 2008 NDPSC Meeting.

The Committee noted that this was an editing error by the Secretariat during preparation of SUSDP 23/1. The Committee also noted that this entry was corrected for inclusion in Poisons Standard Amendment No.2 of 2008 (SUSDP 23/1). As a legislative instrument, the Poisons Standard and Poisons Standard Amendments are required to include an accurate record of the decisions of the NDPSC.

RESOLUTION 2008/54 - 33

The Committee decided to correct the error in the Schedule 3 doxylamine entry to include "(b) for the treatment of children under 2 years of age" in line with the decision of the February 2008 NDPSC Meeting.

Schedule 3 - Amendment

DOXYLAMINE – Amend entry to read:

DOXYLAMINE in oral preparations **except**:

(a) when included in Schedule 2; or

(b) for the treatment of children under 2 years of age.

21.1.4 PIPER METHYSTICUM (KAVA)

The Committee noted an error in the amendment to the Schedule 4 entry for *piper methysticum* (kava) published in SUSDP 23/1, in that "whole of peeled rhizome" in subparagraph (b) should read "whole or peeled rhizome".

The Committee noted that this was a typographical error included in the background paper for the February 2008 NDPSC Meeting and subsequently transferred to the Ratified Minutes and SUSDP 23/1.

RESOLUTION 2008/54 - 34

The Committee decided to correct the error in the Schedule 4 entry for Piper methysticum (kava) at subparagraph (b) by amending "whole of peeled rhizome" to read "whole or peeled rhizome".

Schedule 4 – Amendment

PIPER METHYSTICUM (kava) – Amend entry to read:

PIPER METHYSTICUM (kava) in preparations for human use **except** when included on the Australian Register of Therapeutic Goods in preparations:

(a) for oral use when present in tablet, capsule or teabag form that is labelled with a recommended maximum daily dose of 250 mg or less of kavalactones, and:

(i) the tablet or capsule form contains 125 mg or less of kavalactones per tablet or capsule; or

(ii) the amount of dried whole or peeled rhizome in the teabag does not exceed 3 g,

and, where containing more than 25 mg of kavalactones per dose, compliant with the requirements of the *Required Advisory Statements for Medicine Labels*;

(b) in topical preparations for use on the rectum, vagina or throat containing dried whole or peeled rhizome or containing aqueous dispersions or aqueous extracts of whole or peeled rhizome; or

(c) in dermal preparations.

21.1.5 FLUORIDES

The Committee noted an unintentional consequence of a decision by the June 2008 NDPSC Meeting to include the wording “preparations supplied to registered dental professionals” in the Schedule 2 and Schedule 3 entries for fluorides.

It was noted that the wording would cause a Schedule 4 fluoride preparation to become unscheduled if it was ‘supplied’ to a dental professional (including a dental hygienist, dental therapist, etc), thus enabling that person to both administer and freely supply it to anyone else.

It was agreed that the wording in the Schedule 2 and Schedule 3 fluoride entries be amended to read “preparations for supply to registered dental professionals” as this would address the supply chain issues whilst preventing unauthorised on-supply.

RESOLUTION 2008/54 - 35

The Committee decided to editorially amend the Schedule 2 and Schedule 3 entries for fluorides by amending the wording "preparations supplied to registered dental professionals" to read "preparations for supply to registered dental professionals".

Schedule 2 – Amendment

FLUORIDES – Amend entry to read:

FLUORIDES for human use:

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

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

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

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

(A) Do not swallow; and

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

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

(A) Do not swallow; and

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

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

Schedule 3 – Amendment

FLUORIDES – Amend entry to read:

FLUORIDES for human topical use:

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

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

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

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

(A) Do not swallow; and

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

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

21.1.6 BIFONAZOLE

The Committee noted an error in the Schedule 4 entry for bifonazole in that "bifoconazole" in subparagraph (b) should read "bifonazole.

The Committee noted that this was a typographical error included in the background paper for the June 2005 NDPSC Meeting, being transferred to the Ratified Minutes, the SUSDP 20/2 and subsequent editions of the SUSDP.

RESOLUTION 2008/54 - 36

The Committee decided to correct the error in the Schedule 4 entry for bifonazole at subparagraph (b) by amending "bifoconazole" to read "bifonazole".

Schedule 4 - Amendment

BIFONAZOLE - Amend entry to read:

BIFONAZOLE **except**:

(a) when included in Schedule 2;

(b) in preparations for dermal use containing 1 per cent or less of bifonazole for the treatment of the scalp; or

(c) in preparations for dermal use for the treatment of tinea pedis.

21.1.7 BORON

The Committee noted that the Schedule 4 entry for boron was incomplete in that the wording "more than 3 mg per recommended daily dose" at subparagraph (a) should read "more than 3 mg of boron per recommended daily dose".

RESOLUTION 2008/54 - 37

The Committee decided to editorially amend subparagraph (a) of the Schedule 4 entry for boron by amending the wording "more than 3 mg per recommended daily dose: to read "more than 3 mg of boron per recommended daily dose".

[Secretariat's note: The amendment considered at this Meeting relates to the Schedule 4entry in the consolidated SUSDP23. However, during post-meeting action, it was discovered that the Schedule 4 entry for boron was amended at the June 2008 NDPSC Meeting and therefore does not warrant an editorial amendment.]

21.1.8 TETRACHLORVINPHOS

RESOLUTION 2008/54 - 38

The Committee decided to editorially amend the Schedule 7 entry for tetrachlorvinphos by changing "animal feed" to read "animal feeds".

Schedule 5 – Amendment

TETRACHLORVINPHOS – Amend entry to read:

TETRACHLORVINPHOS **except** in animal feeds containing 0.2 per cent or less of tetrachlorvinphos.

21.1.9 METHOMYL

RESOLUTION 2008/54 - 39

The Committee decided to editorially amend the Schedule 6 entry for methomyl by amending "one per cent" to read "1 per cent".

Schedule 6 – Amendment

METHOMYL – Amend entry to read:

METHOMYL in fly-baits containing 1 per cent or less of methomyl and not less than 0.002 per cent of denatonium benzoate as a bittering agent.

21.1.10 MORANTEL

RESOLUTION 2008/54 - 40

The Committee decided to editorially amend the Schedule 6 entry for morantel to include "or" after paragraph (a) and before paragraph (b).

Schedule 6 – Amendment

MORANTEL – Amend entry to read:

MORANTEL **except**:

(a) when included in Schedule 5; or

(b) in preparations containing 10 per cent or less of morantel.

21.1.11 PICRIC ACID

The Committee noted that the Schedule 6 entry for picric acid should be deleted.

The Committee noted that:

- as picric acid is the synonym for trinitrophenol (AAN), the February 2007 NDPSC Meeting agreed to include a primary entry for trinitrophenol for human therapeutic use in Schedule 4 (along with a cross reference for picric acid) and also agreed to amend the Schedule 6 entry for picric acid to read "trinitrophenol";
- the Ratified Minutes of the February 2007 NDPSC Meeting included an amendment to Schedule 6 which read "trinitrophenol – amend entry to read' instead of "picric acid – amend entry to read";
- the Schedule 6 trinitrophenol entry was subsequently included in SUSDP 22/1 as a new entry, not as an amendment;
- no amendment was included in SUSDP 22/1 to delete the Schedule 6 picric acid entry; and
- the cross-reference "picric acid see trinitrophenol" was included in the SUSDP23 index.

RESOLUTION 2008/54 - 41

The Committee decided to correct the error in Schedule 6 by deleting the entry for picric acid.

Schedule 6 – Amendment

PICRIC ACID – Delete entry.

21.1.12 LENALIDOMIDE

The Committee noted that lenalidomide should be included in SUSDP paragraph 45 regarding dispensed medicine labelling requirements.

The Committee noted that the new medicine lenalidomide was included in Schedule 4 and Appendix D by the June 2008 NDPSC Meeting, but that inclusion in paragraph 45 had been overlooked.

The Committee agreed that as an analogue of thalidomide, lenalidomide should also be included in subparagraph 45(3) under Part 3, Miscellaneous Regulations – Dispensed medicines.

RESOLUTION 2008/54 - 42

The Committee decided to include lenalidomide in subparagraph 45(3) under Part 3, Miscellaneous Regulations – Dispensed medicines.

Part 3, Miscellaneous Regulations – Amendment

sub-paragraph 45(3) – Amend entry to read:

45. (3) acitretin, adapalene, bexarotene, etretinate, isotretinoin, lenalidomide, thalidomide or tretinoin:

(i) for oral use unless it is clearly labelled with warning statements 7, 62 and 76 in Appendix F, Part 1;

(ii) for topical use unless it is clearly labelled with warning statements 62 and 77 in Appendix F, Part 1; or

21.2 SUSDP AMENDMENT

The Committee noted SUSDP 23 Amendment 2. There were editorial amendments or errata to the Amendment.