REVIEW OF NON-PRESCRIPTION ANALGESICS

Prepared for the Therapeutic Goods Administration by David B Newgreen

February 1998
# CONTENTS

Abbreviations used in the Review i

Acknowledgements ii

Summary iii

Recommendations iv

## Introduction 1
- Reasons for the Review 1
- Strengths and volumes of paracetamol oral liquids 1
- Proliferation of warning statements 1
- Accidental poisoning in children 1
- Suicide in adolescents 1
- Paracetamol and alcohol consumption 2

## Terms of reference 2
- Poisons information centres 3

## Paracetamol - the main drug reviewed 5
- Background 5
- Australian data 5
- Poisons information centre enquiries 5
- Survey of general practitioners and pharmacists 5

## What is the problem? 6
- Accidental poisoning in children 6
- Self-poisoning in adolescents 7

## Paracetamol and accidental poisoning 9
- Presentations at hospital accident and emergency departments and admissions 9
- Available presentations and strengths 10

## Problems with the present situation 11
- The number of strengths 11
- The existence of large pack sizes 13
- Confusion with decimal expressions 14
- Perceptions of safety 15
- Poor storage of medicines in the home 15
- Containers 16
- Label design 16
- Body weights 17
- Dose rate 17
- Number of doses and duration of treatment 18
Paracetamol and fever

Enhanced paracetamol toxicity in alcoholics
- Biochemical background
- Literature reports
- The role of fasting
- A controversial editorial
- Recent action in the United States
- Australia - is an alcohol warning label on analgesics needed?

Paracetamol in self-poisoning
- Suicide and parasuicide
- Addition of methionine to paracetamol
- Position in the United States of America
- Position in Denmark
- Position in Hong Kong
- Position in the United Kingdom
  - Responses to problems in the UK
  - Legislative action
    - Pack sizes
    - Labelling
- Position in Australia
- Comparison between Australia and England and Wales
  - Liver transplants
  - Should there be an overdose warning label on paracetamol in Australia?

Labelling and other controls on non-prescription analgesics
- State and Territory controls
  - General
    - Poisons scheduling
    - Complementary therapeutic goods laws
    - Analgesics specifically
      - Paracetamol
      - Aspirin
      - Ibuprofen
      - Mefenamic acid and naproxen
  - Commonwealth controls
    - General
      - Analgesics specifically
        - Paracetamol
        - Aspirin
        - Ibuprofen, mefenamic acid and naproxen
    - Co-regulation - government and industry
    - American labelling of non-prescription analgesics
    - Issues
      - Official publications for warning statements
      - General content of analgesic warning statements
Actual content of analgesic warning statements 47
Warning or caution? 47
Paracetamol 48
Aspirin 49
Therapeutic Goods Advertising Code and cardiovascular disease 51
Ibuprofen 52
Mefenamic acid and naproxen 52
Implementation 53
Packaging 54

Analgesic and antipyretic guidelines 56
Mandatory labelling and packaging 56
Indications 56
Analgesia and antipyresis 56
Aspirin and cardiovascular indications 56
Degrees of pain 57
Dosage 57
Paracetamol dose 57
Aspirin dose 58

Appendix 1- Paracetamol-induced admissions to the Royal Children’s Hospital 1993-1997 60
Appendix 2- Separations from Australian hospitals due to paracetamol poisoning 64
Appendix 3- American warning/caution statements 70
Appendix 4- Suggested content of guideline for paracetamol 74
Appendix 5- Suggested content of guideline for aspirin 76
References and further reading 77
# ABBREVIATIONS USED IN THIS REVIEW

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABS</td>
<td>Australian Bureau of Statistics</td>
</tr>
<tr>
<td>ADEC</td>
<td>Australian Drug Evaluation Committee</td>
</tr>
<tr>
<td>AGRD</td>
<td>Australian Guidelines for the Registration of Drugs vol 2</td>
</tr>
<tr>
<td>AIHW</td>
<td>Australian Institute of Health and Welfare</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine amino tranferase</td>
</tr>
<tr>
<td>ARTG</td>
<td>Australian Register of Therapeutic Goods</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate amino transferase</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration (of the United States of America)</td>
</tr>
<tr>
<td>INR</td>
<td>International Normalised Ratio</td>
</tr>
<tr>
<td>MCA</td>
<td>Medicines Control Agency (of the United Kingdom)</td>
</tr>
<tr>
<td>MEC</td>
<td>Medicines Evaluation Committee</td>
</tr>
<tr>
<td>NAC</td>
<td>N-acetylcysteine</td>
</tr>
<tr>
<td>NABQI</td>
<td>N-acetyl-p-benzoquinoneimine</td>
</tr>
<tr>
<td>NDPSC</td>
<td>National Drugs and Poisons Scheduling Committee</td>
</tr>
<tr>
<td>NHMRC</td>
<td>National Health and Medical Research Council</td>
</tr>
<tr>
<td>NSAID</td>
<td>Non-steroidal anti-inflammatory drug</td>
</tr>
<tr>
<td>RCH</td>
<td>Royal Children’s Hospital (Melbourne)</td>
</tr>
<tr>
<td>SUSDP</td>
<td>Standard for the Uniform Scheduling of Drugs and Poisons</td>
</tr>
<tr>
<td>TGA</td>
<td>Therapeutic Goods Administration</td>
</tr>
<tr>
<td>TGAC</td>
<td>Therapeutic Goods Advertising Code</td>
</tr>
<tr>
<td>TGO</td>
<td>Therapeutic Goods Order</td>
</tr>
<tr>
<td>VISS</td>
<td>Victorian Injury Surveillance System</td>
</tr>
</tbody>
</table>
ACKNOWLEDGEMENTS

The Review acknowledges the advice and assistance provided by:

Mr P Archer
Mrs L Bowler
Mrs B J Capanna and members of the Analgesics Working Party of The PMAA Inc.
Mr T Choy
Mr K P Coulthard
Mrs B David
Ms M Emanuel
Mrs J Graham
Ms P Healey
Ms E A Hender
Dr H A Kilham
Mrs J Kirby
Mr B Lilley
Dr J McGinness
Mr K G McKellar
Mr R D Munro
Dr J Ozanne-Smith
Ms R-M Pennisi
Ms C Perry
Professor L Sansom
Professor F Shann
Dr J Sillince
Dr D Sless
Dr K M Strasser
Mr C Tucker
Professor G W Whelan
Dr I M Whyte
SUMMARY

Concern about various public health issues associated with the use of the popular analgesic drug paracetamol, and the complications that have developed in the labelling of analgesic drugs in general, are the subjects of this Review.

Paracetamol is a safe and effective drug when used in accordance with the directions. It has few unwanted effects, is widely prescribed by doctors, is used in hospitals and may be purchased without prescription from pharmacies; in packets of up to 25 tablets or capsules, it is available through any retail outlet. There are many enquiries directed to poisons information centres and many presentations to hospitals in connection with accidental paracetamol consumption. Most do not result in admission to hospital and there are few cases of serious morbidity thanks to timely intervention with an antidote. The Review has suggested some fine tuning to the labelling and packaging of paracetamol and has also recommended that no new strengths or pack sizes of paracetamol oral liquids should be allowed on to the Australian market. There is a need to dispel the notions that paracetamol is a sedative and that it should always be resorted to in cases of fever.

There is evidence that heavy alcohol drinkers represent a group who are at risk if they take prolonged larger doses of paracetamol for the relief of pain. Because the subject is controversial and the biochemistry complex, the Review considers that education of the medical and pharmacy professions is preferable to a specific warning label at this stage.

The use of paracetamol in parasuicidal gestures that results in admissions to hospitals is increasing although not the extent in the UK. The survey carried out during the Review confirms this trend. The application of warning labels is often the regulator’s immediate reaction but unless the content is carefully crafted, the message may be counterproductive. Evidence from the UK also questions their value. Restrictions on availability in the UK are to be introduced and the effect of this and other initiatives should be monitored in Australia. Unlike other reports, this Review does not favour the compulsory inclusion of the amino acid methionine in all paracetamol products.

The labelling of aspirin has become an issue in light of increasing knowledge of its pharmacological and therapeutic effects. The Review has proposed a new format for the warnings and consolidated them as one statement. The off-label uses in cardiovascular disease by the public has been recognised and accommodated by directing consumers to their doctors. Similar formats are proposed for the nonsteroidal anti-inflammatory agents.

February 1998
RECOMMENDATIONS

Recommendation 1.1

Medical and pharmacy organisations remind their members of the toxicity of paracetamol in overdose with special reference to toxic doses and the delayed adverse effect on the liver.

Recommendation 2.1

As a matter of TGA policy, strengths of uncompounded paracetamol oral liquids other than those containing 24mg/mL, 48mg/mL, 50mg/mL and 100mg/mL should not be placed on the Australian Register of Therapeutic Goods for supply in Australia. If necessary, the SUSDP should be amended accordingly.

Recommendation 2.2

As a matter of TGA policy, packs of uncompounded paracetamol oral liquids containing volumes greater than those already on the market for each strength for supply in Australia should not be placed on the Australian Register of Therapeutic Goods. If necessary, the SUSDP should be amended accordingly.

Recommendation 2.3

Manufacturers of paracetamol oral liquids who wish to supply measuring devices with each bottle of a paracetamol oral liquid ensure that the calibrations correspond with the doses shown on the label to discourage calculation and guesswork.

Recommendation 2.4

The importation and manufacture (other than for export or re-export) of medicine measures for domestic use that are calibrated in other than metric units be prohibited.

Recommendation 2.5

The Pharmaceutical Society of Australia request pharmacists and staff to (i) ensure that purchasers of paracetamol oral liquids have a suitable measuring device and; (ii) demonstrate its use at the point of sale.

Recommendation 2.6

All doses of uncompounded paracetamol oral liquids containing 120mg/5mL, 240mg/5mL and 250mg/5mL should (i) be in whole numbers of millilitres and (ii) omit the decimal point and the post-decimal zero (eg. 5mL not 5.0mL). Minor variations to the 15mg/kg dose to be disregarded in the interests of safety and ease of administration.
Recommendation 2.7

Community service announcements sponsored by government, the professions and industry should (i) stress the importance of not leaving medicines in general and paracetamol in particular within reach of children; (ii) draw the public’s attention to the existence to different strengths of paracetamol; (iii) emphasise the need to read the label; and (iv) direct the public to seek the advice of a pharmacist or a doctor if they do not understand the label.

Recommendation 2.8

The provision in Therapeutic Goods Order No.20 that enables dropper packs containing not more than 2g of paracetamol to be exempted from the need to be fitted with a child resistant closure should be repealed.

Recommendation 2.9

Age/weight range tables on labels should be uniform across the industry and be based on contemporary Australian figures.

Recommendation 2.10

Dose tables on labels should preferably show age/weight/millilitre dose OR age/millilitre dose but not weight/millilitre dose to discourage the need for calculations by the carer.

Recommendation 2.11

A new paediatric dose for paracetamol based on 15mg/kg should be referred to the Medicines Evaluation Committee for its consideration to replace the present dose based on 12.5mg/kg.

Recommendation 2.12

In the event of the Medicines Evaluation Committee supporting a dose based on 15mg/kg, the TGA and the industry agree on an implementation strategy.

Recommendation 2.13

In the interests of paediatric health and safety, all labels for uncompounded paracetamol oral liquids, at next printing or before 1 January 2000, include statements to the effect that:

* not more than 4 doses should be given in 24 hours.
* the medicine should not be administered for more than 48 hours without seeking medical advice.
Recommendation 3.1

Professional organisations and departments of health (a) remind medical practitioners, pharmacists and health centre sisters that (i) fever as such is not harmful; (ii) paracetamol is not automatically indicated for fever; (iii) paracetamol is not indicated for sleeplessness and; (b) request practitioners to advise mothers and other carers accordingly.

Recommendation 3.2

The Medicines Evaluation Committee be asked to consider the appropriateness of limiting any antipyretic indications for paediatric paracetamol medicines in the Australian Register of Therapeutic Goods and in advertisements (including labels) to “reduces fever” or similar, without elaboration, except in the context of limits to the duration of treatment.

Recommendation 4.1

The editor of the Australian Prescriber be requested to arrange for, and publish, a review article about enhanced toxicity of paracetamol when it is taken by moderate to heavy habitual alcohol drinkers.

Recommendation 4.2

In the course of their detailing to medical practitioners and pharmacists, sponsors’ representatives mention that paracetamol dosages and the duration of treatment with it may need modification if the patient is a moderate to heavy habitual alcohol drinker.

Recommendation 4.3

The TGA monitor the outcomes of the American labelling initiative concerning analgesics and alcohol drinking.

Recommendation 4.4

No warnings on the label of paracetamol, aspirin and the NSAIDs in relation to alcohol consumption should be required at present.

Recommendation 5.1

That paracetamol preparations should not be compulsorily co-formulated with methionine.

Recommendation 5.2

The TGA monitor the UK data on morbidity and mortality following paracetamol poisoning after all of the UK legislative initiatives have been in operation for one year.
Recommendation 6.1.1

Warning statements for analgesics remain in the SUSDP for the time being.

Recommendation 6.1.2

When all States and Territories have legislation to complement the *Therapeutic Goods Act* 1989, warning statements applicable to any substance for therapeutic use should be transferred from Appendix F - Part 1 of the SUSDP to (a) a new Order under section 10 of the Act; or (b) a schedule to Therapeutic Goods Order No.48 “General requirements for labels of drug products”, or a succeeding corresponding order.

Recommendation 6.1.3

In the meantime, the NDPSC explore a means of granting exemptions to the application of warning statements in particular cases, based on the knowledge of its members, advice from evaluation committees, merit and commonsense. Such exemption to be applicable in all jurisdictions simultaneously.

Recommendation 6.2

The proposed new analgesic warning labels should be tested for usability before being written into the SUSDP.

Recommendation 6.3

Sponsors should be guided by publications such as “Writing about medicines for people: usability guidelines for consumer medicine information” by David Sless and Rob Wiseman (Department of Health and Family Services, Canberra, 1997) in drafting labels, package inserts and consumer medicine information text and “Designing better medicine labels. Report to PHARM” by D Rogers et al (Communication Research Institute of Australia, 1995) in drafting labels, package inserts and consumer medicine information text.

Recommendation 6.4

The NDPSC consider a new warning statement [notionally numbered 99] applicable to paracetamol to read:

**WARNING** - Prolonged use of this medication without a doctor’s advice or in more than the recommended dose may be harmful.

Recommendation 6.5

The NDPSC consider the following new warning statements to apply to aspirin products for inclusion in Appendix F - Part 1 of the SUSDP.[note: the numbers assigned to the proposed warnings are notional only]
100. **WARNING** - Unless a doctor has told you to, do not use [this product]/[name of product]
- for a long time;
- in the last 3 months of pregnancy;
- if you have asthma or a stomach ulcer;
- if you are allergic to aspirin or anti-inflammatory medicines;
- in children under 2 years of age or in older children or teenagers with chickenpox, influenza or fever.

See a doctor before taking [this product]/[name of product] for thinning the blood or for your heart.

101. **WARNING** - Unless a doctor has told you to, do not use [this product]/[name of product]
- for a long time;
- in the last 3 months of pregnancy;
- if you have asthma or a stomach ulcer;
- if you are allergic to aspirin or anti-inflammatory medicines;
- in children under 2 years of age or in older children or teenagers with chickenpox, influenza or fever.

**Recommendation 6.6**

Subject to proposed SUSDP warning statement no.100 being adopted, clause 4 of the Therapeutic Goods Advertising Code should be amended by adding the following exception to the entry for cardiovascular system diseases; “(v) when prescribed in the Standard for the Uniform Scheduling of Drugs and Poisons for aspirin”.

**Recommendation 6.7**

The NDPSC consider the use of warning statement no.102 to replace those currently used for ibuprofen:

102. **WARNING** - Unless a doctor has told you to, do not use [this product]/[name of product]
- for a long time;
- in the last 3 months of pregnancy;
- if you have asthma or a stomach ulcer;
- if you are allergic to aspirin or anti-inflammatory medicines.

**Recommendation 6.8**

The NDPSC consider the use of warning statement no.103 replacing those currently used for naproxen and mefenamic acid.

103. **WARNING** - Unless a doctor has told you to, do not use [this product]/[name of product]
- for a long time;
- if you have asthma or a stomach ulcer;
- if you are allergic to aspirin or anti-inflammatory medicines.
Recommendation 6.9

Following consultation with industry, sufficient time should be allowed for replacement of the old warning labels by the new and provision be made for either format to be used for an agreed period.

Recommendation 6.10

The NDPSC consider amending the entry in Schedule 2 for paracetamol under sub-paragraph (c)(i) by deleting the words “or in a container with a child-resistant closure”.

Recommendation 6.11

Therapeutic Goods Order No.20 be amended to require solid dose forms of paracetamol when present as either (a) the only therapeutically active substance or; (b) when combined with codeine or dihydrocodeine, to be packed exclusively in blister or strip packaging, subject to clause 6 of the Order.

Recommendation 7.1

The Medicines Evaluation Committee give consideration to the content of Appendix 4 as the basis for a guideline on paracetamol.

Recommendation 7.2

The Medicines Evaluation Committee give consideration to the content of Appendix 5 as the basis for a guideline on aspirin.

Recommendation 7.3

Subject to Recommendation 7.2 being agreed to, the TGA notify sponsors of aspirin products to remove specific doses of aspirin for children from labels when revised styles of SUSDP warning statements are in operation or earlier at the discretion of the sponsor with the words “on medical advice” to replace the childrens’ doses.
INTRODUCTION

Reasons for the review

Strengths and volumes of paracetamol oral liquids

The Therapeutic Goods Administration (TGA) received letters from two professional sources expressing concern about aspects of the presentation of paracetamol oral liquids used mainly for infants and children. One of the letters was from a paediatrician in private practice about a child who had swallowed the 200mL contents of a bottle of paracetamol oral liquid (strength unstated). The paediatrician advocated maximum pack sizes of 100mL for the 120mg/5mL and 50mL for the 240mg/5mL and 250mg/5mL concentrations. In each case, the maximum quantity of paracetamol that could be consumed is 2.4 or 2.5g. The second letter was from three senior clinicians and the chief pharmacist at a children’s hospital. Their objection was to the confusion brought about by the many strengths of paracetamol oral liquids on the market. Arising from the correspondence, the TGA obtained information from poisons information centres around Australia indicating that many queries directed to the centres were in connection with exposures to paracetamol, especially when presented as an oral liquid. A journal article (Smith and Temple, 1997) that described a case in New Zealand of an overdose in a child from an incorrectly administered paracetamol elixir was a further factor supporting a review.

Proliferation and sources of warning statements

The second precipitating factor arose from an industry source. The Proprietary Medicines Association of Australia Inc. had written to the TGA raising its objections to the increasing number of warning statements to be placed on labels of non-prescription analgesics, especially aspirin. Further, the statements arose from different sources. Some of the warning statements were neither part of a legislative instrument nor part of the evaluation process for a particular product.

Accidental poisoning in children

A Monash University Accident Research Centre report (Routley et al, 1996) on accident-caused presentations of children to four Victorian hospitals showed that poisoning with pharmaceuticals had increased over the period 1987 to 1994. Paracetamol was prominent among them and presentations due to exposure to it were increasing at a greater rate than for other drugs, especially in the last year of the survey.

Suicide in adolescents

A Victorian Suicide Task Force identified paracetamol as an agent used by young people in attempted suicides and made recommendations to place extra restrictions on the supply of paracetamol and antidepressants but no data on the number of cases formed part of the report. Similarly, the Commonwealth Youth Suicide Prevention Advisory Group included as an option, an examination of self-poisoning trends with target drugs, especially paracetamol and the tricyclic
antidepressants. The addition of methionine to paracetamol preparations was also suggested in each report as worthy of consideration.

In the United Kingdom, there was major concern about the number of hospital admissions and deaths due to self-poisoning with paracetamol, notably by adolescents. Arising from a number of studies, the Medicines Control Agency placed severe restrictions on the availability of paracetamol by retail, some of which took effect in September 1997 with the remainder to be in full operation in late 1998.

**Paracetamol and alcohol consumption**

The most recent regulatory action has been the decision by the Food and Drug Administration (FDA) of the United States of America to require an alcohol warning label on containers of aspirin, paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) that can be purchased without a prescription. The FDA had also issued a revision of its monograph governing the labelling of non-prescription analgesics in 1996 but this did not propose a warning label in connection with alcohol and the analgesics.

All of these factors pointed to the timeliness of a review in an Australian context.

**Terms of reference**

The TGA required a review of all of the correspondence received in relation to labelling and packaging and to produce a report and recommendations to address issues of public health and safety in relation to the use of analgesics as well as the concern of both industry and the TGA for some clarity and simplicity in the administration of the requirements related to analgesics.

A considerable part of the Review is devoted to paracetamol because of its prominence in accidental and self-poisoning and because of the recent changes of availability in the United Kingdom and the content of labels in the United States. Aspirin figures less as a “problem drug” in the 1990s when it is compared with the 1970s, but it affords a good example of labelling requirements that have become unwieldy and in need of streamlining. Like aspirin, the non-prescription NSAIDs have been subject to an increasing number of warning statements. The non-prescription NSAIDs have also been subject to a curious regulation that required them to be evaluated by the Australian Drug Evaluation Committee, rather than the Medicines Evaluation Committee, because they are prescription-only in larger pack sizes. As this matter has been addressed in an earlier review, it will not be discussed in much detail other than to support that review’s recommendation to have the regulation amended.

In making certain of its recommendations, the Review has chosen not to place itself in the shoes of various expert committees, but rather, to flag certain topics for consideration of those committees that normally deal with a particular piece of legislation. There are not always easy solutions to labelling and packaging requirements when those requirements are derived from different laws and especially when some are Commonwealth and others are State/Territory based. Industry would like to be able to refer to a single document that sets out all of the labelling and packaging requirements. Under the present legislative regimes, such is not always possible or even desirable, but there is nothing to prevent any person preparing a comprehensive guide to labelling and packaging of pharmaceuticals in general as long as the sources of the mandatory and policy
requirements are fully cited. Provided such a document were accurate, readily available and were updated and circulated promptly to subscribers eg. by a disk, the only disadvantage would be that the guide could not be used as authoritative evidence in legal proceedings. An example of a comprehensive guide is the booklet *Advertising Therapeutic Goods to the Public* which was produced by the National Coordinating Committee on Therapeutic Goods at the request of industry.

Questions of copyright, especially with regard to the SUSDP, will be need to be resolved as the law should be readily available to everyone, including individuals, at reasonable cost.

Labelling of analgesics represents one example of the present difficulties faced by both industry and government departments. There is little value, however, in having a guide for the labelling of analgesics alone; a more comprehensive document for medicines is required. A second broad issue raised by one manufacturer of analgesics was that of New Zealand-style consumer information panels on labels and suggested that this might encourage compliance with directions for use and warnings and at the same time, promote harmonisation with New Zealand. This was a valuable suggestion but was beyond the Review’s terms of reference. Should such an initiative be pursued, it should apply to all non-prescription medicines and not just analgesics.

**Poisons information centres**

In August 1997, the TGA wrote identical letters to the poisons information centres in each State and the Northern Territory seeking information about accidental poisoning with paracetamol. Each centre replied, but it was not possible to obtain an Australia-wide picture on the subject because the data in the replies were not presented uniformly. This raises some wider issues about data collection by poisons information centres in this country. From discussions with several of the centres, it was learned that there is not a standardised method of data collection although there are now moves to use a format in 1998 based on that used in New South Wales. The Review understands that progress is slow, due in part, to budgetary constraints within individual centres and the need for pharmacy departments of the host hospitals to provide funds for expenses other than salaries. The discontinuation of the Commonwealth’s role in national data collection and the maintenance of the national poisons register has also contributed to the slow progress in establishing an integrated system.

It is outside the scope of the Review to make recommendations about the structure, conduct and performance of Australia’s poisons information centres but there is clearly a need for specific funding (i) to appoint a short-term manager with a view to facilitating improvements to the current arrangements in the national interest; and (ii) for an annual conference of directors of the centres. Once a uniform data collection system is operating, there would be a role for a person to analyse the data in order to identify, investigate and alert health authorities to actual and potential problems. It would also be necessary to connect the data obtained from poisons information centres with numbers of presentations and admissions and thence to outcomes. These matters would be most appropriately placed on the Australian Health Ministers’ Advisory Council’s agenda.
During the Review, it was clear that there were large numbers of enquiries to the centres about suspected poisoning with analgesics, especially paracetamol; there is also evidence of increasing numbers of presentations to hospitals. Admissions, due to accidental poisonings with analgesics were low and serious outcomes were relatively few due to timely interventions during admissions to hospitals. Reliance, therefore, on numbers of enquiries to poisons information centres in determining policies would be a mistake unless a correlation between enquiries and outcomes were established. The number of enquiries may indicate the awareness by the public of the services provided by the centres and people should not be discouraged from using them.
PARACETAMOL - THE MAIN DRUG REVIEWED

Background

The pharmacology, toxicology and therapeutics of paracetamol are well documented in standard references (Insel, 1996). There is also an extensive literature, and an Australian protocol, on the treatment of paracetamol poisoning. The history of the drug in Australia has been researched by Mercovich (1988).

Paracetamol’s popularity increased considerably following the associations between aspirin and renal papillary necrosis in the late 1960s and the 1970s and later, with Reye’s syndrome. Because paracetamol is effective and well tolerated, lacks many of the side effects of aspirin and is available without a prescription, it has earned a place as a common household analgesic. The usual strength of each tablet or capsule is 500mg with a recommended adult dose of one or two tablets or capsules four hourly to a maximum of eight daily. There are also oral liquids, chewable tablets and suppositories available in a variety of strengths and many products where paracetamol is compounded with other therapeutically active substances.

Its main disadvantage is its toxicity in acute overdose or following chronic treatment with larger therapeutic doses in younger children and in habitual alcohol drinkers. Hepatotoxicity can occur after an ingestion of 10 to 15g (20 to 30 tablets) in adults or 200 to 250mg/kg; a dose of 25g (50 tablets) is potentially fatal without early intervention. Symptoms during the first day are nausea, anorexia and abdominal pain and these may continue for a week or more. Clinical signs of liver damage are observed two to six days after ingestion of a toxic dose. In non-fatal cases, hepatic lesions are reversible over a period of weeks or months. Treatments have included the administration of L-methionine, L-cysteine and N-acetylcysteine (NAC).

Australian data

Poisons information centre enquiries

Figures obtained from poisons information centres throughout Australia show that paracetamol is a major subject of telephone enquiries from the public; for example, in 1996, the New South Wales Poisons Information Centre answered enquiries arising from 4351 exposures out of a total of 103,469 calls (73,673 exposures); the Victorian centre responded to 914 paracetamol-related calls out of a total of 47,263 calls (28,047 exposures)[note the difference in rates between the centres]. Paracetamol was the substance which singly generated most calls to each centre.

Appendix 2 contains data from the Australian Institute of Health and Welfare on separations due to paracetamol poisoning whether by accidental overdose or by self-poisoning.

Survey of general practitioners and pharmacists

A study (Campbell and Oates, 1992) surveying childhood poisoning in New South Wales also sought to determine doctors’ and pharmacists’ appreciation of the toxicity of a number of drugs and poisons. For paracetamol, 30% of the responding (65% of 150) general practitioners ranked paracetamol has having high toxicity but 60% of the responding (45% of 150) pharmacists surveyed
ranked it in the bottom half of the list of the drugs and poisons mentioned in the questionnaire. It is unclear if the preceding results mean that about 30% of each group of professionals agreed that paracetamol should be ranked as having high toxicity because if 60% of the pharmacists ranked it in the bottom half of the list, does this mean that 40% placed it in the top half? The authors noted their concern that many respondents did not appear to be aware of the high toxicity to young children of anticonvulsants, iron, paracetamol, digoxin and quinine. In particular, pharmacists, although likely to give advice about the toxicity of iron and quinine, rarely gave precautionary advice about paracetamol or digoxin.

**What is the problem?**

**Accidental poisoning in children**

In a review of the international literature (Penna and Buchanan, 1991), only seven deaths and 14 cases of hepatotoxicity in children were found. Arising from earlier studies (Rumack, 1984; Meredith et al. 1978), a view emerged that children were less susceptible to the hepatotoxic effects of paracetamol because of developmental differences in the metabolism of the drug and its detoxification pathways. Acute poisoning of children that results in serious outcomes is uncommon (Kumar et al, 1990).

Paracetamol is metabolised mainly by conjugation with glucuronide and sulphate, the products of which are excreted in the urine. A lesser pathway is by oxidation by cytochrome P450 to the highly reactive and toxic metabolite, \(N\)-acetyl-\(p\)-benzoquinoneimine (NABQI, also known NAPQI). NABQI is, however, detoxified by glutathione. If NABQI is not removed, it covalently binds with hepatocyte proteins and brings about hepatic necrosis. In children, the sulphation and oxidative pathways are believed to be more efficient than in the adult which may explain reduced toxicity arising from acute paracetamol overdose. In neonates, the sulphation conjugation is not well developed but the oxidation pathway is. Chronic dosing with paracetamol in neonates can cause an accumulation of NABQI because glutathione stores become depleted faster than they can be replenished.

In children, chronic poisoning therefore represents the more insidious problem. Nahata et al (1984) showed that paracetamol may accumulate substantially after repeated therapeutic doses over two to three days even at doses as low as 13mg/kg every four hours. Penna et al (1993) have cautioned about prescribing paracetamol on a p.r.n. basis. For this reason, the recommended dose, frequency and duration of treatment must be strictly complied with. The safe upper limit for children is 90mg/kg daily.

The large number of enquiries to poisons information centres and the increasing numbers of presentations to hospitals following an accidental overdose with, or self-poisoning from, paracetamol, on the face of it, suggest a significant public health problem. An American study (Veltri and Rollins, 1988) compared the frequency and severity of 10,134 cases of poisoning due to paracetamol, aspirin and ibuprofen that were reported to a poison control centre. They found that most cases were managed without referral to a health care facility and specific therapeutic intervention was not necessary. Most symptoms, when they did develop, were not life-threatening. To complete the picture, outcomes must also be measured and if possible, related to enquiries and presentations. Also to be considered is the number of homes with paracetamol on the premises. An Australian Bureau of Statistics “Safety in the home” survey in 1992 estimated that in households with a child under five years of age, paracetamol solid dose forms and oral liquids were present in 89% and 62% of them, respectively. From the Australian data examined, there is a marked
difference between numbers of enquiries, exposures and presentations on the one hand, and actual admissions on the other. Permanent damage and serious morbidity after treatment is uncommon and deaths are exceedingly rare. The outcomes would unquestionably be different if comprehensive protocols involving the administration of NAC and other antidotes were not available. This should not engender a sense of complacency because prevention is always better than cure and although NAC has a good safety record (Dawson et al, 1989), there are isolated cases of fatalities in adults and children (Mant et al, 1984; ed. Lancet, 1984); these, however, have been associated with excessive doses. The study in Appendix 1 of this Review disclosed several cases of relatively minor adverse reactions to this antidote and these were managed satisfactorily.

The Review suggests several measures to reduce the frequency of maladministration of paracetamol, especially to children, but recognises that in view of the ubiquity of paracetamol, total elimination of accidental poisoning with this drug is unlikely. Householders have a major role to play in reading labels and storing medicines properly. Community service announcements by whomsoever sponsored, need to reinforce these messages.

The many enquiries to the poisons information centres suggest that there is an awareness among the public of the potential danger of untreated or delayed treatment of paracetamol overdose. Further, Australia’s poisons scheduling and product registration systems have probably made a significant contribution to the low morbidity and mortality outcomes, although it is not possible to assert a causal relationship in the absence of controls.

Self-poisoning by adolescents

The data and anecdotal evidence indicate that there is an increasing frequency of self-poisoning among teenage girls with solid dose paracetamol products.

There have been several studies that have examined adolescents’ knowledge about the toxicity of paracetamol. Huott and Storrow (1997) surveyed a sample of 13 to 18 year-olds who presented at acute care or emergency departments at two American hospitals to determine their subjects’ knowledge of the poisonous nature in overdose of a number of non-prescription medicines. For paracetamol, 57% recognised a potential for overdose. These authors believe that emergency physicians should “adjust their assessments of individual overdose patients’ suicidal intents accordingly”.

Gilbertson et al (1996) compared the use, availability and knowledge of toxicity among British and American adolescents. Although 90% of all 1,147 students in the 12-19 year-old age group surveyed recognised that paracetamol could kill, the great majority overestimated the lethal dose. These authors asserted that along with wide availability and a poor understanding of the drug’s side effects, gross overestimation of the number of tablets that could kill contributed to its frequent use in adolescent suicidal behaviour. There was an erroneous belief, especially among British students, that paracetamol could induce sedation.
Warning labels to containers do not seem to have been favoured by British authors and there is at best, lukewarm support for educational programs as a means of addressing the specific problem.

Australian health professional bodies should inform their members of the problems of paracetamol toxicity so that the public can be suitably counselled..

**Recommendation 1.1**

Medical and pharmacy organisations remind their members of the toxicity of paracetamol in overdose with special reference to toxic doses and the delayed adverse effect on the liver.
PARACETAMOL AND ACCIDENTAL POISONING

To an extent, this Review was precipitated by concern expressed about accidental poisoning of children with paracetamol when presented as an oral liquid. The term “oral liquid” is defined in the British Pharmacopoeia 1993 as consisting of solutions, suspensions or emulsions of one or more active ingredients in a suitable vehicle. It is used likewise in this Review. The emphasis in this chapter is directed to oral liquids having paracetamol as the only active constituent.

Presentations at hospital accident and emergency departments and admissions

Data obtained from the Australian Institute of Health and Welfare (AIHW) about separations from Australian hospitals from July 1993 to June 1996 where paracetamol is implicated in accidental poisoning form Appendix 2 to this Review. The table below is a summary for various age groups.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Female 0-9</td>
<td>88</td>
<td>106</td>
<td>78</td>
<td>57</td>
<td>133</td>
<td>105</td>
</tr>
<tr>
<td>Male 0-9</td>
<td>105</td>
<td>131</td>
<td>92</td>
<td>88</td>
<td>151</td>
<td>140</td>
</tr>
<tr>
<td>Female 10-20</td>
<td>153</td>
<td>136</td>
<td>86</td>
<td>71</td>
<td>124</td>
<td>116</td>
</tr>
<tr>
<td>Male 10-20</td>
<td>36</td>
<td>27</td>
<td>17</td>
<td>23</td>
<td>28</td>
<td>24</td>
</tr>
<tr>
<td>Female 20-30</td>
<td>115</td>
<td>93</td>
<td>57</td>
<td>52</td>
<td>103</td>
<td>104</td>
</tr>
<tr>
<td>Male 20-30</td>
<td>48</td>
<td>58</td>
<td>31</td>
<td>32</td>
<td>51</td>
<td>43</td>
</tr>
<tr>
<td>Female &gt;30</td>
<td>101</td>
<td>34</td>
<td>51</td>
<td>50</td>
<td>109</td>
<td>89</td>
</tr>
<tr>
<td>Male &gt;30</td>
<td>62</td>
<td>48</td>
<td>30</td>
<td>44</td>
<td>64</td>
<td>40</td>
</tr>
<tr>
<td>TOTALS</td>
<td>708</td>
<td>643</td>
<td>442</td>
<td>416</td>
<td>763</td>
<td>661</td>
</tr>
</tbody>
</table>

TABLE. Separations for the sex/age groups for cases of accidental poisoning by paracetamol in half-yearly intervals from the second half of 1993 to the first half of 1996 (Source: Australian Institute of Health and Welfare).

The figures in this table were obtained by using ICD9 code 965.4 (essentially paracetamol) with external code E850.4 (Accidental poisoning by drugs, medicinal substances, and biologicals). This external code includes accidental overdose of drug, wrong drug given or taken in error, and drug taken inadvertently. It also covers accidents in the use of drugs in medical and surgical procedures. It does not include administration with suicidal or homicidal intent or intent to harm nor does it cover the correct drug properly administered in therapeutic or prophylactic dosage, as the cause of adverse event. As would be expected, children make up the biggest single group.

For the three years from July 1993 to June 1996, there were 1242 children under five years of age admitted to Australian hospitals for accidental poisoning with paracetamol (see Appendix 2), averaging 414.
A Victorian Injury Surveillance System (VISS) study (Routley et al, 1996) quantified the number of children under five years of age presenting at three large Melbourne hospitals and one country hospital for paracetamol poisoning. From 1989 to 1993 in the case of the Melbourne hospitals and from July 1991 to June 1995 for the country hospital, there were 455 presentations resulting in 115 admissions (25%). Paracetamol poisoning was the leading single cause of both presentations and admissions to hospital. In this series, poisonings occurred more frequently from the liquids (suspensions and elixirs (45%); drops (9%)) than from solid dose forms (22%).

Statewide, from July 1987 to June 1994 (seven years), there was an average of 55 admissions per year for children in the under 5 years age group. If Victoria has about one-quarter of the Australian population, then about 100 admissions might be expected each year in that State alone on the basis of the data from Appendix 2. The VISS data, however, gives an average of 55. The years from which the two sets of data were compiled overlap somewhat with the VISS data covering an earlier period than the AIHW figures. It is difficult to reconcile these different rates although the hospital admissions data in Victoria showed that from the financial year 1992-1993 to the next, there was a sharp increase in paracetamol admissions which, if taken in isolation would bring Victorian figures more into line with the national data. On the other hand, admissions to the Royal Children’s Hospital for accidental poisoning with paracetamol (see Appendix 1) had not shown any increase over the period studied.

Available presentations of oral liquids

There are four strengths of uncompounded paracetamol oral liquids registered for supply in Australia with the 50mg/mL strength being presented as drops and as an elixir. The strengths are:

* 50mg/mL in bottles of 50mL, supplied with a calibrated dropper [2.5g/bottle]
* 100mg/mL in bottles of 20mL, supplied with a calibrated dropper [2.0g/bottle]
* 120mg/5mL in bottles of 100mL, 150mL and 200mL [2.4g, 3.6g and 4.8g/bottle]
* 240mg/5mL in bottles of 100mL and 200mL [4.8g and 9.6g/bottle]
* 250mg/5mL in bottles of 100mL and 200mL [5.0g and 10.0g/bottle]

The 50mg/mL and 250mg/mL are shown separately because, although the concentration of paracetamol is the same in each pack, they are flavoured differently and are distinctly presented.

The Australian Pharmaceutical Formulary and Handbook 15 (APF) includes formulas that contain 120mg and 240mg of paracetamol in each 5mL dose. The British Pharmacopoeia 1993 (BP) has monographs for Paediatric Paracetamol Oral Solution that contains 2.4%w/v of paracetamol and for Paracetamol Oral Suspension. The BP directs that in the latter case, a strength of 2.4%w/v shall be supplied. This percentage equates to 120mg/5mL. The United States Pharmacopeia XXII (USP) has monographs on Acetaminophen Oral Solution and Acetaminophen Oral Suspension but gives no direction on strengths to be supplied.
The oral liquids are either elixirs where the paracetamol is dissolved using a co-solvent system or suspensions which must be shaken before use. Some presentations are coloured by the addition of a suitable colouring agent, usually a shade of red but others are colourless. Manufacturers use a variety of flavouring agents to mask the taste of paracetamol which is bitter. The closures on the containers of the oral drops are fitted with a screw cap covered by a plastic tamper-proof security wrapper which is discarded after first use. Either the original screw cap or the supplied screw-on dropper is used thereafter. Manufacturers are now using child-resistant closures on the unopened container and the dropper assembly even though there is an exemption from the need to use this form of closure for packs containing less than 2g of paracetamol. The larger volume containers have re-closable child resistant screw-cap closures.

Overall, there are about 50 uncompounded paracetamol oral liquids entered on the Australian Register of Therapeutic Goods (ARTG) but at any one time, not all of them are necessarily available for supply in Australia. Because pack sizes are disregarded for the purposes of allocating a registration number to a particular product, the number of line items potentially available is about 75.

**Problems with the present situation**

There is considerable anecdotal information about the problems associated with uncompounded paracetamol oral liquids but quantified data are not readily at hand. From information supplied by clinicians and poisons information centres in Australia, the following general remarks may be made.

**The number of strengths**

Criticisms have been made (Shann, 1991; TGA correspondence, 1996; Berlin, 1997; Smith and Temple, 1997) about the number of variants of strength (as listed above) of paracetamol oral liquids as leading to confusion on the part of some carers. For example, 5mL of the “standard” presentation contains 120mg but if 5mL of the drops or 5mL of the higher strength elixir were given, the child would receive 500mg or 240mg of paracetamol, respectively. Administered at the usual frequency in this circumstance, a serious outcome could develop especially in the case of the drops because this presentation is more concentrated. It appears that some people believe that all “liquid paracetamols” (unlike presentations of some popular decongestant/antihistamine oral liquids) are the same, pack volume being the only difference.

As dosage requirements vary from person to person, many drugs are available in different strengths but it is rare to find any drug, other than paracetamol, available in oral liquid form in so many strengths. A multiplicity of strengths is a cause for concern; the discontinuation of 20, 40 and 80 units/mL of insulin and their replacement by the one strength of 100 units/mL with dosage being adjusted on the basis of volume alone has been helpful in reducing errors in supply and administration.

Several clinicians have put to the Review that there should be only one strength of uncompounded paracetamol oral liquid on the Australian market with a concentration of either 50mg/mL or 60mg/mL. A suitable dose would accommodate all age groups. A unique strength would avoid mix-ups and confusion in the home and would remove the anomaly that the highest of the present strengths is used for babies, the second highest for children over four or five years of age and the weakest for children in between. A more or less similar situation occurs with amoxycillin oral liquids but the consequences of overdose with this drug are relatively minor when
compared with paracetamol; they are Schedule 4 poisons and the 100mg/mL drops are not prescribed as often as the 125mg/5mL and 250mg/5mL strengths. Had the potential problems with paracetamol been predicted, there would have been a case for standardising the strength years ago. To introduce such a restriction at this juncture would possibly create more problems during the changeover than it was designed to overcome especially as there are relatively few cases of serious morbidity and no fatalities in this country under the present arrangements. A number of community pharmacists who were contacted during the Review said that they thought there were very few problems associated with the present range although several were not aware that one brand contained 250mg/5mL rather than 240mg/5mL. Several hospital pharmacists have called for caution with the 100mg/mL drops (Margarey, 1991; Parsons, 1993).

Recent changes to United Kingdom legislation have limited the concentration of paracetamol in oral liquids for children under 12 years of age, to 120mg/5mL in a pack of up to 100mL for sale to the public without a prescription. This is impractical because the dose volumes needed to administer an adequate amount of paracetamol to an infant or to a 10 year old are excessive, impracticable and inconvenient; only the younger child is reasonably well accommodated by this strength. If anything, a case could be made for the discontinuation of the 120mg/5mL strength because children up to 4 or 5 years could be treated with the 100mg/1mL drop. The taste of the drops is unpleasant and may well be rejected by toddlers and pre-school age children when perceptions of bitterness would have developed.

That such a variety of strengths of paracetamol oral liquids is available in the face of human error, inadvertence or ignorance and having regard to the serious consequences that can flow from carelessness or a mistake, it is tempting to recommend the sequential discontinuation of each strength other than one of, say 50mg/mL. But does the evidence justify such a step? It is true that there are many presentations to hospitals due to paracetamol overdose in children and there are thousands of enquiries about paracetamol to poisons information centres but there are few admissions especially when compared with the ubiquity of paracetamol oral liquids. In the Royal Children’s Hospital (RCH) series in Appendix 1, there were no deaths and no liver transplants over five years.

As the law stands, there is little to prevent a sponsor placing yet another strength of paracetamol oral liquid on the market, subject to the particular product being safe and efficacious and meeting quality standards. In public health terms, however, a registering authority might be abdicating its duty if it were to approve a product whose introduction would compound an existing problem even though the product seen in isolation fulfilled all of the usual criteria. In the course of the Review, exception was taken by the representatives of some companies to a policy not to register any new strengths of paracetamol oral liquids as such an action would be discriminatory and would inhibit enterprise. There was support, however, from several senior clinicians and hospital pharmacists for “drawing a line in the sand” in relation to the number of strengths and pack sizes of paracetamol oral liquids.
Recommendation 2.1

As a matter of TGA policy, strengths of uncompounded paracetamol oral liquids other than those containing 24mg/mL, 48mg/mL, 50mg/mL and 100mg/mL should not be entered on the Australian Register of Therapeutic Goods for supply in Australia. If necessary, the SUSDP should be amended accordingly.

The existence of large pack sizes

Concern has also been expressed at the availability of pack sizes of 200mL, especially in the 240 and 250mg/5mL strengths. The basis of this concern is that in the “standard”or “regular” strength of 120mg/5mL, the amount per 200mL bottle of paracetamol is 4.8g or, in the higher concentrations, 9.6g and 10g. Taken all at once, there would be sufficient paracetamol in the one bottle of liquid to cause serious harm or even death to a child in untreated cases or if treatment were delayed.

It was not possible to determine from the RCH study if the pack size, of itself, contributed to the number of admissions because such information was not usually recorded in the case notes.

Industry put to the Review that the larger pack sizes were in response to consumer demand especially in the case of larger families where the multiple or frequent purchase of the 100mL pack would be inconvenient and costly. There is a clear price advantage to the public in purchasing the 200mL pack size of the 240mg/5mL of the market leader’s paracetamol oral liquids as compared with 100mL of the 120mg/5mL presentation. An examination of the prices of the market leader’s range for 1g of paracetamol in an oral liquid showed the following order from lowest to highest:

- 240mg/5mL, 200mL size
- 240mg/5mL, 100mL size
- 100mg/1mL, 20mL size
- 120mg/5mL, 200mL size
- 120mg/5mL, 100mL size

The most popular size and strength is therefore the most expensive way of buying 1g of paracetamol. There is thus a financial disincentive for a manufacturer to produce larger volume pack sizes.

For the purposes of the Therapeutic Goods Act 1989, therapeutic goods are separate and distinct from other therapeutic goods if, among other things, the name, strength, indications or sponsor differ; pack size is to be disregarded. This does not prevent the TGA from refusing the register a particular good in a pack size that might be regarded an unacceptable risk to health. Instances have already occurred where certain pack sizes of some medicines have not been accepted.
Recommendation 2.2

As a matter of TGA policy, packs of uncompounded paracetamol oral liquids containing volumes greater than those already on the market for each strength for supply in Australia should not be placed on the Australian Register of Therapeutic Goods. If necessary, the SUSDP should be amended accordingly.

Confusion with decimal expressions

Despite the metrication of medicines in Australia in March 1965 and the use of metric measures for food, clothing, money, fuel and distances, there are people who have difficulty with comprehending and attaching significance to quantities such as 0.8mL which they mistake for 8mL; 2.0mL sometimes mistaken for 20mL; or 2.5mL, mistaken for either 25mL or rarely, 10mL (two times five). Such misunderstandings are more likely to occur and have serious consequences arising from the repeated administration of an incorrectly measured dose of paracetamol when supplied as drops, given the higher concentration of paracetamol present in this presentation.

Many different kinds of measures are available on the Australian market. One commonly sold brittle plastic conical measured is marked in graduations on one side of 2½ML, 5ML, 10ML, 20ML, 30ML and 40ML and on the other 4ML, 8ML and 15ML. A soft plastic conical measure was marked on one side with graduations 2.5, 5, 10, 15, 20, 30 and 40 with the abbreviation mL at the top; the other side was marked at 5, 10, 15, 20, 30 and 40 mL in figures with lines corresponding to 3, 4, 6, 7, 8, 9, 11, 12, 13 and 14 mL.

A tapered measuring cup, thought to be American, was marked on one side with graduations of 5, 10, 15, 20, 25 and 30 ML and also in CC. On the other side, there were marked graduations of 2, 4, 6 and 8 drams corresponding to ¼, ½, ¾ and 1 FL.OZ respectively. There were unmarked graduations for 1,3,5, and 7 drams corresponding to 1/8, 3/8, 5/8 and 7/8 FL.OZ, respectively.

Also available in Australia are numerous Hong Kong manufactured measuring devices that are clearly intended for the American market. The devices include droppers, syringes and measuring spoons marked dually in millilitres and in teaspoonfuls measures such as ¼ and ½ tsp. In a study on the use of 34 errors made with dispensing cups reported by Litovitz in 1992, most cases involved a two- to threefold dosing error; paracetamol was implicated in 18% of the errors. The use of, and confusion between, the abbreviations used in the USA for teaspoonfuls and tablespoonfuls accounted for 47% of the errors but this is not fully relevant to Australia. The study revealed that some consumers thought that the cup was the unit of measure (18%) and some assumed that the full dispensing cup was the actual dose (12%). The author recommended (i) that labels should clearly state the dose followed by the words “not one cupful”; (ii) an analysis of the costs and benefits of contrasting the colour of the lettering against the colour of the cup itself; and (iii) consumer education. (References to recommendations on spoon measures are omitted for Australian purposes).
Recommendation 2.3

Manufacturers of paracetamol oral liquids who wish to supply measuring devices with each bottle of a paracetamol oral liquid ensure that the calibrations correspond with the doses shown on the label to discourage calculation and guesswork.

Recommendation 2.4

The importation and manufacture (other than for export or re-export) of medicine measures for domestic use that are calibrated in other than metric units be prohibited.

Recommendation 2.5

The Pharmaceutical Society of Australia request pharmacists and staff to (i) ensure that purchasers of paracetamol oral liquids have a suitable measuring device and; (ii) demonstrate its use at the point of sale.

Recommendation 2.6

All doses of uncompounded paracetamol oral liquids containing 120mg/5mL, 240mg/5mL and 250mg/5mL should (i) be in whole numbers of millilitres and (ii) omit the decimal point and the post-decimal zero (eg. 5mL not 5.0mL). Minor variations to the approved dose/kg to be disregarded in the interests of safety and ease of administration.

Perceptions of safety

In the recommended doses and at the recommended frequency of administration, paracetamol is a safe drug having minimal unwanted effects. Paracetamol oral liquids are Schedule 2 poisons and are available only from pharmacies. In packets of up to 25 tablets or capsules (other than those marketed for children’s use), paracetamol is available from any retailer. The ready availability of paracetamol and its prominent advertising in the electronic media and in the print media, including advertising boards on trams and buses, have led some experts to believe that a false sense of safety is conveyed to the public despite the use of mandatory warning statements as part of the advertisement.

Poor storage of medicines in the home

The careless storage of medicines in the home is an obvious risk factor in childhood poisoning. The requirement to store some medicines, notably antibiotics, in the refrigerator has encouraged some carers to store other liquid medicines similarly even though there is no pharmaceutical reason so to do. The contents of refrigerators are easily accessible to children and this method of storage contradicts the mandatory expression, “Keep out of reach of children” that appears on all scheduled poisons.
Inquisitive children may also take solid dose forms from a handbag especially in cases where only one tray, packed in a blister pack, is present.

**Recommendation 2.7**

Community service announcements sponsored by government, the professions and industry should (i) stress the importance of not leaving medicines in general and paracetamol in particular within reach of children; (ii) draw the public’s attention to the existence to different strengths of paracetamol; (iii) emphasise the need to read the label; and (iv) direct the public to seek the advice of a pharmacist or a doctor if they do not understand the label.

**Containers**

Paracetamol oral liquids, except those containing not more than 2g of paracetamol, are required by law to be packed in containers fitted with child-resistant closures. Children learn to remove such closures and because the closures are sometimes a little difficult to remove from, and replace on, the bottle, a careless person may elect not to use them at all. Crystallisation of the vehicle around the screw-cap is said to discourage the cap’s proper replacement.

Drops of paracetamol oral liquid and the accompanying dropper are now fitted with child resistant closures and the exception mentioned above is no longer appropriate.

**Recommendation 2.8**

The provision in Therapeutic Goods Order No.20 that enables dropper packs containing not more than 2g of paracetamol to be exempted from the need to be fitted with a child resistant closure should be repealed.

**Label design**

The label content of paracetamol oral liquids contains a great deal of information. One sponsor provides a table of all the paracetamol oral liquids for the various age ranges while others suggest different strengths for particular ages. Comment has been made that labels are insufficiently differentiated among one another for a given brand even though some sponsors use different principal colours to distinguish between the 120mg/5mL strength and the 240mg/5mL strength.

Several brands have photographs of a child or children (sometimes with an adult female, presumably portraying the mother) of different ages appropriate to the strength of the product. It is unclear if these pictures are regarded by the public as connected to the age of the child for whom the particular strength is intended or whether they are simply a collection of happy family members. Other medicines picture attractive family groups on their labels presumably to indicate that the product is indicated for all age groups or that after taking the medicine, the subjects are much improved in health. Some research on this topic would be valuable.

**Body weights**
Examination of the oral liquids containing paracetamol shows that the dose ranges differ between brands. With one exception (currently being revised to conform to Australian Guidelines for the Registration of Drugs vol 2 (AGRD vol 2)), doses are based on 12.5mg of paracetamol per kg of body weight. For a given age range, however, the tables of weights of children are not always the same and doses are correspondingly different. For example, for children aged 1-2 years, one sponsor cites a range of 9.9 to 12.1kg while others quote 10.2 to 12.6kg. These translate to doses of 5.0 to 6.5mL (120mg to 156mg) and 5 to 7mL (120mg to 168mg), respectively. Such differences are minor and would not be expected to have much effect on safety or efficacy. The fact, however, that these differences are shown on labels may raise queries in consumers’ minds. The table of average weights of children in the age group one month to six years in AGRD vol 2 was obtained by averaging the weights for the 50th percentile for girls and boys (Source: MIMS 1997 pp.XCII, XCVI, C and CIV). Given the weight variation between individuals at a given age, the lighter child will, for the same volume of medicine receive greater than 15mg/kg, and the heavier child less.

**Recommendation 2.9**

Age/weight range tables on labels should be uniform across the industry and be based on contemporary Australian figures.

**Recommendation 2.10**

Dose tables on labels should preferably show age/weight/millilitre dose OR age/millilitre dose but not weight/millilitre dose to discourage the need for calculations by the carer.

**Dose rate**

The present dose regime is based on 12.5mg/kg but references such as the APF 16 recommend 15 to 20mg/kg every four hours when required to a maximum daily dose of 90mg/kg or 4g whichever is the lesser. The *RCH Pharmacopoeia* recommends 15mg/kg; the *Princess Alexandra Hospital for Children Drug Handbook* 1993 quotes 15 to 20mg/kg to a maximum of 75mg/day. *The Australian Immunisation Handbook* - 6th ed (National Health and Medical Research Council,1997) recommends the routine use of paracetamol to reduce the unpleasant side effects following DTP vaccination at a dose of 15mg/kg within 30 minutes before the injection, with the dose to be repeated at 3 to 4 hourly intervals as required up to a maximum of six doses in 24 hours. There is also literature support for the 15mg/kg dose (Frank and Coulthard, 1988)
Until the late 1980s, doses were based on 10mg/kg. This was subsequently increased to 12.5mg/kg and the change was successfully implemented by industry by the production of leaflets, stickers and charts for use by health professionals and the public.

**Recommendation 2.11**

A new paediatric dose for paracetamol based on 15mg/kg should be referred to the Medicines Evaluation Committee for its consideration to replace the present dose based on 12.5mg/kg.

**Recommendation 2.12**

In the event of the Medicines Evaluation Committee supporting a dose rate based on 15mg/kg, the TGA and the industry agree on an implementation strategy.

*Number of doses and duration of treatment*

In August 1997, the TGA wrote to sponsors of paracetamol oral liquids requesting each to supply copies of the labels used for products to be supplied in Australia. In some cases, the products, although entered on the Australian Register of Therapeutic Goods, were not being marketed at present or would soon be discontinued. These have been excluded from the comments below. In others, the sponsors had indicated that new labels were being drafted.

In all cases, the labels complied with statutory requirements but various deficiencies were noted in some cases as the product predated the AGRD vol 2. There are statements in the AGRD vol 2 (at page 65) concerning the maximum number of doses that should be given in 24 hours and that the duration of administration should not exceed 48 hours without medical advice. The first of these relates to ensuring the total daily dose is within safe limits; the second is concerned with the need for medical advice to be sought and a proper diagnosis made, and also because of the inability of the body to deal with toxic metabolites that may have accumulated. In the study that forms Appendix 1 to this Review, there were instances where the dose was given for longer than it should have been but it is not known if the particular product included reference to the advisory statement about not giving the medicine for more than 48 hours.

Also of note was that the word “fever” often preceeded “pain” on some labels even though the latter is the more important indication for the use of paracetamol. One sponsor included a “nutritional information [telephone] line” for the benefit of consumers. In no sense is paracetamol a nutritional product and such a notion should not be conveyed to the public. The phrase “ideal for children” appeared on one set of labels of a grandfathered product; it is considered that the word “ideal” is not appropriate for therapeutic goods.
**Recommendation 2.13**

In the interests of paediatric health and safety, all labels for uncompounded paracetamol paediatric formulations, at next printing or before 1 January 2000, should include statements to the effect that:

* not more than 4 doses should be given in 24 hours;
* the medicine should not be administered for more than 48 hours without seeking medical advice.
PARACETAMOL IN FEVER

Antipyresis is the major use for paracetamol in children, including those who are in hospital as medical patients (Penna et al, 1993). Fever is most commonly caused by infections but can also result from tissue injury, endocrine, immunological and inflammatory causes, and the administration of drugs such as the antibiotics. While some fevers result from serious bacterial infections, the majority are caused by benign, self-limiting viral infections.

The popular view is that fever causes the child discomfort and this can be relieved to some extent by the administration of paracetamol. Even though paracetamol will reduce the temperature by 1º or 2ºC only, such a reduction is often enough to make the child feel more comfortable. If pain is present, with or without fever, the case for treatment with the drug is stronger. It is the analgesic action of paracetamol that probably explains its benefits rather than its antipyretic action (Kramer et al, 1991; DeBuse, 1994). Some workers have concluded that the principal rationale of antipyretic therapy is to reduce not only parental anxiety, but also that of doctors and nurses (Kramer et al, 1985).

Paracetamol is recommended for treatment of DTP (triple antigen) reaction, the first dose being given before the injection is administered (National Health and Medical Research Council, 1997). There are also specialised uses for it (Shann, 1995).

A view has emerged that children with self-limiting viral infections that are accompanied by a mild rise in temperature should not be treated with antipyretics such as paracetamol. A major study (Kramer et al, 1991) in which febrile children were treated with paracetamol versus placebo, found that there were no differences in mood, comfort, appetite or fluid intake between the groups; the only difference being a greater activity and alertness among one-third of the children who had received the drug. As stated by the authors, treat the child and not the thermometer. The basis for not using paracetamol in fevers is that fever reduces viral shedding, the duration of the illness and helps in the immune response. Animal studies have shown an increased mortality in those subjects with a severe infection given an antipyretic compared with those not so treated. Nor should paracetamol be used for minor irritability or as a sedative (Day and Abbott, 1994).

Contrary to popular belief, antipyretics will not prevent febrile convulsions although Day and Abbott (1994) indicate that paracetamol may be of some value for infants with a history of febrile convulsions. Further, even if a febrile convolution occurs in response to an infection, brain damage does not result. It is the rapid increase in body temperature rather than the actual elevated temperature that precipitates a convolution.

Despite the reservations some authors (Day and Abbott, 1994; Spain, 1995) have about the extent of use of paracetamol as an antipyretic in the home, paracetamol oral liquids, and to a lesser degree, the chewable tablets, are widely used. Some manufacturers even place the word “fever” ahead of the word “pain” on their labels. As the television advertising of medicines for children is not permitted by the industry code of practice, either professional or word of mouth recommendations must be the major sources of advertising. Widely circulated journals such as the Australian Pharmacist (Shann, 1991; South, 1997) and the Australian Prescriber (Shann, 1995) have canvassed the issue of indications but there is little evidence of the public being more selective in medicating a child with fever. Berlin (1997) has even described the United States as “a fever
phobic country”, the term “fever phobia” having been coined some years earlier (Schmitt, 1980). In an attempt to rationalise approaches to the treatment of fever in children, Scmitt suggested:

* define fever as a temperature exceeding 37.8°C, orally;
* use the term “fever therapy” rather than “fever control”;
* only treat the fever if the temperature exceeds 39°C and then only if the child is uncomfortable; low grade fevers do not need drugs;
* do not wake a sleeping child to give an antipyretic;
* signs and symptoms are more important than the temperature;
* adopt a calm approach;

together with advice about when and when not to sponge.

The arguments for and against fever reduction have been summarised by Drwal-Klein and Phelps (1992) in a comprehensive review paper on antipyretic therapy in the febrile child.

If the perception that fever is always a bad thing and requires intervention with drugs could be dispelled, then demand for antipyretics would diminish. If demand and thence supply were reduced, there would be less paracetamol in the home and arguably fewer cases of accidental poisoning with or without toxic sequelae. If fewer homes had paracetamol oral liquids on hand, there would be a reduction in the number of presentations to hospitals with savings to the hospital system and a more efficient allocation of resources. But if a child needs paracetamol at night for relief of pain, ought he or she be discriminated against when most homes are likely to have an analgesic tablet on hand for adults with pain? The number of admissions, as opposed to presentations, for accidental overdose with paracetamol is small and even if demand for paracetamol liquids were diminished, any reductions in admissions from this cause is going to be small.

**Recommendation 3.1**

Professional organisations and departments of health (a) remind medical practitioners, pharmacists and health centre sisters that (i) fever as such is not harmful; (ii) paracetamol is not automatically indicated for fever; (iii) paracetamol is not indicated for sleeplessness and; (b) request practitioners to advise mothers and other carers accordingly.

**Recommendation 3.2**

The Medicines Evaluation Committee be asked to consider the appropriateness of limiting any antipyretic indications for paediatric paracetamol medicines in the Australian Register of Therapeutic Goods and in advertisements (including labels) to “reduces fever” or similar, without elaboration, except in the context of limits to the duration of treatment.
ENHANCED PARACETAMOL TOXICITY IN ALCOHOLICS

Biochemical background

About 95% of paracetamol is converted by the liver to sulphate and glucuronide conjugates which are excreted in the urine. About 5% is converted to the toxic metabolite, N-acetyl-p-benzoquinoneimine (NABQI) which is normally oxidised by glutathione. Alcohol lowers liver glutathione levels causing a decreased capacity to detoxify NABQI and also induces the microsomal enzymes P450IIE1 and P450IA2 which increase the proportion of paracetamol that is converted to NABQI. If excessive levels of NABQI are produced due to a dose-related saturation of the conjugative pathways and glutathione levels are depleted, hepatic necrosis develops over 12 hours.

The vulnerability of the alcohol consumer, especially alcoholics, to paracetamol does not necessarily occur during drinking when ethanol competes with paracetamol for its microsomal metabolism and depending on its concentration, may even inhibit it (Sato and Lieber, 1981). The problem arises when the alcohol is withdrawn, during which time microsomal inhibition persists but the alcohol no longer has an inhibitory effect. It is during this time that paracetamol is most likely to be taken because of the headache due to hangover. Doses which are normally safe thus become toxic in alcoholics. In cases of toxicity in alcoholics, levels of aspartate aminotransferase (AST) typically exceed 1000 U/L and are twice those of alanine aminotransferase (ALT), paracetamol blood levels are low or normal and prothrombin times are also elevated. Paracetamol hepatotoxicity in chronic alcoholics is differentiated from simple alcoholic hepatitis by the high serum levels of AST. Suicide patients have normal liver test results and high blood levels of paracetamol but the converse is the case in alcoholics taking paracetamol for therapeutic purposes.

Literature reports

Numerous papers (Edwards and Oliphant, 1992; Embey and Fraser, 1977; Floren et al, 1987; Goldfinger et al, 1978; Himmelstein et al, 1984; Johnson et al, 1981; Kumar and Rex, 1991; LaBrecque and Mitros, 1980; Leist et al, 1985, Lesser et al, 1986; Licht et al, 1980; McClain et al, 1980; O'Dell et al, 1986; Wooten and Lee, 1990; Zimmerman and Maddrey, 1995) have described individual cases where paracetamol in both recommended and high doses, against a background of alcohol consumption, have resulted in liver damage. There have also been a number of series, sometimes including case reports, of the paracetamol-alcohol syndrome (Denison et al, 1987; McClain et al 1988; Whitcomb and Block, 1994; Zimmerman and Maddrey, 1995). Schiødt et al (1997) examined the records of paracetamol toxicity in a Texas public hospital and found that hepatotoxicity was associated with suicidal intent or with accidental overdose. The accidental misusers had a higher rate of morbidity and mortality than those who attempted suicide even though the latter group had taken more paracetamol. The survey found a higher frequency of chronic alcohol abuse among the patients with accidental overdoses. The doses of paracetamol among the accidental group were, however, usually more (mean ± SD = 11g ± 7g; median = 12g) than the maximum recommended daily dose of 4g. The reasons for taking such large doses were for the relief of toothache, abdominal pain and headache. A recent report ( Johnston and Pelletier, 1997) has described two fatalities where the patients had taken excessive doses of alcohol and paracetamol plus other drugs such as codeine and dextropropoxyphene. The authors also compiled a table setting out the clinical profile of 53 relatively young, relatively healthy patients with unintentional
paracetamol toxicity. While some patients were alcoholics, many had no evidence of medical or social complications from their use of alcohol. Seventeen patients died but in six of these, there were concurrent, potentially life-threatening conditions. The daily quantity of paracetamol ranged from 1.3g to 20g. The mean was 7g and in 41 cases (n=50), the maximum recommended daily dose of 4g had been exceeded. In several cases, other drugs were also taken. Daily consumption figures for alcohol were not available except for the two cases reported by the authors. In line with a 1986 study by Seeff et al, the consequences were not due to a deliberate suicidal intent on the part of the patients but rather, for the relief of various painful conditions such as dental pain, or of symptoms of a cold. Johnston and Pelletier acknowledge the absence of information on the quantity of alcohol ingestion and that the mortality rate might be higher in their review due to selective reporting of those cases which had a more serious outcome. These authors noted that paracetamol was present in many prescription and non-prescription drugs and the wide use of it and of alcohol were significant in increasing the potential for the syndrome described. They submitted that prevention was the most effective way in reducing the incidence of the syndrome and recommended:

1. clear labelling of both prescription and non-prescription paracetamol products;
2. a warning about the increased potential for toxicity in the setting of alcohol use; and
3. education of patients who use alcohol and health care providers about the syndrome.

Edwards and Oliphant have also advocated the addition of a warning label to containers of paracetamol pointing out its potential for producing toxicity in chronic alcohol users. Neither groups of authors, however, suggested any precise wording of the warning nor the implications of such an initiative. In Australia, all paracetamol products must reveal the presence and quantity of paracetamol on the main label. There are also general mandatory warnings about long term use of paracetamol (and aspirin) and manufacturers have included on their labels a maximum daily dosage of eight paracetamol 500mg tablets in conformity with the Australian Guidelines for the Registration of Drugs, vol 2. There are no mandatory requirements for alcohol-specific warnings unless the analgesic is combined with one of the substances listed in Appendix K of the Standard for the Uniform Scheduling Scheduling of Drugs and Poisons (SUSDP) - typically an antihistamine - where the warning relates to enhanced sedative activity rather than deleterious effects on the liver (in the case of paracetamol) or the stomach (in the case of aspirin).

The role of fasting

Despite the substantial body of literature that cautions against the use of maximum or excessive doses of paracetamol in chronic alcoholics, doubts were cast on the view that alcohol consumption was the major concern by Whitcomb and Block in 1994. These authors reviewed 126,779 discharge summaries over six and a half years at the Pittsburgh Medical Center and extracted 49 cases of paracetamol hepatotoxicity, being determined by serum AST exceeding 1000 U/L. Twenty-one (43%) took paracetamol for therapeutic purposes and the other 28 took it as a deliberate overdose for non-therapeutic purposes. All patients exceeded the maximum recommended daily dose of 4g. Of the 21 patients who took the paracetamol for therapeutic use, there were 10 cases where the dose was ‘moderate’ being less than 10g/day. Three of the 10 were recent alcohol users and only four had any history of chronic alcohol use; eight, however, had documented fasting before the development of symptoms of paracetamol toxicity. In six of the group of 10, paracetamol had been consumed at amounts for 4 to 10g/day for a week before admission and caloric intake was markedly diminished.
In the case of eight patients who took excessive overdoses (>10g/day) of paracetamol for therapeutic use, all were recent alcohol users or chronic alcoholics and five had also fasted but were not chronic users of paracetamol.

Whitcomb and Block concluded that fasting was the more significant factor leading to symptoms of paracetamol toxicity when the drug was taken in moderate overdose (4 to 10g in 24 hours) but in excessive overdose, alcohol was the more significant factor.

Support for the contributory role of fasting to paracetamol hepatotoxicity had previously been reported by Eriksson et al. (1992) - but was not cited by Whitcomb and Block - where a 25 year-old healthy man with no history of alcohol abuse developed gastroenteritis with abdominal cramp and vomiting and diarrhoea while on holiday. To relieve the abdominal pain, he had taken a maximum of 5-6g paracetamol in repeated doses of 0.5-1g, two or three times a day before flying home. Gastroenteritis, due to campylobacter, with dehydration was thought to have contributed to the toxic effect. The patient was discharged 10 days after admission.

*Analgesic Guidelines* (Victorian Drug Usage Advisory Committee, 1997), at page 49 also notes that fasting, which results in reduced hepatic glutathione, may be an even more important factor in causing toxicity than a high alcohol intake or the use of enzyme-inducing drugs.

Zimmerman and Maddrey in 1995 recognised the role of fasting but supported the increasingly accepted view that regular users or alcohol, especially chronic alcoholics, who take paracetamol for therapeutic reasons are at risk of hepatic injury. Even in doses in the “non-toxic” range (<6g/d), 60% of the 67 predominantly alcoholic patients in their series showed signs of hepatic injury. The authors referred to “the towering levels” of AST usually accompanied by a lower level of ALT as providing a virtual pathognomic marker. They recommended that people who consume more than 60g of alcohol daily (about six standard drinks) should not take more than 2g of paracetamol daily and called for a greater awareness of the phenomenon by the medical and lay communities. A similar view was expressed by Schiødt et al (1997) but neither went as far as recommending a warning on containers.

**A controversial editorial**

The Whitcomb and Block paper is referred to in some detail because it was the subject of a controversial editorial in the *Journal of the American Medical Association* (Strom, 1994). The editorial pointed out that given the rarity of paracetamol hepatotoxicity when the drug is used in recommended doses, the data do not necessarily indicate that alcohol abusers or fasting patients should avoid using paracetamol in favour of other non-prescription analgesics such as salicylates or other NSAIDs. The editorial went on to say “... if patients (especially alcoholics) were to switch from using acetaminophen [paracetamol] to using salicylates or other NSAIDs, the number or (of) cases or (of) acetaminophen-induced hepatotoxicity that would be prevented would be dwarfed by the number of excess deaths from gastrointestinal bleeding”. The editorial concluded by referring to FDA-initiated alcohol warnings on all non-prescription analgesics that were formerly prescription-only and that some companies had implemented such a policy already. Strom’s editorial was sharply criticised by Lee (1995) under the evocative heading, “The selling of acetaminophen” as an apologia for the drug and Whitcomb (1995) himself criticised the editorial because it sidestepped the pathophysiological issue of enhanced toxicity raised by his and Block’s paper and it emphasised the absence of patients taking <4g daily. In a subsequent review (Trinkhaus et al, 1997) of the public health issues in relation to Tylenol in the United States, the manufacturer was implicitly criticised for not mentioning in a letter to physicians (about paracetamol/alcohol) that the writer of
the editorial in *JAMA* had received grants and consulting fees from McNeil although a footnote to the *JAMA* editorial had mentioned these connections.

**Recent action in the United States**

In 1993, the FDA’s Arthritis and Nonprescription Drugs Advisory Committee began to study the combination of analgesics with alcohol and recommended a warning statement but the FDA decided not to act until more data were obtained. The FDA did, however, impose an alcohol warning label on those analgesics which had been “switched” from prescription to non-prescription status. This became effective in 1995.

The FDA announced on 14 November 1997 in *HHS News* that it intended to require a warning label on all non-prescription pain relievers that include aspirin and other salicylates, paracetamol, ibuprofen, ketoprofen and naproxen sodium. For paracetamol-containing products, the warning statement would state:

> Alcohol warning: If you drink three or more alcoholic beverages daily, you should ask your doctor whether you should take [product name] or other pain relievers. [Product name] may increase your risk of liver damage.

The warning for aspirin and the NSAIDs is similarly worded except that “stomach bleeding” replaces “liver damage”. Combinations of paracetamol with aspirin or a NSAID must refer to both liver damage and stomach bleeding. In Australia, such combinations are not used and in any case, would be Schedule 4 poisons.

The FDA has requested manufacturers of analgesics to include an alcohol warning while formal requirements were being drafted. One large company, Johnson & Johnson, has already placed a warning statement on its paracetamol products and has demanded that its competitors follow suit. Johnson & Johnson’s subsidiary, McNeil has questioned the purpose of the FDA in its intention to carry out a survey of consumers as several advisory committees have already made the recommendation to add the label. Another company, Whitehall-Robins, has objected to the inclusion of the statement on its ibuprofen products. A 90 day comment period (ending in February 1998) is available during which time the public may respond to the FDA’s proposal.

The quantity of alcohol mentioned in the proposed warning is half the amount noted in the Zimmerman and Maddrey paper but whereas these authors set an upper limit of 2g daily of paracetamol for alcoholics, the FDA has left the dose open to the maximum previously approved, being 4g subject to medical advice.
In considering the position in the United States, it is essential to recognise that litigation, or the threat of it, often forces the inclusion of warnings on medicines. The present response is a case in point. In 1994, a former White House aide to President George Bush sued McNeil Consumer Products alleging negligent failure to warn of the possible dangers of mixing Tylenol with alcohol and for breach of implied warranties. The plaintiff, Antonio Benedi was accustomed to drinking three or four glasses of wine on each weekday and more at weekends. He had been taking paracetamol 500mg (Tylenol Extra-Strength) in the recommended doses for five days for the flu. He developed hepatic and renal failure and required a liver transplant which was successful. The jury found for Benedi. An appeal by McNeil was dismissed, the court finding that the company had acted with “reckless indifference to the health of its consumers”. Benedi wrote an open letter to the New York Times warning about the hazards of Tylenol when combined with alcohol. The cost of the open letter was borne, however, by a subsidiary of American Home Products which manufactures Advil, a brand of ibuprofen. Because of the invective that had developed in what had become a trade war, television networks refused to run competing advertisements (Slattery et al, 1996). In light of the Benedi case, it has been suggested by some medico-legal commentators that consumers have a need to know and should be afforded a suitable level of protection (Trinkhaus et al, 1997). With this background, it is not surprising that McNeil has demanded (FDC Reports, 1997) that its competitors voluntarily and immediately place the alcohol warning on their labels because its absence may be seen as a marketing advantage to them when compared with McNeil’s products.

It is important to note that not only is litigation a more potent force in the United States than in Australia but that the former country, unlike most other others, does not have a graded system of controls on availability of drugs nor does it have a product by product evaluation scheme (Aldred, 1988).

### Australia - is an alcohol warning label on analgesics needed?

Paracetamol-induced liver damage in the presence of alcohol drinking has not been reported to any great extent in Australia and when it has been mentioned (Brotodihardjo et al, 1992), it has been incidental to surveys of admissions to hospitals arising from frank paracetamol overdose. The group most at risk are alcoholics who have an acute or chronic painful condition which has not responded to the recommended doses of paracetamol and in an effort to relieve the pain, patients have taken larger doses.

Paracetamol is used in hospitals and detoxification clinics to relieve severe bone ache and headache experienced as part of the opioid withdrawal syndrome. Very often, the patient has a mixed dependency - alcohol and opioids - yet paracetamol remains the preferred option in these cases because there is nothing better, given that aspirin and the NSAIDs could exacerbate an already inflamed gastric mucosa with the possibility of haemorrhage.

Advice from a professorial clinician who specialises in substance dependence indicates that there is a lack of awareness among general practitioners of the increased risk alcoholics face if they consume larger or excessive doses of paracetamol. It was felt that, at least in the first instance, the medical and pharmacy professions should be made aware of the potential problem.

Should any Australian warning be contemplated, it would have to be carefully composed in order to discourage the deliberate co-consumption of paracetamol and alcohol in cases of attempted suicide and parasuicide. The FDA wording appears to have avoided giving any signal that combining paracetamol with alcohol might be an encouragement to suicide but it remains to be seen how the message will be interpreted by the public. At the same time, the consumption of several
recommended doses of paracetamol after over-indulgence in alcohol on an occasional basis should not contraindicate the drug to relieve a headache due to a hangover; paracetamol is preferred over aspirin and NSAIDs in this circumstance as pointed out in the *JAMA* editorial. Any statement would also have to take into account the recommendations of the National Health and Medical Research Council’s recommendations about safe levels of consumption of alcohol for men and women.

The FDA warning advises drinker consumers to consult their doctors if they should take any paracetamol at all. The logistical and resource implications of this proposal must be taken into account especially in a country such as Australia where the bulk of the cost of a medical consultation is borne by the government. If the warning is considered or perceived as an over-reaction, it is likely to fall into disrepute. It is also possible that, as well as medical practitioners, poisons information centres, pharmacists and manufacturers will receive many enquiries especially if the warning label is mentioned in the media.

There may be a case for a warning that makes reference to alcohol because of (i) the lack of recognition of the problem in both professional circles and the community generally, (ii) the unrestricted availability of paracetamol tablets and capsules in packs of up to 25; and (iii) the perception that unscheduled drugs are so safe that they can be treated with little respect. That the FDA has decided to take action must be accorded due weight given its prominence in drug regulation. Australian decisions such as *Rogers v. Whitaker* (1992) 67 ALJR 47 where the expression “material risk” was used and interpreted by the High Court, are also considerations. In light of these, the Review is tempted to recommend the inclusion of a warning label, especially as so many activities and practices are now globally spread. Australian owned companies, on their own initiative or those Australian companies having American principals, may choose to include an alcohol warning label as a perceived potential safeguard against litigation or at least minimising its consequences. Any such decision, however, must be based on good evidence, not encourage the very action it is aimed at preventing and relate to Australian conditions.

Also to be taken into account, if indeed an alcohol warning label is needed, is to avoid suggesting that people who use paracetamol long term, such as those with osteoarthritic pain, are alcoholics. This may sound odd but in practice, such an association is possible in the minds of some people. For example, patients receiving vitamin B$_{12}$ injections were distressed to see on the package insert that the vitamin was used for AIDS and were worried that they might have the disease.

On balance, there are insufficient Australian data to support the need for this warning label at this time. The Australian drug regulatory scheme has certain safeguards that are not present in the USA, and other countries do not seem to have followed the American example. In the United Kingdom, no definite association between chronic alcohol intake and toxic effects of paracetamol has been recognised. In a group of 560 patients admitted to the liver failure unit of King’s College Hospital for paracetamol-associated liver disease, Makin et al (1995) found no evidence that excess alcohol consumption alone was a high risk factor. Not only was there no difference in the clinical outcome of heavy drinkers and non-drinkers after paracetamol overdose but there was also no significant difference in the size of the overdose. However, a significant higher mortality rate was found in a small group of nine chronic alcoholics that had taken a significantly larger overdose of paracetamol than the non-drinking group. The apparent association of severe hepatotoxicity and excess alcohol consumption is largely a reflection of the population that is most likely to take an overdose. Young, single people are likely to drink more than older married people and the incidence of relationship problems is much higher in heavy drinkers. In turn, heavy drinkers are between twenty and sixty times more likely to attempt suicide than the non-drinking population. Ten years previously, Prescott (1986) concluded that although a few individuals have a real increase in
susceptibility to paracetamol, the majority of cases of hepatotoxicity that occur in heavy drinkers are the result of a large overdose.

**Recommendation 4.1**

The editor of the *Australian Prescriber* be requested to arrange for, and publish, a review article about enhanced toxicity of paracetamol when it is taken by moderate to heavy habitual alcohol drinkers.

**Recommendation 4.2**

In the course of their detailing to medical practitioners and pharmacists, sponsors’ representatives mention that paracetamol dosages and the duration of treatment with it may need modification if the patient is a moderate to heavy habitual alcohol drinker.

**Recommendation 4.3**

The TGA monitor the outcome of the American labelling initiative concerning analgesics and alcohol drinking.

**Recommendation 4.4**

No warnings on the label of paracetamol, aspirin and the NSAIDs in relation to alcohol consumption should be required at present.
PARACETAMOL IN SELF-POISONING

Suicide and parasuicide

In recent years, considerable attention has been directed to the use of paracetamol as an agent in self-poisoning. At this point, it is worthwhile mentioning that, in the legal sense, suicide is the taking of one’s own life with that intention. The authorities require unequivocal evidence of such intent before classifying a death as suicidal. Many psychiatrists believe that such a definition is too restrictive and that a decision should be made on the balance of probabilities. The Australian Bureau of Statistics (ABS) states that, as the number of deaths that coroners have been unable to determine as being accidental or suicide has increased from 1982 to 1992, it is possible that the number of suicides reported for that period is understated.

Parasuicide is a term referring to any act deliberately undertaken by a person who mimics the act of suicide, but which does not result in a fatal outcome. It is a self-initiated and deliberate act in which the person injures himself or takes a substance in excess of the therapeutic dose or the habitual level of consumption, and which he believes to be pharmacologically active. It therefore encompasses both failed suicides (“attempted suicide”) and gestures, often impulsive, in which the person does not really intend to end his life. It is predominantly encountered among people between 15 to 25 years. At all ages, women have higher rates than men but this lessens after 50 years of age. There is a high repetition rate.

Suicide and parasuicide have been extensively studied. Based on UK data, the following comparisons are made: parasuicide is commoner among females, especially those under 45 years; it occurs more often in lower classes; there is no association with physical illness; and psychopathy is common (Kreitman, 1994). Self-poisoning is the commonest form of parasuicide, the usual agents being the analgesics and the psychotropic drugs

Paracetamol figures prominently in cases of self-poisoning in both adults and adolescents. Finding definitive Australian data on the subject and establishing causal relationships is difficult. These difficulties were summed up by Buchanan et al (1986) who wrote, “Statistics on overdose and other forms of suicide are notoriously difficult to interpret. They depend so much on such matters as hospital admission policy and definitions that simple comparisons across nations or even among hospitals within the same country need to be undertaken with great caution”. This Review fully concurs with this statement.

The following affords an example of the difficulties and how certain figures at face value may give the wrong impression of the true state of affairs. In England and Wales in 1990, paracetamol was mentioned in 547 deaths in coroners’ returns where the drug was taken either alone, co-formulated with other drugs or with other medicines. An analysis of their data revealed, however, that paracetamol was the probable cause of death in 150 of the 547 cases, 115 being definite and 35 probable (Spooner and Harvey, 1993). The same authors (who are employed by the industry supported Paracetamol Advisory Group) analysed the data from 1975 and showed that paracetamol deaths ie. cases with definite or provable hepatic necrosis, accounted for between 12% and 30% of the total number where the drug had been mentioned in the official figures. Although such a rigorous analysis makes an important contribution to the discussion, the fact remains that in England and Wales, the number of deaths where paracetamol was the likely cause has increased
over the period 1975 to 1990 and the proportion has increased since 1984. The virtual disappearance of the barbiturates may account, in part, for the increased proportion of paracetamol and for that matter, other drugs in the figures.

Reliance on the ICD-9-CM (Official Australian Version) presents problems because a significant number of separations from one State was not included for 1993-94 and in another, data were not available from public psychiatric hospitals. Codes are not always substance-specific but fortuitously, code 965.4 (Aromatic analgesics, not elsewhere classified, Acetanilide, Paracetamol and Phenacetin) effectively relates to paracetamol only because the other substances captured by the code - acetanilide and phenacetin - are not included in pharmaceuticals in Australia. It is worth mentioning at this point, that while aggregated Australia-wide data are reasonably available from the Australian Institute of Health and Welfare, it is necessary to apply to each State/Territory health authority to obtain the admission numbers for each of them. Data obtained from the Institute (personal communication, 1998) showed that for the period July 1993 to June 1996, there was an average of 2055 separations each year for self-inflicted injury with paracetamol. The table below contains data extracted from Appendix 2 to this Review. Code 965.4 was linked to external code E950.0 - suicide attempts with analgesics, antipyretics and antirheumatics - and includes injuries in suicide and attempted suicide and self-inflicted injuries specified as intentional.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Female 10-19</td>
<td>318</td>
<td>321</td>
<td>223</td>
<td>175</td>
<td>335</td>
<td>340</td>
</tr>
<tr>
<td>Male 10-19</td>
<td>143</td>
<td>77</td>
<td>44</td>
<td>41</td>
<td>79</td>
<td>73</td>
</tr>
<tr>
<td>Female 20-30</td>
<td>212</td>
<td>228</td>
<td>175</td>
<td>173</td>
<td>297</td>
<td>278</td>
</tr>
<tr>
<td>Male 20-30</td>
<td>114</td>
<td>105</td>
<td>79</td>
<td>75</td>
<td>136</td>
<td>119</td>
</tr>
<tr>
<td>Female &gt;30</td>
<td>354</td>
<td>205</td>
<td>155</td>
<td>188</td>
<td>311</td>
<td>322</td>
</tr>
<tr>
<td>Male &gt;30</td>
<td>96</td>
<td>108</td>
<td>79</td>
<td>82</td>
<td>141</td>
<td>161</td>
</tr>
<tr>
<td>TOTALS</td>
<td>1029</td>
<td>1044</td>
<td>755</td>
<td>745</td>
<td>1301</td>
<td>1293</td>
</tr>
</tbody>
</table>

Table. Separations for the sex/age groups for cases of intentional self-poisoning by paracetamol in half-yearly intervals from the second half of 1993 to the first half of 1996. (Source: Australian Institute of Health and Welfare)

Hunter Area Toxicology Service figures, extrapolated to the whole of Australia (Whyte, personal communication, 1998) suggest, however, a figure of about 8200 for self-poisoning. The differences are explained by the Hunter’s decision to regard all self-poisoning cases as admissions whereas the Institute’s figures would not necessarily include all presentations.
Because of the difficulties mentioned by Buchanan et al, the following extracts are quoted from the Australian literature:

- In 1975 and 1976, only two patients were admitted to St Vincent’s Hospital, Melbourne after overdosing on paracetamol. From January 1977 to March 1981, 103 patients were so admitted (Breen et al, 1982).

- Of 747 cases of self-poisoning in the Newcastle NSW area from 1980 to 1982, paracetamol was taken in 7.9% of cases (Hardwicke et al, 1986).

- Paracetamol was present either alone or with other drugs in 21 out of 158 (13%) of cases of self-poisoning in a two week period at St Vincent’s Hospital, Sydney (Ray et al, 1986).

- From 1985 to 1990 in western Sydney, there were about 55 cases each year on average of hepatotoxicity from self-poisoning with paracetamol. Severe liver injury occurred in 6.9% of cases and there was a 1% frequency of fulminant hepatic failure. No deaths were noted (Brotodihardjo et al, 1992).

- Among Tasmanian children and adolescents, paracetamol alone or in combination accounted for 51% of ingestions with medications being implicated in 71% of all cases of self-harm. Medicines are more frequently resorted to in females than in males and often involve analgesics, hypnotics and psychotropic drugs. The consumption is often impulsive (Tulloch et al, 1994).

- From 1987 to 1993, there were 391 admissions in the Hunter region of New South Wales due to self-poisoning with paracetamol (including combinations other than with dextropropoxyphene). This figure represented 12.9% of self-poisoning (excluding alcohol). There were no deaths primarily or secondarily caused by it (Buckley et al, 1995).

- From 1993 to 1997, paracetamol self-poisoning accounted for an average 0.06% of all admissions to the Royal Children’s Hospital, Melbourne. An increasing frequency was noted (this Review, 1998).

- The Australian Institute of Health and Welfare data compiled from data obtained from each State and Territory health authority showed that the number of separations from hospitals due to paracetamol had declined from financial years 1993-94 (1494 females, 579 males) to 1994-95 (1099 females, 401 males) only to rise for 1995-96 (1934 females, 710 males) above the 1993-4 levels for both sexes.

At best, only broad conclusions can be drawn from these papers. Paracetamol is being used more often in cases of self-poisoning by drugs than previously. Despite this, the clinical outcomes are usually good because of the availability of, and early intervention with, NAC. Adolescent girls represent a particular predisposition to using paracetamol as shown by the Tasmanian study and the evidence obtained in the course of this Review. Self-poisoners with paracetamol accounted for 80 admissions to the Royal Children’s Hospital from 1993 to 1997 and girls outnumbered boys by about five to one. The Victorian Task Force Report on Suicide Prevention specifically identified “over the counter” paracetamol tablets, as well as prescription drugs, as the means most often used by females to overdose and recommended restriction of supply of paracetamol to pharmacists and the recording of the purchaser’s name and address. The Task Force also recommended that
methionine should be added to all paracetamol formulations. No figures were present in the report to show the number of cases of suicide attributable to paracetamol.

**Addition of methionine to paracetamol**

Some authors (Krenzelok, 1997; Spender, 1997; Hobson, 1997) and reports (Routley et al, 1996; Australian Institute of Suicide Research and Prevention, 1997) have proposed the inclusion of methionine in paracetamol medicines. The (UK) Consumers Association publication *Which?* held a similar view (Anon, 1994) but the director of the Scottish Poisons Information Bureau was reported as saying in *The Scotsman* on 7 April 1994 that *Which?* was scaremongering. Hobson (1997) has argued that the efficacy of paracetamol would not be affected by the addition of methionine, would not cost much and would be more effective than warning labels and restrictions on availability. The basis for proposing the addition of methionine, which dates from 1974 (McLean) is that it probably acts by promoting the synthesis of glutathione which detoxifies NABQI. To be an effective public health measure, methionine would have to be added to all paracetamol products. There are no firm data available, however, to show that paracetamol-induced liver damage would be prevented (Jones et al, 1997). Further, the propriety of medicating every person who takes paracetamol for a legitimate purpose raises a serious issue of principle especially as methionine, at higher than normal dietary levels produces cellular changes to the kidneys, liver and spleen. The cost of paracetamol/methionine tablets would be considerably greater; in oral liquids, the smell and taste of methionine would be unacceptable and difficult to mask. Even if methionine were co-formulated with paracetamol, overdoses are still likely and the presence of methionine may add complications to present treatment protocols (Brandon, 1994). Hobson (1997) dismisses Brandon’s argument that methionine may cause damage at low antidotal doses and the minor side effects of taste and smell would be beneficial in the overdose; she also points out that Brandon is employed by the industry-sponsored paracetamol information agency. Krenzelok (1997) only partially supports the addition of methionine to paracetamol. His view is that the combination might have a place in developing countries where there are insufficient financial resources to justify the expense of NAC treatment.

**Recommendation 5.1**

That paracetamol preparations should not be compulsorily co-formulated with methionine.

**Position in the United States of America**

Different methods of data collection make difficult comparisons with Australia. In 1995, there were 42,712 intentional exposures to paracetamol preparations with 63 deaths (Litovitz et al, 1996). This figure is much closer to Australian than British estimates.
Costs of admissions and days off sick that are related to paracetamol have been estimated at $US86.9 million per year (Bond and Novak, 1995 per Jones et al, 1997). Home treatment with NAC post-discharge was been proposed as means of reducing hospital costs (Dean et al, 1996).

**Position in Denmark**

In 1984, paracetamol became available to the public without prescription but from pharmacies only. In Denmark, detailed figures are available on sales of medicines. After paracetamol became available without a prescription, sales doubled but they had been rising before that. In fact, the number of daily defined doses (3g) increased from 1 million in 1976 to 47 million in 1986. The number of hospital admissions as a result of paracetamol overdose increased from 26 to 202 and the number of deaths from one to three or four. The increase in sales was accompanied by a relative decrease in the number of hospital admissions and deaths from paracetamol overdose. Ott et al (1990) remarked on the difference in Denmark when compared with the experience in the UK. The authors attributed the low death rate to the absence of dextropropoxyphene-paracetamol combinations in Denmark.

**Position in Hong Kong**

Hospital admissions to the Prince of Wales Hospital due to paracetamol poisoning increased slightly from 1991 to 1994. The rates of admission with toxic plasma levels were higher in 1994 than in 1991 (10.8 compared with 0.6/100,000) but the annual incidence of paracetamol-induced liver damage remained unchanged at 0.3/100,000. There were no cases of fulminant liver damage and no deaths (Chan, 1996).

**Position in the United Kingdom**

Paracetamol is the most frequently used substance for deliberate self-poisoning in the UK with overdoses in adolescents being especially common. Paracetamol-induced liver damage accounts for over half of all cases referred to liver units because of fulminant liver failure and is the cause of at least 150 deaths per year in the UK. In the north of England, paracetamol was involved in 43% of presentations for both deliberate self-poisoning and accidental poisoning in a 12 week prospective survey (Thomas et al, 1996); in the Lothian and Border regions of Scotland, non-narcotic analgesics were involved in about 30% of 352 cases from 1983 to 1991. There were 15 males and 23 females and there was little fluctuation in frequency (0-5 deaths/year) over the years among both sexes (Obafunwa and Busuttil, 1994); another Scottish study (McCloone and Crombie, 1996) showed that from 1981-1983 to 1991-1993, there were increases of 54.6% and 65.8% in males and females, respectively, in paracetamol self-poisoning. Hypnotics and sedatives had declined markedly in the same period; in South Glamorgan, Wales, paracetamol was the most commonly ingested poison in details from admission data accounting for 43.4% of cases in 1992-1993 compared with 31.3% in 1987-1988. As noted by other authors, repetition of self-poisoning was common. Despite the increase in admissions, the mortality declined from 0.5% to 0.1% over the two years that were studied.

Not only are there questions about morbidity and mortality, the issue of cost has been raised. There are an estimated 70,000 overdoses each year in the UK, most of which show no sign of important liver or kidney damage (Fagan and Wannan, 1996). The Department of Health puts the hospital visits figure at 30,000 to 40,000. The cost to the National Health Service of treating patients with severe liver damage is £6-8 million per year and the cost of maintaining a liver transplant recipient is between £3000 and £5000 a year. Moreover, the dose-dependent nature of
paracetamol poisoning suggests that many parasuicides could be prevented, intensive care resources would be freed up and more organs could be made available for elective transplant (O’Grady, 1997).

An estimated 30 million packs of paracetamol are sold annually in the UK.

Why paracetamol? This question was asked (McCloone and Crombie, 1996) because the self-poisoning figures on aspirin, which is equally available, have not changed. These authors were not attracted to reducing pack sizes because of inconvenience to those people who make regular but safe use of paracetamol. No definitive answer to this question has been found but ready availability is frequently mentioned in the literature. The perception that paracetamol is a sedative may be a contributing factor as drugs with a demonstrated sedative effect on the central nervous system, such as the barbiturates and the tricyclic antidepressants, have been used in parasuicides and suicides.

Responses to the problem in the UK

Many authors have advocated various ways of reducing morbidity and mortality. Public education and in some cases, school education in particular, about the dangers of paracetamol in overdose have their advocates (Fagan and Wannan, 1996; Gilbertson et al. 1996; O’Grady, 1997). Not all share this view. A senior registrar in psychiatry (Taylor, 1997) argued that providing such education was an advertisement for an accessible suicide method. Taylor, citing Hawton et al (1995, 1996) observed that knowledge that paracetamol overdose can kill did not stop 77% of such overdoses in Oxford. He emphasised the potential benefits of placing hurdles in the way of obtaining large amounts of paracetamol because any hurdle may give time for reflection and change of mind especially as many paracetamol overdose are taken on impulse. This commentary was criticised by the original authors (Wannan and Fagan, 1997) on the grounds that Taylor’s views were not researched based. Their theme was “respect for autonomy includes making public all options”. Further criticism was advanced by Pounder and McAllister (1997) who drew attention to the inaccuracy of mortality statistics. In particular, the co-formulation of paracetamol with dextropropoxyphene (co-proxamol) was cited as a confounding factor in official figures. Despite the large number of paracetamol overdoses, few deaths result from paracetamol and these authors said that restricting its sales may reduce morbidity but it also carries the risk of precipitating a shift to the use of other, more toxic, drugs with a resultant increase in overall mortality. A different form of objection to increasing restrictions on paracetamol centred on the effect on general medical practice and the destruction of public confidence in a safe drug for pain and fevers (O’Connell, 1997).

The most detailed paper on the means of harm reduction resulting from paracetamol self-poisoning (Hawton et al, 1996) isolated the factors which might have deterred patients from taking paracetamol overdoses. The subjects in the study were 80 consecutive self-poisoning patients who were admitted to a hospital in Oxford from September 1992 to March 1993. After analysing their data, the authors concluded that limiting the number of tablets available in all over-the-counter preparations to 25 or fewer tablets is the most pragmatic initial approach to the problem. Warning labels, blister-packs and source of purchase were not considered sufficient. The blunt warning statement, “An overdose of paracetamol can kill” was considered as a deterrent to only a minority and carried the risk that the drug might become more attractive to those intent on suicide. Fagan and Wannan (1996) were unconvinced that any form of warnings on labels and packets would act as a deterrent to overdose especially among those who seek manipulative gain by their actions.
The most common theme in the British literature to reduce morbidity and mortality has been legislative action to reduce availability by restricting package size. Blister packing was also seen as of assistance because the time needed to punch tablets out of a blister pack would allow the implications of the act to register with those whose action is impulsive.

Legislative action

Pack sizes

In an effort to reduce the number of deaths and hospital admissions in the UK due to paracetamol overdose, pack sizes of up to 16 tablets will be the maximum available at general retail outlets and 32 at pharmacies although in “justifiable circumstances”, 100 tablets may be supplied without a prescription. Up to 100mL of oral liquids containing 2.4% of paracetamol (120mg/5mL) will also be available as a general sale item for children under 12 years of age (Anon (b),(c), 1997). Single ingredient and combination products are equally affected. As Hawton et al (1996) state: “It should become apparent relatively soon whether or not a reduction in the number of tablets per container would have the desired effect in terms of reduced morbidity and mortality from paracetamol self-poisoning”. How the authorities intend to force supermarkets and their checkout operators to prohibit the sale of multiple small packs has not been fully addressed. Nor does there seem to be any means of preventing retailers from strapping together two or more packets of those that are available as general sale items (Thomas, 1993; Coleman, 1997).

A similar restriction was introduced in France in the early 1980s when the quantity of paracetamol was limited as a single sale to 8g. According to one report (Garnier and Bismuth, 1993), this measure was regarded as being successful because fatal cases are rare (<10 per year) even though the incidence of paracetamol poisoning is high. In support of the view that reducing pack size reduces morbidity and mortality, a study was carried out comparing the situation in England and Wales with that in France (Gunnell et al, 1997). Trends in sales correlated with trends in non-fatal overdoses in both countries for 1976 -1993 and 1974 - 1990, respectively. Sales figures were likewise correlated with suicides in both countries. Fatality rates were four times as high in England and Wales as in France. The authors concluded that trends towards greater availability of paracetamol are paralleled by increases in its use for both non-fatal overdose and suicide. As noted above, the limited quantity available in France as a single purchase supports, but is not conclusive evidence for, placing tighter restricitions on the sale of paracetamol in the UK. These and other data have clearly influenced recent UK policies.
Labelling

Labels will be required to include the statements,

“Immediate medical advice should be sought in the event of an overdose, even if you feel well”; and

“Do not take with any other paracetamol-containing product”.

Product information leaflets (package inserts) will be required to state:

“Immediate medical advice should be sought in the event of an overdose, even if you feel well, because of the risk of delayed, serious liver damage”.

This sentence will be required on packs that do not contain a leaflet.

The new UK warning labels in relation to overdose are similar to those used on American packs of paracetamol (see Appendix 3).

It is difficult to predict the likely outcomes of the UK initiatives especially as changes have been made to more than one variable. Increased publicity is also a factor in its own right either as encouraging more overdoses or advancing the message that the authorities wish to convey. Doubts have been cast on the adverse influence of the media in television portrayals of paracetamol self-poisoning even following an increase in paracetamol overdoses after the first broadcast of drama series set in a hospital (Simkin et al, 1995).

Given the major restrictions found necessary in the UK and that paracetamol self-poisoning appears to be rising in Australia, close attention should directed to the outcomes of the UK initiatives.

### Recommendation 5.2

The TGA monitor the UK data on morbidity and mortality following paracetamol poisoning after all of the UK legislative initiatives have been in operation for one year.

### Position in Australia

Suicide is now the leading cause of death due to injury in Australia, ahead of motor vehicle accidents and homicide. The Victorian Suicide Prevention Task Force’s report, *Suicide Prevention*, July 1997 points out that the suicide rate had increased since 1964 and drug overdosage accounts for just over 15%. The report, at page 74, stated that the ease of access to prescription drugs and over-the-counter paracetamol tablets was the means most often used by females to overdose. For paracetamol, the report noted: “The difficulty of reducing access to paracetamol tablets is one the Task Force believes is not insurmountable and recommended the creation of a small expert working party to investigate, *inter alia*, whether the drug should be obtainable only from pharmacies at which the name and address of the purchaser would be recorded should be considered and the inclusion of methionine in paracetamol preparations (recommendation 5.28).
The Report did not, however, state the number of cases of death due to paracetamol poisoning. In its response to the Task Force’s report, the Victorian Government (at page 5) said that there were significant public health issues associated with recommendation 5.28 and that it would refer the matter to the National Drugs and Poisons Scheduling Committee for consideration.

Comprehensive data that incorporate outcomes of paracetamol poisoning do not seem to be available in this country. Separations (discharges, deaths and transfers) are available but these do not yield information about morbidity or mortality. It is possible, however, to take data from the Hunter Area Toxicology Service in New South Wales and apply them to Australia as a whole.

In the Hunter area (pop. about 400,000), over the period 1987 to 1996, paracetamol initially accounted for about 12% of all admissions for self-poisonings rising to about 26% in 1996 (Whyte, 1998) with the second five-year period being stable at 20-25%. There were 966 admissions for deliberate self-poisonings with all paracetamol products out of a total of 4670 admissions. Drug use in the Hunter area has been shown to represent Australia as a whole (Buckley et al, 1995) and by extrapolation, Whyte et al (1998) estimate that there would be 8200 paracetamol poisonings in Australia in 1996. Two deaths were from poisonings involving paracetamol were entered on the Hunter database over the 10-year period from January 1987 to December 1996. Neither patient received a liver transplant. At this rate, there would an expected nine deaths yearly in Australia due to self-poisoning with paracetamol.

**Comparison between Australia and England and Wales**

As previously mentioned, paracetamol accounts for about 150 deaths per year in England and Wales (population 53,000,000) as adjusted by the Spooner and Harvey analysis of coroners’ figures. As the population of England and Wales is three times that of Australia’s, then using the England and Wales figure of 150 deaths as a reference point, 50 deaths would be expected each year in this country. If the extrapolation from the Hunter figures to the whole of Australia is correct in estimating nine deaths per year, the death rate in Australia due to paracetamol is one-sixth to one-fifth that in England and Wales. The epidemiological picture between the countries is therefore very different.

The comparison between England and Wales and France (Gunnell et al, 1997) suggested, although inconclusively, that the smaller general sale pack sizes of 16 tablets in France compared with 25 in the UK may reduce suicide and liver failure. When the data and the conclusions drawn in relation to both the UK and France are compared with Australia, where the unscheduled pack size is 25, other factors must be considered. The use of bottles of “loose” paracetamol tablets, even though fitted with child-resistant closures seem to be more popular in the UK than in Australia where strip or blister packaging is the norm, despite legislative provisions that allow either to be used. This Review has elsewhere recommended (Recommendations 6.10 and 6.11) that strip packs be the only form of packaging allowed in Australia for paracetamol as the single active agent and when combined with codeine or dihydrocodeine, except where provided for in prescribed circumstances.
Another difference between Australian and UK practice is that poisons information centres are accessible to, and are used by, the Australian public whereas in the UK, the centres cater only for professional enquiries. For example, about 70% of calls received by the New South Wales centre in 1996 were from family members, carers, the actual consumer of the substance or from friends.

Liver transplants

The Australian Liver Transplant Registry recorded all liver transplants in Australia from January 1985 to December 1995. There were 947 transplants, of which two (0.2%) were related to acute hepatic failure involving paracetamol. Since 1988, Gow et al (1997) at the Austin Repatriation Medical Centre in Melbourne have treated 14 patients with paracetamol-induced fulminant hepatic failure, 13 of whom were managed conservatively. These authors have criticised the criteria for liver transplants at King’s College Hospital, London because it is as important not to transplant in patients who will recover as it is to transplant when it is really needed. By contrast, the number of liver transplants in the UK for 1995/96 alone was 1340, 52 of which (3.8%) were attributed to paracetamol toxicity (O’Grady et al, 1991). These differences between Australian and UK data further illustrate that circumstances in one country cannot always be translated to another.

Should there be an overdose warning label on paracetamol in Australia?

That two major countries have decided to place warnings on paracetamol products in connection with overdose cannot be ignored. The events or circumstances leading up to the need to include these warnings are different in both the USA and the UK and each differs from Australia. At present, Australian data do not support the need for specific overdose warnings and it is important that any such warnings do not encourage the actions they are designed to help prevent. Elsewhere, this Review has proposed an updated version of the general warning prescribed for paracetamol in the SUSDP. The maximum number of tablets or capsules to be taken daily is shown on the labels and there is a graded system of controls on availability. Strip packages are preferred in this country.

The major concern in Australia is the increasing number of self-poisonings by teenagers, especially with paracetamol and if this trend continues along with increasing morbidity and mortality, the need to have a UK/USA label could be considered, although the value of warning labels on their own has been queried (Hawton et al, 1996; Fagan and Wannan, 1996; Hancock et al, 1992).

This Review has made recommendations elsewhere for an updated warning label for paracetamol and the discontinuation of “loose” bottles as containers for paracetamol.
LABELLING AND OTHER CONTROLS ON NON-PRESCRIPTION ANALGESICS

For the purposes of the Review, the expression “non-prescription analgesic” refers to aspirin, paracetamol and the NSAIDs - ibuprofen, mefenamic acid and naproxen. It is possible that other NSAIDs may be made available without prescription in future.

State and Territory controls

General

Poisons scheduling

State law on control of medicines predated the Commonwealth’s entry into the field. The States’ main influence flows from the poisons classification system popularly known as “scheduling” (which determines distribution) and in concert with Commonwealth laws also affects labelling, packaging, advertising and the licensing of manufacturers.

Complementary therapeutic goods laws

State laws designed to complement specifically the Therapeutic Goods Act 1989 (Cth) are in operation in Victoria (the Therapeutic Goods (Victoria) Act 1994) and in New South Wales (the Poisons and Therapeutic Goods Act 1966). These two Acts, by different means, effectively apply the Commonwealth Act to sponsors and manufacturers of therapeutic goods, the activities of whom are not captured by the Commonwealth Act for Constitutional reasons. The State Acts also provide for further controls along the distribution chain, especially at the retail level or in circumstances corresponding to supply by retail, such as vending machines.

Analgesics specifically

Analgesics are regulated by means of poisons acts and regulations (by whatever title) in terms of their manufacture, distribution, packaging and labelling. Manufacturers of analgesics and preparations of them must hold a licence. A licence is also required by those wholesalers whose analgesics are included in a poisons schedule.

Identification of the analgesic is found in the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP) which has been adopted by reference, in full or in part, by State/Territory law. If a substance is not identified in the schedules to the SUSDP, it is not a poison and poisons legislation does not apply. By an indirect means sometimes known as “reverse scheduling”, a substance may be exempted from inclusion in a poisons schedule if certain conditions are met. Thus, if aspirin tablets are packed in small quantities and are labelled and packaged according to particular requirements, they are not subject to the same limitations on distribution that would apply to the same substance in other circumstances.
**Paracetamol**

Paracetamol and its preparations generally fall within Schedule 2 of the SUSDP and as such, are available to the public from pharmacies only. Substances in this schedule may be advertised directly to the public. When paracetamol is combined with aspirin or caffeine, products containing them are in Schedule 4 and are thus obtainable only on prescription. In packs of 25 or fewer tablets or capsules that contain 500mg or less of paracetamol, poisons scheduling does not apply and in these circumstances, paracetamol can be sold anywhere subject to specified labelling and packaging conditions. Corresponding provisions apply to the less popular dose forms of powders when containing not more than 1000mg in quantities of 12 or less. Even if the labelling, packaging and quantity conditions are met, any preparations of paracetamol that are labelled for children under seven years of age, such as oral liquids and chewable tablets are in Schedule 2.

Paracetamol must be labelled with either warning statement no.34 or no.35 (below) as required by paragraph 11(o)(ii) of the SUSDP:

**WARNING** - This medication may be dangerous when used in large amounts or for a long time (period).

or

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

If a substance is not included in a poisons schedule, these and other warning statements when located in Appendix F of the SUSDP do not, and cannot apply. Small packs of paracetamol are such a case because they are not poisons within the meaning of the SUSDP and State/Territory legislation. A reading of the Schedule 2 entry for paracetamol, however, shows that as one of several conditions of paracetamol not being in Schedule 2, either one of two statements, set out in full within the Schedule 2 entry must be shown on the label. The two statements are identical with those in Appendix F - Part 1 ie. statements 34 or 35. In other words, for paracetamol to be exempt from a poisons classification, the product must:

* not contain any other therapeutically active substance;
* be packed in blister or strip packaging or in containers with a child-resistant closure;
* not contain more than 25 tablets or capsules or 12 individually wrapped powders;
* not contain more than 500mg per tablet or capsule or 1000mg per powder;
* be labelled with one of the two labels (above); and
* not be labelled for treatment for children under 7 years of age.

In terms of labelling, the differences between a packet of up to 25 paracetamol tablets and a packet of more than 25 tablets are that the latter must bear the signal heading “PHARMACY MEDICINE” and the words “KEEP OUT OF REACH OF CHILDREN; a dose may be quoted for children under 7 years and the warning statement must immediately precede the directions for use as required by paragraph 3.1.7.2 of the SUSDP. The latter, however, does not seem to have been complied with by a number of manufacturers and its usefulness is doubtful.

There is no SUSDP requirement for paracetamol, when included in a poisons schedule, to be packed in blisters or strips or in a container with a child-resistant closure, but if the paracetamol is
eligible for supply as an unscheduled substance, it must be so packed as a condition of its exemption from Schedule 2. The packaging requirements for paracetamol, whether in a poisons schedule or not, are found in Therapeutic Goods Order No.20. The need for any reference to packaging in the schedule entry seems superfluous at first sight as these requirements are in Therapeutic Goods Order No.20. The need is explained because the Orders issued under the Therapeutic Goods Act 1989 do not apply to individuals and partnerships trading only within one State unless the State applies the Commonwealth provisions as has occurred in Victoria and New South Wales, these being the only jurisdictions to have passed legislation complementing the Commonwealth Act.

Aspirin

The regime that applies to aspirin is similar in principle to that applying to paracetamol but there are some labelling differences reflecting the drugs’ different pharmacological properties. Thus, sponsors have a choice of using not only warnings statements nos.34 or 35 but also no.36 which states:

“For use under medical supervision only”.

This option would not be used for aspirin when supplied for its traditional purposes but for cardiovascular indications in purpose-packed and labelled strengths of 100mg. It may also be used in sustained-release aspirin tablets which are usually medically prescribed.

Aspirin also attracts statements nos.37 and 38 which state, respectively,:

“Consult a doctor before giving this medication to children or teenagers with chicken pox, influenza or fever”.

“CAUTION - Do not use for children under 2 years old unless a doctor has told you to”.

The situation with aspirin has, however, become increasingly complicated because of persuasive proposals by various advisory committees for manufacturers to place more cautionary and advisory statements on packages of aspirin. In large part, the statements have emanated from Commonwealth committees and their implementation would normally be through the SUSDP and then given legal force by State or Territory law. The requirement to place such extra statements on labels seems to have been by fiat or the threat of making their inclusion a condition of registration rather than by the mechanism of the SUSDP.

The warning statement that sponsors were obliged to place on packages of aspirin arose from the 1970s when the association between the prolonged use of aspirin and kidney damage was recognised. This resulted in the formulation of SUSDP warnings statements nos.34 and 35 and the use of either one at the discretion of the sponsor. Historically, the wording of no.34 had previously been used for phenacetin and was adopted for analgesics generally. In practice, the industry has preferred the use of the longer no.35, presumably because the presence of the word “dangerous” may be discouraging to purchasers.

Following the connection between aspirin, Reye’s syndrome, chicken pox or influenza or fever and children or teenagers, another warning statement (no. 37) was introduced. Warning statement no.38 cautions against giving aspirin to children under two years of age except on medical advice.
In 1996, the ADEC issued two resolutions (nos. 5418 and 5581) in relation to the use of aspirin in its role as an inhibitor of platelet aggregation. The resolutions centred on the inclusion of cardiovascular indications in the Product Information. An additional warning/advisory statement on the label was jointly recommended by both the ADEC and the MEC stating “See your doctor before taking this product for your heart or for other new uses of aspirin, because serious effects could occur with self-treatment”. This FDA-inspired initiative was taken because it was (and is) common practice for hospitals and general practitioners to recommend that appropriate patients purchase popular brands of aspirin for “thinning the blood” even though there was nothing on the ARTG or the label alluding to this use. Arising from a spirited protest from the PMAA, sponsors were then told that the resolutions should be regarded as advisory only.

The proliferation of warnings was recognised by the TGA, industry and the various committees. The ADEC resolved (no.6072) that a special meeting should be convened between interested parties “in order to achieve a single, comprehensive revision of the labelling of aspirin and all NSAIDs”. Sponsors were notified by the TGA of these resolutions in 1996. At about the same time, there was a series of proposals, but without the force of law, that there should be additional warnings about:

* allergy to aspirin;
* the contraindication of aspirin in the presence of asthma;
* cross-sensitivity with the NSAIDs;
* contraindications in patients with a gastric ulcer; and
* contraindications in the third trimester of pregnancy.

Some sponsors have placed some or all of these warnings on their labels while others have limited their warnings to those prescribed by law. Still others have additional warnings about the combination of aspirin with anti-coagulants.

Ibuprofen

Ibuprofen was formerly a Schedule 4 poison but the NDPSC accepted an ADEC recommendation to transfer the drug, subject to various formulation, pack size and strength conditions to Schedule 3. Under the same conditions, it was later transferred to Schedule 2 where it remains. Unlike paracetamol and aspirin, there is no provision for ibuprofen to be exempted from poisons scheduling.

The SUSDP warning statements applicable to ibuprofen are no.35 and no.71. The latter states:

“Do not use during the last three months of pregnancy”.

Mefenamic acid and naproxen

Mefenamic acid and naproxen are Schedule 2 poisons provided they are supplied in packs of up to 30 or 12 dosage units, respectively; are not formulated with any other therapeutically active
substance; and are solely indicated for the treatment of spasmodic dysmenorrhoea. There is no exemption that would enable either drug to be sold outside of a poisons schedule.

The SUSDP warning statement applicable to either drug when in Schedule 2 is no.34 or no.35.

Commonwealth controls

General

The Therapeutic Goods Act 1989 establishes the Australian Register of Therapeutic Goods. Unless the goods are “exempt goods” within the meaning of the Act, therapeutic goods must be entered in the Register before a person to whom the Act applies can lawfully supply them in Australia. Manufacturers must be licensed. The Act also provides for certain standards, one of which is the use of child-resistant containers for nominated drugs.

To assist industry, the TGA produces various guidelines. The current issue of the Australian Guidelines for the Registration of Drugs, vol 2 sets out, for example, doses of analgesics for adults and children. The guidelines are not the law but sponsors are expected to comply with them as the represent TGA policies based on advice from advisory committees that include experts drawn from the professions, academia and industry. Sponsor may put a case to the TGA to allow a departure from the guidelines and each is considered on its merits in relation to a particular product.

It is essential to recognise the deliberate nature of the interdependence of the State and Federal regimes.

Analgesics specifically

Paracetamol

The only specific references to paracetamol are found in Therapeutic Goods Order No.20 wherein all solid dose forms of it must be supplied in blister or strip packs or in containers fitted with a child-resistant closure, except in special circumstances described in clause 6 of the Order. The Order also requires paracetamol liquids, except drops where the bottle contains not more than 2g, to be in containers fitted with a child-resistant closure. It is also a general requirement of another standard, Therapeutic Goods Order No.48, that any SUSDP warning statements appear on the label. A warning statement, however, is defined in the Order as “any relevant warning statement specified in Appendix F - Part 1 of the Standard for the Uniform Scheduling of Drugs and Poisons...”. Thus, from the perspective of therapeutic goods control, only those warning statements that are included in Appendix F - Part 1 of the SUSDP form part of the Order but not if the warning statements are written within the schedule entry itself.

Aspirin

Aspirin is subject to the same packaging requirements as described above for paracetamol.
Taken together, the SUSDP and the two Orders comprehensively and properly - even if untidily - regulate the labelling and packaging of paracetamol and aspirin in the interests of public health and safety.

Ibuprofen, mefenamic acid and naproxen

There are no specific labelling or packaging requirements under Commonwealth legislation for these substances.

Co-regulation - government and industry

The Media Council of Australia produces a document called the Therapeutic Goods Advertising Code which applies to the content of advertisements for publication or broadcast by the constituent members of the Council and associated organisations. The Code is not the law but parts of it are adopted by reference in the Therapeutic Goods Regulations. Penalties are provided for those breaches of the Code that are specifically identified in the Regulations.

A general principle of the Code (but one that is not adopted by reference in the Regulations) is that advertisements for therapeutic goods (which include analgesics such as paracetamol) must not be directed to children (clause 3.1.4). Clause 5 of the Code relates specifically to advertisements for analgesics with clause 5.3 being adopted by reference in the Regulations. Clause 5.3 prohibits any statement claiming the analgesic is safe; that it will relax, relieve tension, sedate or stimulate or make unsubstantiated claims about faster action and the like. The Code is a good example of co-regulation which appears to be working well.

American labelling of non-prescription analgesics

There are fundamental differences between Australia and the United States of America in terms of control over medicines. The major differences are that the USA does not have a graded series of controls over the distribution of poisons and neither individually evaluates non-prescription medicines nor registers them. The FDA produces detailed and prescriptive monographs which define practically all aspects of labelling and packaging. The FDA’s Internal Analgesic, Antipyretic, and Antirheumatics Drug Products for Over-the-Counter Human Use; Proposed Amendment to the Tentative Final Monograph (Vol.61, No.115, 61 FR 30002 of Thursday, June 13, 1996) is a document of about 80,000 words. Examples of analgesic product labels in their actual size for several drugs recently purchased in New York appear in Appendix 3 together with a typewritten copy of the text to make the reading easier.
**Issues**

The proliferation of warning labels (especially in the case of aspirin), the split controls between State and Commonwealth jurisdictions, and the imprecise legal status of some statements have caused both industry and the regulatory authorities some concern. There is agreement that there should be a comprehensive revision of warning label statements for the non-prescription analgesics.

*Official publications for the warning statements*

The mandatory warning statements are found in the SUSDP and they are applied via State law and as part of Therapeutic Goods Order No.48, as described above.

The statements can be considered from a traditional “poisons” point of view or from a “therapeutic” point of view. Under present arrangements, the former prevails. The present scheme has the advantage of applying Australia-wide without any need to consider the legal personality of the supplier. It does not rely on complementary State/Territory laws to have force. Because the SUSDP applies to substances rather than particular products, there are no complications in connection with the administration of the ARTG or applying the label to therapeutic goods that were “grandfathered” when the *Therapeutic Goods Act* 1989 came into effect. Its main practical disadvantage is that there is no provision for an exemption in a particular case, short of a sponsor gaining approval from each State/Territory health authority. An example of this occurred when an adrenaline aerosol indicated for anaphylaxis was required to include an asthma warning. A specific amendment was made but such a requirement introduces delay.

Alternatively, the warning statements for substances used therapeutically could be transferred to a therapeutic goods order. The order could be one exclusively for warning statements but in order to reduce the number of reference documents, the warning statements could be included in an extra schedule to Therapeutic Goods Order No.48. As there has been a world-wide (South Africa, United Kingdom, Canada, United States of America, New Zealand and partly in this country) shift away from using legislation that controls poisons for therapeutic use to controlling medicines as such, there is an argument for supporting the transfer of the analgesic warning statements to such an order. Specific exemptions may also be obtained under section 14 of the *Therapeutic Goods Act* 1989 in cases where the rigorous application of a warning label is inappropriate. Exemptions would be expected infrequently in such cases. A further advantage by using a therapeutic goods order as the repository document for warning statements is that intra-schedule warning statements that apply as one of conditions of exemption from the schedule could be deleted from the SUSDP. The disadvantages are that for complete legislative control, complementary laws would have to operate in all jurisdictions and there is little point in having an order for analgesics only.
If the warning statements are transferred to an order, the statements must apply to all therapeutic goods that are on the ARTG (including grandfathered goods) and not just those entered on the ARTG after the order takes effect.

**Recommendation 6.1.1**
Warning statements for analgesics remain in the SUSDP for the time being.

**Recommendation 6.1.2**
When all States and Territories have legislation to complement the *Therapeutic Goods Act* 1989, warning statements applicable to any substance for therapeutic use should be transferred from Appendix F - Part 1 of the SUSDP to (a) a new Order under section 10 of the Act; or (b) a schedule to Therapeutic Goods Order No.48 “General requirements for labels of drug products”, or a succeeding corresponding order.

**Recommendation 6.1.3**
In the meantime, the NDPSC explore a means of granting exemptions to the application of warning statements in particular cases, based on the knowledge of its members, advice from evaluation committees, merit and commonsense. Such exemption to be applicable in all jurisdictions simultaneously.

**General content of analgesic warning statements**

The content of any warning statement should be readily understood by the public. It should be short and simple. Technical terms should be avoided if possible; for example, with aspirin, expressions such as “trimester” should be replaced by “3 months”; “platelet aggregation inhibitor” by “blood thinner” (or similar). The size of the type should not be so small that a magnifying glass is needed.

In designing labels, it is important for regulators and industry to ensure that intended users not only understand the words they read but what actions they take thereafter. The study of communication is a specialised skill and the advice of experts in this field should be obtained before writing into law any warning statements. Expressions whose meanings are perfectly plain to a health professional may not be so readily understood by the layperson who purchases the medicine. An established framework to achieve such performance-based labelling is desirable but as this is beyond the scope of this Review, no recommendations will be made. Performance based labelling is not a substitute for certain pieces of information to be present and in a prescribed manner such as the name and quantity of the active drug.

Warning statements on labels alone are not sufficient to remind the public that medicines have adverse as well as beneficial effects. Hancock et al (1992) in a study on the Reye’s warning on aspirin found that less than 10% of men and women obtained their information from the packet, and the remainder, in about equal proportions, obtained theirs from either the media or from doctors, pharmacists, families or friends. The authors state that package labelling is not sufficient as the main medium because few patients read or assimilate the information on labels. Warnings on labels
must be more prominent if they are to be taken heed of. Hancock at al favoured sale from pharmacies where verbal and written professional advice may be obtained, education of children, articles in magazine and newspapers and household letterbox drops.

This Review notes a forthcoming initiative by the Pharmaceutical Society of Australia, the Pharmacy Guild of Australia and the Society of Hospital Pharmacists of Australia that will be directed to the public and will support the quality use of medicines, including advice to read labels.

**Recommendation 6.2**

The proposed new analgesic warning labels (below) should be tested for usability before being written into the SUSDP.

**Recommendation 6.3**

Sponsors and government should be guided by publications such as “Writing about medicines for people: usability guidelines for consumer medicine information” (2nd ed.) by David Sless and Rob Wiseman (Department of Health and Family Services, Canberra, 1997) and “Designing better medicine labels. Report to PHARM” by D Rogers et al (Communication Research Institute of Australia, 1995) in drafting labels, package inserts and consumer medicine information text.

*Actual content of warning labels.*

**Warning or Caution?**

In its 1996 proposed amendment to the tentative final monograph (cited above), the FDA stated, ‘The signal word “warning” has been used routinely in all labeling in OTC drug monographs instead of the word “caution”. Accordingly, the word “caution” is not being included Sec 343.50(c)(1)(v)(B) and in this proposed monograph’. By way of explanation, the FDA stated, ‘The agency notes that historically there has not been a consistent usage of the signal words “warning” and “caution” in OTC drug labeling...In some instances either of these signal words is used to convey the same or similar precautionary information. FDA has considered which of these signal words would be most likely to attract consumers’ attention to that information describing conditions under which the drug product should not be used or its use discontinued. The agency concludes that the signal word “warning” is more likely to flag potential dangers so that consumers will read the information being conveyed. Therefore, FDA has determined that the signal word “warning” rather than the word “caution” will be used routinely...’ This Review agrees.
Paracetamol

At present, one of two warning statements may be used. The words of the statement are drawn from Appendix F - Part 1 of the SUSDP in the case of poisons or as a condition of exemption from inclusion in a poisons schedule where the product is not a poison.

Statement no. 35 is the longer of the two and is used by most manufacturers. It predated, and its intent has largely been superseded by, national therapeutic goods legislation which has features such as labelling standards and the adoption of the Therapeutic Goods Advertising Code. The Therapeutic Goods Advertising Code requires reference to “temporary” relief from pain due to headache and arthritic disorders, and it is superfluous to restate the same adjective in the general warning statement. Secondly, the phrase ...”should be used strictly as directed” is superfluous because a dose must appear on the label and in the case of aspirin and paracetamol, manufacturers usually place a maximum daily dose of these drugs on the label. There is also a guideline on daily maximum doses for aspirin and paracetamol in the AGRD vol 2.

Warning statement no.34 (or the almost identical no.44) is a shorter message than contained in no.35 as it emphasises danger when the drug is taken in excessive doses or for a long period. In practice, many people do take paracetamol for extended periods; notably for the relief of pain in osteoarthritis. Any new message should be tailored to the known properties of the particular drug and its clinical use but at the same time, emphasise that the drug is not without its harmful effects if taken inappropriately. A new warning statement that accepts that paracetamol is appropriately used for chronic pain under medical supervision, but recognises that excessive doses could be unsafe, should be considered. At the same time, warnings about fatalities may be counter-productive; this aspect is discussed in the chapter, “Paracetamol and self-poisoning”.

**Recommendation 6.4**

The NDPSC consider a new warning statement [notionally numbered 99] applicable to paracetamol to read:

**WARNING** - Prolonged use of this medication without a doctor’s advice or in more than the recommended dose may be harmful.

If the goods are to be exempted from the operation of Schedule 2 of the SUSDP, the new entry for paracetamol would read:

Paracetamol **except:**

(a) when included in Schedule 4;

(b) in individually wrapped powders or sachets of granules each containing 1000mg or less of paracetamol as the only therapeutically active constituent other than effervescent agents, when:
(i) in a primary pack containing not more than 12 such powders or sachets;

(ii) is labelled with the statement:

**WARNING** - Prolonged use of this medication without a doctor’s advice or in more than the recommended doses may be harmful; and

(iii) not labelled for the treatment of children under 7 years of age;

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

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

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

(iii) the primary pack is labelled with the statement:

**WARNING** - Prolonged use of this medication without a doctor’s advice or in more than the recommended doses may be harmful; and

(iv) not labelled for the treatment of children under 7 years of age.

Aspirin

Aspirin represents a good example of labelling that has become cluttered and complicated. The complications have arisen from new uses for aspirin and, despite the drug’s long history, the recognition of serious adverse effects, contraindications and drug interactions.

The Review believes that sets of combined warning statements applicable to various aspirin formulations should replace those used at present. Thus, a packet of aspirin tablets 300mg would attract warning statement no.100 only and not statements 37 and 38 with either 34 or 35 or 36. Applied to one of the leading brands of dispersible aspirin, the number of words used in the warning would be reduced from 94 to 67. Statement no 100 would be used when aspirin was the only active agent, except for those aspirin products prepared, packed and labelled for inhibition of platelet aggregation and in sustained release preparations containing 650mg or more of aspirin, in which cases, the present warning statement no.36 would continue. No.101 would be used when aspirin is combined with other drugs and the reference to cardiovascular use is inapplicable.

The two statements are identical except for the last sentence in statement no.100. The Review included this sentence in recognition of the reality that is occurring in the market place where members of the public purchase aspirin tablets that are registered and labelled for analgesia, but on medical advice, use the same product for the inhibition of platelet aggregation and other cardiovascular diseases. In a sense, the sentence is advisory rather than strictly a warning but for these conditions, the treatment should be always medically initiated and consumers would be unwise to self-prescribe for such serious conditions. An authoritative statement from the American
Heart Association (Hennekens et al, 1997) advocates the use of aspirin in reducing the risk of myocardial infarction but refers to the need for medically prescribed dose selection. By contrast, one distinguished clinical pharmacologist (Lasagna, 1987) was critical of the American authorities for depriving the public of important new information about aspirin and cardiovascular disease.

### Recommendation 6.5

The NDPSC consider the following new warning statements to apply to aspirin products for inclusion in Appendix F - Part 1 of the SUSDP. [note: the numbers assigned to the proposed warnings are notional only]

100. **WARNING** - Unless a doctor has told you to, do not use [this product]/[name of product]

   - for a long time;  
   - in the last 3 months of pregnancy;  
   - if you have asthma or a stomach ulcer;  
   - if you are allergic to aspirin or anti-inflammatory medicines;  
   - in children under 2 years of age or in older children or teenagers with chickenpox, influenza or fever.

   See a doctor before taking [this product]/[name of product] for thinning the blood or for your heart.

101. **WARNING** - Unless a doctor has told you to, do not use [this product]/[name of product]

   - for a long time;  
   - in the last 3 months of pregnancy;  
   - if you have asthma or a stomach ulcer;  
   - if you are allergic to aspirin or anti-inflammatory medicines;  
   - in children under 2 years of age or in older children or teenagers with chickenpox, influenza or fever.

If the goods are to be exempted from the operation of Schedule 2 of the SUSDP, the new entry would read:

**ASPIRIN except:**

(a) when included in Schedule 4 or 6;
(b) in individually wrapped powders or sachets of granules each containing 650mg or less of aspirin as the only therapeutically active constituent other than an effervescent agent when enclosed in a primary pack that:

(i) contains not more than 12 such powders or sachets of granules;

(ii) is labelled with the following statement:

**WARNING** - Unless a doctor has told you to, do not use [this product]/[name of product]
- for a long time;
- in the last 3 months of pregnancy;
- if you have asthma or a stomach ulcer;
- if you are allergic to aspirin or anti-inflammatory medicines;
- in children under 2 years of age or in older children or teenagers with chicken pox, influenza or fever.

See a doctor before taking [this product]/[name of product] for thinning the blood or for your heart.

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

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

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

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

**WARNING** - Unless a doctor has told you to, do not use [this product]/[name of product]
- for a long time;
- in the last 3 months of pregnancy;
- if you have asthma or a stomach ulcer;
- if you are allergic to aspirin or anti-inflammatory medicines;
- in children under 2 years of age or in older children or teenagers with chicken pox, influenza or fever.

See a doctor before taking [this product]/[name of product] for thinning the blood or for your heart.

Therapeutic Goods Advertising Code and cardiovascular disease

The Therapeutic Goods Regulations adopt by reference that part of the Therapeutic Goods Advertising Code dealing with “prohibited representations”. One such prohibited representation is “cardiovascular system diseases, ailments or defects (including high or low blood pressure) other than (i)...(ii)...(iii)...(iv) a statement to the effect of “aids or assists in the maintenance of peripheral circulation”. As aspirin is used frequently for inhibition of platelet aggregation and for suspected myocardial infarction, the advisory sentence proposed for warning label no.100 may contravene the code. Regulation 9 enables the Secretary, by notice in the Commonwealth of Australia Gazette to
permit the “a prohibited representation to be included on the label of therapeutic goods, or in information included in the package in which therapeutic goods are contained, if the representation is necessary for the appropriate use of the goods”. As this permission is exercised case by case and as there are many products on the market containing aspirin as the only active agent, a more efficient method would be to amend the code itself.

Recommendation 6.6

Subject to proposed SUSDP warning statement no.100 being adopted, clause 4 of the Therapeutic Goods Advertising Code should be amended by adding the following exception to the entry for cardiovascular system diseases: “(v) when prescribed in the Standard for the Uniform Scheduling of Drugs and Poisons for aspirin”.

Ibuprofen

Labels nos.35 and 71 can be combined in a new single label and be extended to asthma, ulcers and cross-sensitivity to aspirin and other NSAIDs. If other NSAIDs are switched from Schedule 4 to Schedule 2 or Schedule 3, the same new warning can be applied.

Recommendation 6.7

The NDPSC consider the use of warning statement no.102 to replace those currently used for ibuprofen when included in Schedule 2:

102. **WARNING** - Unless a doctor has told you to, do not use [this product]/[name of product]

- for a long time;
- in the last 3 months of pregnancy;
- if you have asthma or a stomach ulcer;
- if you are allergic to aspirin or anti-inflammatory medicines.

Statement no.102 differs from no.101 by the omission of the Reye’s reference.

Mefenamic acid and naproxen

At present, statements 34 or 35 may be used.
**Recommendation 6.8**

The NDPSC consider the use of warning statement no.103 to replace those currently used for naproxen and mefenamic acid when included in Schedule 2:

103. **WARNING** - Unless a doctor has told you to, do not use [this product]/[name of product]

- for a long time;
- if you have asthma or a stomach ulcer;
- if you are allergic to aspirin or anti-inflammatory medicines.

The proposed new statement no.103 omits the reference to the last three months of pregnancy because mefenamic acid and naproxen are available without prescription for the treatment of spasmodic dysmenorrhoea only. If either were indicated for other purposes and the Schedule 2 entry amended accordingly, statement no.102 would be substituted.

The consequential changes to Appendix F - Part 3 of the SUSDP would therefore read:

**Aspirin**

(a) when prepared, packed and labelled solely for inhibition of platelet aggregation.  
(b) in sustained release preparations containing 650mg or more of aspirin.  
(c) when combined with any other therapeutically active constituent.  
(d) except as above

**Ibuprofen when included in Schedule 2**

**Mefenamic acid when included in Schedule 2**

**Naproxen when included in Schedule 2**

**Paracetamol when included in Schedule 2**

**Implementation**

If the NDPSC agrees to the new format of warning labels for the analgesics, adequate time must be extended to industry to comply. The supply of incorrectly labelled containers at all levels of distribution is an offence. So that suppliers are not unwittingly breaking the law, at least two years should elapse before the new labelling is enforced although manufacturers may choose to introduce the new format at an earlier print run. Alternatively, specific provision should be made in the
SUSDP for the old and the new warning statements to be used as alternatives until an agreed date, following consultation with industry.

**Recommendation 6.9**

Following consultation with industry, sufficient time should be allowed for replacement of the old warning labels by the new with provision made for either format to be used for an agreed period.

**Packaging**

As mentioned above, foil or blister packs or child resistant closures are mandatory for aspirin and paracetamol in solid dose forms. The requirement is applied for unscheduled aspirin and paracetamol preparations as an intra schedule condition of the products being exempted from Schedule 2. If the product is scheduled, the mandatory foil or blister pack or child resistant closure flows from the inclusion of aspirin and paracetamol in Schedule 1 of Therapeutic Goods Order No.20.

The use of containers, other than foil or blister packs for aspirin and paracetamol, does not seem to be common although the Review understands that a bottle fitted with a child resistant closure of 25 tablets would be cheaper than the same quantity in foil or blister packs. As bottles of “loose” tablets, despite being fitted with a child resistant closure, represent a greater hazard in both accidental childhood poisoning and parasuicidal gestures, the option of using this form of packaging for paracetamol when presented singly or with codiene or dihydrocodeine, should be discontinued other than in those circumstances (hospital packs, cases of hardship where there is difficulty in opening a container) prescribed by clause 6 of Therapeutic Goods Order No.20. The recommendation below is largely a preventative measure but in view of the problems of paracetamol poisoning in the UK where “loose” packs have been commonly available and the rising frequency of self-poisoning by adolescents in Australia, prudence would suggest an amendment to Australian law.

In the case of soluble or dispersible aspirin, foil or blister wrappers are preferred over bottles for reasons of chemical stability. The need to mandate foil or blister wrappers for ordinary aspirin tablets as the only form of child resistant closure does not seem justified when compared with paracetamol.

**Recommendation 6.10**

The NDPSC consider amending the entry in Schedule 2 for paracetamol under sub-paragraph (c)(i) by deleting the words “or in a container with a child-resistant closure”.

**Recommendation 6.11**

Therapeutic Goods Order No.20 be amended to require solid dose forms of paracetamol when present as either (a) the only therapeutically active substance or; (b) when combined with codeine or dihydrocodeine, to be packed exclusively in blister or strip packaging, subject to clause 6 of the Order.

There may need to be an accommodation in both labelling and packaging in the SUSDP for these analgesics when they are intended for animal use as the present and suggested labels comprehend human use only.
ANALGESIC AND ANTIPYRETIC GUIDELINES

The Australian Guidelines for the Registration of Drugs, vol.2 (AGRD vol 2) has specific guidelines on aspirin (p.55) and paracetamol (p.65). Each guideline emphasises dosages. The AGRD vol.2 does not have guidelines on ibuprofen, mefenamic acid and naproxen. Aspirin and paracetamol are frequently included in preparations containing a wide variety of other drugs such as decongestants, antihistamines and antitussives where the analgesic is present to relieve the aches and pains associated with colds and flu. This chapter refers only to products that are indicated for their analgesic and antipyretic properties.

There are other formulations where codeine is present to enhance the analgesic action of the product but the advantages of the combinations used in non-prescription medicines, when compared with aspirin or paracetamol alone, are unproven despite their popularity (Watt, 1993). The addition of doxylamine to paracetamol and low dose codeine has been shown in some studies to be superior to placebo and also to paracetamol with codeine. This combination has appeal with migraine patients.

Mandatory labelling and packaging

Analgesics that are included in a poisons schedule attract the signal headings of the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP) and a range of warning statements that are found in Appendix F - Part 1. Labelling, packaging and other conditions apply to small packs of aspirin and paracetamol that enable them to be exempted from a poisons schedule. These details are found within the Schedule 2 entries for aspirin and paracetamol in the SUSDP.

Orders issued under the Therapeutic Goods Act 1989 require child-resistant closures for some analgesics but in prescribed circumstances, this requirement is waived.

Indications

Analgesia and antipyresis

Examination of the ARTG for analgesics has shown a more or less similar range of representative indications as having been accepted and these are shown in Appendices 4 and 5. There are additional indications for children’s formulations containing paracetamol. These are set out in Appendix 4.

Aspirin and cardiovascular indications

Aspirin is increasingly prescribed by medical practitioners and hospitals for inhibition of platelet aggregation to prevent thromboses. It is also used for other cardiovascular diseases such as prevention of carotid vertebral artery disease, prevention of transient ischaemic attack and for uncomplicated myocardial infarction. Indications of this kind are prohibited under the Therapeutic Goods Advertising Code (TGAC) but in specific cases, a sponsor may apply for an exemption under Regulation 9 of the Therapeutic Goods Regulation to make such a claim. The rationale for prohibiting such representations is that the prevention, diagnosis and treatment of cardiovascular
disease should be medically initiated and monitored. Lasagna (1987) has questioned whether the best approach is to deprive the public of important new information about aspirin and cardiovascular disease [in this case, reducing the risks of death and/or non-fatal myocardial infarction in patients with a previous infarction or unstable angina pectoris] or to clearly educate the public about what is definitely known, what is not known, and what are the apparent costs and risks of action and inaction. The American Heart Association (Hennekens et al, 1997) has called on the FDA to expand its approved uses of aspirin beyond current package labelling that indicates aspirin can help people experiencing the symptoms of a myocardial infarction and also prevent a second myocardial infarction. Given that dose requirements vary for antithrombotic activity and patients with cardiovascular disease are likely to be taking other drugs, the Review considers that the principle underlying the prohibition should remain. The fact is, however, that members of the public purchase aspirin with or without medical advice for “thinning the blood”. For this reason, the Review has suggested that a health message should be incorporated into the new consolidated warning applicable to aspirin with a consequential amendment to the TGAC. The message would state, “See a doctor before taking [this product]/[name of product] for thinning the blood or for your heart”, and would apply to solid dose forms containing aspirin as the only therapeutically active agent.

**Degrees of pain**

Although pain is a highly subjective experience, some analgesics are more appropriate to certain painful conditions and their intensity than others. For single substance analgesics, the intensity of the pain in the above indications may be described as “mild”, “mild to moderate” or “moderate”. Where the single analgesic is combined with codeine or with codeine and doxylamine, the pain may be described as “moderate”, “moderate to strong”, “stronger” or “strong” without further description but the expression “severe pain” is not acceptable and should be reserved for prescription only medicines. Reference may be made to the enhanced analgesic effect due to doxylamine where it is present. Doxylamine may be described as a calmative. Where other analgesics or adjuvant drugs are present, sponsors should ensure that the elimination rates of each drug are similar and that the ratios of one drug to another are appropriate.

**Dosage**

**Paracetamol dose**

The AGRD vol 2 sets out the adult dose for paracetamol. No change is suggested to the present regimens for adults or for children in the 7-12 year age group. The paediatric dosage recommendations are presently based on 12.5mg/kg but Recommendation 2.11 of this Review suggests that this might be increased to 15mg/kg on the basis of modern authoritative references.

*Particular attention is directed to the paragraph on page 65 of the AGRD vol 2 which states, “Doses should be given every 4 to 6 hours as required with not more than 4 doses in 24 hours. The product should not be administered for more than 48 hours without seeking medical advice”. Examination of a number of paediatric products of paracetamol showed that one or both of these caveats were absent probably because the goods were registered before the guidelines were published. The maximum safe daily dose for children is 90mg/kg. Repeated dosing over several days, especially in the younger child can deplete stores of glutathione sometimes resulting in hepatotoxicity (Penna et al, 1993). If the new dose rate is accepted, it is all the more important that these caveats are present. At any rate, the Review has made a recommendation on the matter in an earlier chapter.*
Should not the statements about maximum daily doses for adults and children and the 48 hour limitation on duration of treatment for children form part of the SUSDP warning label? There are arguments for taking this approach; all of the warning statements would be located in the one document and would apply to all products, prospectively and retrospectively. Paracetamol is, however, a component of many products. Rigidly applying the statements is bound to produce some contradictions and anomalies in compound preparations where the dose, frequency of administration, duration of action other constituents and the indications for the product as a whole must be taken into consideration. Because such products are individually evaluated, the flexibility offered by guidelines is a major advantage. Examination of uncompounded paracetamol tablets and capsules shows that the maximum number of tablets or capsules to be taken daily (equivalent to 4g) appears routinely on labels. The same applies to combinations of paracetamol with codeine. The maximum number of doses in 24 hours and duration of treatment with paracetamol oral liquids are not always present and should be added to label text, as in Recommendation 2.13.

**Recommendation 7.1**

The Medicines Evaluation Committee give consideration to the content of Appendix 4 as the basis for a guideline on paracetamol.

**Aspirin dose**

There has been criticism (Hancock et al, 1992) that doses of aspirin for children appear on the label when there are mandatory statements warning against using it in children under 2 years of age and in circumstances which may predispose to Reye’s syndrome. Doses have been included in the AGRD vol 2 in the interests of harm minimisation and to give guidance in the rare instances when aspirin may be prescribed. Aspirin may be used in children with juvenile chronic arthritis but in such cases, the dose is greater than previously used for self-limiting pain and in any case, its role in this disorder has been largely superseded by the NSAIDs. There appears to be little justification for including a dose for children under 12 years of age. The proposed new warning label for aspirin is worded in a manner that recommends that medical advice is obtained before giving aspirin to children and teenagers. If the new warning is adopted, the opportunity could then be taken to delete specific doses for children from aspirin labels. Sponsors who wish to delete the childrens’ doses earlier could do so and replace them with the words, “on medical advice” or similar.
**Recommendation 7.2**

The Medicines Evaluation Committee give consideration to the content of Appendix 5 as the basis for a guideline on aspirin.

---

**Recommendation 7.3**

Subject to Recommendation 7.2 being agreed to, the TGA notify sponsors of aspirin products to remove specific doses of aspirin for children from labels when a revised style of SUSDP warning statements are in operation or earlier at the discretion of the sponsor with the words “on medical advice” to replace the childrens’ doses.
Appendix 1 - PARACETAMOL-INDUCED ADMISSIONS TO THE ROYAL CHILDREN’S HOSPITAL 1993 - 1997

Aim

The aim of this study was to document children and adolescents admitted to the Royal Children’s Hospital, Melbourne after ingestion of paracetamol during the years 1993 - 1997. The study covers accidental overdose and self-poisoning.

Method

The medical records of all children and adolescents with poisoning due to paracetamol who were admitted to the Royal Children’s Hospital for the five year period 1993 - 1997 were reviewed. The records examined related to admissions and not to presentations only.

Each admission was analysed in terms of sex and age; length of stay (LOS); the dose form of paracetamol and if available, the pack size; the estimated amount of paracetamol consumed; the maximum amino aspartate transaminase (AST) concentration; the maximum recorded serum concentration of paracetamol; the treatment administered; and the reasons for the poisoning.

Results

For the calendar years 1993 - 1997, 123 children and adolescents were admitted to the hospital because of accidental and deliberate self-poisoning due to paracetamol, representing about 0.1% of all admissions. The hospital admits about 25,000 patients each year with acute admissions accounting for just over half of the total (Royal Children’s Hospital Annual Report, 1996).

<table>
<thead>
<tr>
<th>YEAR</th>
<th>NUMBER</th>
<th>FEMALE &gt;11 YR</th>
<th>MALE &gt;11 YR</th>
<th>FEMALE &lt;11 YR</th>
<th>MALE &lt;11 YR</th>
<th>CHARCOAL ONLY</th>
<th>NAC NIL ANTIDOTE</th>
<th>AV. LOS (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1993</td>
<td>18</td>
<td>9</td>
<td>2</td>
<td>1</td>
<td>6</td>
<td>10</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>1994</td>
<td>27</td>
<td>9</td>
<td>1</td>
<td>9</td>
<td>8</td>
<td>14</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>1995</td>
<td>30</td>
<td>18</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>12</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>1996</td>
<td>21</td>
<td>13</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>11</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>1997</td>
<td>27</td>
<td>19</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>10</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>TOTAL</td>
<td>123</td>
<td>68</td>
<td>12</td>
<td>18</td>
<td>25</td>
<td>57</td>
<td>44</td>
<td>22</td>
</tr>
<tr>
<td>%</td>
<td>100</td>
<td>55</td>
<td>10</td>
<td>15</td>
<td>20</td>
<td>46</td>
<td>36</td>
<td>18</td>
</tr>
</tbody>
</table>

TABLE. Age and sex distribution, treatment and average length of stay in cases of admission due to paracetamol poisoning at the Royal Children’s Hospital, 1993 - 1997.
Sex and age

Girls accounted for 86 (70%) of all admissions and boys for 37 (30%). There were two clear age groups - adolescents and children up to six years of age. The former group consisted of 80 (65%) adolescents (68 girls and 12 boys) who deliberately self-poisoned and the latter comprised 8 children (7%) (3 girls and 5 boys) who received the wrong dose or doses, and 35 (28%) (16 girls, 19 boys) who helped themselves to the medicine.

Preparations involved

In the case of the adolescents, liquid dose forms never figured but among the 43 children accidentally poisoned with paracetamol, 27 (63%) consumed oral liquids, four of which were in the form of drops containing 100mg/mL. In the remaining 16 (37%) instances, solid dose forms were taken.

Paracetamol in combination with other drugs accounted for 45 cases (37%) and in 78 cases (63%), it was the sole substance consumed. Combinations included a collection of separate products as well as products where paracetamol was part of the formulation, notably those containing codeine such as Panadeine and Panadeine Forte. There were insufficient data to determine if pack size was a factor in admission rates.

Treatment and intervention

Activated charcoal was administered in 57 cases (46%) as the sole antidotal intervention; N-acetylcysteine (NAC) was given intravenously in 44 cases (36%), charcoal having been previously given in many of these. Neither of these treatments was recorded in 22 cases (18%).

Average length of stay (LOS)

It was not always possible to determine from the records the precise LOS. Assuming no admission was less than one day, the average LOS was two days with the longest being nine days. As some patients were discharged on the same date as they were admitted, two days over-represents the average period of hospitalisation.

Morbidity and mortality

There were no deaths and no liver transplants recorded in this series.

A 5 year-old girl who had been given ten doses each of 10mL of an unrecorded strength of paracetamol oral liquid had a maximum AST of 20,000 U/L. She developed hepatic failure and encephalopathy. Such a high laboratory value is rare in cases of acute paracetamol poisoning but there was a suggestion that the patient had a mycoplasma infection which can produce an encephalopathy and so contribute to the raised AST level. She recovered after nine days hospitalisation. Another case with a near fatal outcome arose when a 3 year-old girl was admitted 30 hours after consuming up to 100mL of the 250mg/5mL preparation (pack size unrecorded) which had been temporarily left in the child’s bedroom instead of its usual storage place. Oral NAC was followed by intravenous NAC and haemofiltration. Her maximum AST was 3939U/L and the maximum recorded INR was 2.0.
Discussion

Self-poisoning

Paracetamol figures prominently in self-poisoning by adolescent girls. In this survey, there were over five times as many girls as boys in this category. For the years studied, there was an increased trend for adolescent girls to self-poison but as the numbers of boys was small, it was not possible to discern any trend with them. Adolescents who were attending nearby special centres for behavioural or social problems were prominent in the group. Previous suicidal attempts using drugs and other methods of self-harm were common. Reasons for self-poisoning were poor self-image, family conflict, social stress and depression. Impulsivity was often noted.

As the hospital treats adolescents with behavioural disorders, the proportion of self-poisoners to accidental poisonings, being about 2:1, may over-represent the ratio for the State. On the other hand, as a paediatric hospital, the RCH would be expected to admit a larger number of poisoned children than a general hospital. The RCH would also admit patients transferred from other hospitals when more specialised paediatric treatment is necessary.

The quantities of paracetamol taken are not known with any accuracy as they depend on patients’ and associates’ recollections and numbers of tablets (if any) left in the container.

Accidental poisoning

The number of accidental poisonings due to paracetamol resulting in admission to the Royal Children’s Hospital has declined over the period surveyed. The number also represents a declining proportion of paracetamol admissions as the number of admissions from self-poisonings with this drug has increased.

The accidental poisonings are of two types. One follows from storage errors or inadvertence on the part of the carer and the other is due to incorrect administration of the medicine. The former is the more common and occurs when (i) paracetamol oral liquids are stored in the refrigerator; (ii) children take tablets from drawers, cupboards and handbags; (iii) children climb up to reach high shelves where medicines are stored; and (iv) medicines are left in the sickroom.

Maladministration of the drug may take the form of an incorrectly measured dose and/or the dose being given too often. Examples of these are (i) a child was given two doses of 70mL of paracetamol elixir 120mg/5mL instead of 7mL; (ii) an excessive dose was given repeatedly, apparently on medical advice; (iii) giving the same number of millilitres of drops containing 100mg/1mL as had been previously given with the 120mg/5mL elixir; (iv) the administration of 25mL of the 240mg/5mL elixir instead of 2.5mL. In this case, the mother mistook the maximum
calibration on the 40mL medicine measure for 4mL and arising from that, gave ten times too much; and (v) a mother gave 6mL of the 100mg/1mL drops followed by two 3mL doses instead of 0.6mL and 0.3mL, respectively. There was one example of excessive frequency of dosing. In that case, a medically prescribed oral elixir containing promethazine hydrochloride 6.5mg, paracetamol 120mg, and codeine phosphate 6.5mg in 5mL (Painstop Syrup) was given two hourly instead of four hourly because each parent administered a dose at the prescribed interval without the other knowing.
Histogram showing admissions to the Royal Children’s Hospital by sex for paracetamol poisoning, 1993 - 1997

Bar graph showing admissions to the Royal Children’s Hospital by sex for paracetamol poisoning, 1993 - 1997

acc = accidental poisoning  s-p = self-poisoning
Appendix 2 - SEPARATIONS FROM AUSTRALIAN HOSPITALS DUE TO PARACETAMOL POISONING

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Female Separations</th>
<th>Male Separations</th>
<th>Bed Days</th>
<th>ALoS</th>
<th>Bed Days</th>
<th>ALoS</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>3</td>
<td>5</td>
<td>1.00</td>
<td>7</td>
<td>1.17</td>
<td></td>
</tr>
<tr>
<td>1-4</td>
<td>81</td>
<td>94</td>
<td>1.04</td>
<td>94</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>5-9</td>
<td>4</td>
<td>5</td>
<td>1.25</td>
<td>6</td>
<td>1.20</td>
<td></td>
</tr>
<tr>
<td>10-14</td>
<td>29</td>
<td>59</td>
<td>2.03</td>
<td>5</td>
<td>3.40</td>
<td></td>
</tr>
<tr>
<td>15-19</td>
<td>124</td>
<td>248</td>
<td>2.00</td>
<td>31</td>
<td>1.97</td>
<td></td>
</tr>
<tr>
<td>20-24</td>
<td>87</td>
<td>161</td>
<td>1.85</td>
<td>24</td>
<td>1.38</td>
<td></td>
</tr>
<tr>
<td>25-29</td>
<td>28</td>
<td>38</td>
<td>1.36</td>
<td>24</td>
<td>2.42</td>
<td></td>
</tr>
<tr>
<td>30-34</td>
<td>32</td>
<td>53</td>
<td>1.66</td>
<td>18</td>
<td>1.76</td>
<td></td>
</tr>
<tr>
<td>35-39</td>
<td>25</td>
<td>416</td>
<td>16.64</td>
<td>11</td>
<td>3.55</td>
<td></td>
</tr>
<tr>
<td>40-44</td>
<td>16</td>
<td>28</td>
<td>1.75</td>
<td>12</td>
<td>3.67</td>
<td></td>
</tr>
<tr>
<td>45-49</td>
<td>7</td>
<td>9</td>
<td>1.29</td>
<td>10</td>
<td>2.60</td>
<td></td>
</tr>
<tr>
<td>50-54</td>
<td>6</td>
<td>10</td>
<td>1.07</td>
<td>5</td>
<td>2.80</td>
<td></td>
</tr>
<tr>
<td>55-59</td>
<td>6</td>
<td>35</td>
<td>5.83</td>
<td>1</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>60-64</td>
<td>4</td>
<td>34</td>
<td>8.50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>65-69</td>
<td>2</td>
<td>19</td>
<td>9.50</td>
<td>3</td>
<td>3.00</td>
<td></td>
</tr>
<tr>
<td>70-74</td>
<td>1</td>
<td>7</td>
<td>7.00</td>
<td>1</td>
<td>11.00</td>
<td></td>
</tr>
<tr>
<td>75-79</td>
<td>1</td>
<td>6</td>
<td>6.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>80-84</td>
<td>1</td>
<td>110</td>
<td>110.00</td>
<td></td>
<td>2.00</td>
<td></td>
</tr>
<tr>
<td>&gt;=85</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>457</td>
<td>1325</td>
<td>2.80</td>
<td>251</td>
<td>454</td>
<td>1.81</td>
</tr>
</tbody>
</table>

1/7/83-31/12/93

Separations for poisoning by analgesics (ICD9 code 965.4) with external code E950.4
(suicide and self-inflicted injury) by sex, age group and average length of stay

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Female Separations</th>
<th>Male Separations</th>
<th>Bed Days</th>
<th>ALoS</th>
<th>Bed Days</th>
<th>ALoS</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-14</td>
<td>61</td>
<td>247</td>
<td>4.66</td>
<td>9</td>
<td>47</td>
<td>5.22</td>
</tr>
<tr>
<td>15-19</td>
<td>257</td>
<td>604</td>
<td>2.37</td>
<td>70</td>
<td>164</td>
<td>2.34</td>
</tr>
<tr>
<td>20-24</td>
<td>120</td>
<td>245</td>
<td>2.04</td>
<td>73</td>
<td>139</td>
<td>1.90</td>
</tr>
<tr>
<td>25-29</td>
<td>92</td>
<td>169</td>
<td>1.80</td>
<td>41</td>
<td>88</td>
<td>2.15</td>
</tr>
<tr>
<td>30-34</td>
<td>59</td>
<td>169</td>
<td>2.85</td>
<td>33</td>
<td>63</td>
<td>1.91</td>
</tr>
<tr>
<td>35-39</td>
<td>43</td>
<td>250</td>
<td>5.81</td>
<td>23</td>
<td>49</td>
<td>2.13</td>
</tr>
<tr>
<td>40-44</td>
<td>47</td>
<td>153</td>
<td>3.26</td>
<td>16</td>
<td>29</td>
<td>1.81</td>
</tr>
<tr>
<td>45-49</td>
<td>26</td>
<td>71</td>
<td>2.73</td>
<td>10</td>
<td>35</td>
<td>3.50</td>
</tr>
<tr>
<td>50-54</td>
<td>7</td>
<td>17</td>
<td>2.43</td>
<td>4</td>
<td>9</td>
<td>2.25</td>
</tr>
<tr>
<td>55-59</td>
<td>13</td>
<td>30</td>
<td>2.31</td>
<td>2</td>
<td>4</td>
<td>2.00</td>
</tr>
<tr>
<td>60-64</td>
<td>3</td>
<td>12</td>
<td>4.00</td>
<td>2</td>
<td>2</td>
<td>1.00</td>
</tr>
<tr>
<td>65-69</td>
<td>9</td>
<td>22</td>
<td>2.56</td>
<td>1</td>
<td>1</td>
<td>1.00</td>
</tr>
<tr>
<td>70-74</td>
<td>1</td>
<td>3</td>
<td>3.00</td>
<td>4</td>
<td>15</td>
<td>3.75</td>
</tr>
<tr>
<td>75-79</td>
<td>1</td>
<td>5</td>
<td>5.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;=85</td>
<td>1</td>
<td>5</td>
<td>5.00</td>
<td>1</td>
<td>4</td>
<td>4.00</td>
</tr>
<tr>
<td>Total</td>
<td>740</td>
<td>2040</td>
<td>2.76</td>
<td>289</td>
<td>649</td>
<td>2.26</td>
</tr>
</tbody>
</table>
### Separations for poisoning by analgesics (ICD9 code 965.4) with external code E950.4 (accidental poisoning) by sex, age group and average length of stay

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Female</th>
<th></th>
<th></th>
<th>Male</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Separations</td>
<td>Bed Days</td>
<td>ALoS</td>
<td>Separations</td>
<td>Bed Days</td>
<td>ALoS</td>
</tr>
<tr>
<td>&lt;1</td>
<td>4</td>
<td>4</td>
<td>1.00</td>
<td>5</td>
<td>10</td>
<td>2.00</td>
</tr>
<tr>
<td>1-4</td>
<td>101</td>
<td>105</td>
<td>1.04</td>
<td>125</td>
<td>134</td>
<td>1.07</td>
</tr>
<tr>
<td>5-9</td>
<td>1</td>
<td>1</td>
<td>1.00</td>
<td>1</td>
<td>1</td>
<td>1.00</td>
</tr>
<tr>
<td>10-14</td>
<td>25</td>
<td>63</td>
<td>2.52</td>
<td>4</td>
<td>5</td>
<td>1.25</td>
</tr>
<tr>
<td>15-19</td>
<td>101</td>
<td>194</td>
<td>1.92</td>
<td>23</td>
<td>35</td>
<td>1.52</td>
</tr>
<tr>
<td>20-24</td>
<td>60</td>
<td>91</td>
<td>1.52</td>
<td>31</td>
<td>54</td>
<td>1.74</td>
</tr>
<tr>
<td>25-29</td>
<td>33</td>
<td>59</td>
<td>1.79</td>
<td>27</td>
<td>71</td>
<td>2.63</td>
</tr>
<tr>
<td>30-34</td>
<td>22</td>
<td>52</td>
<td>2.36</td>
<td>23</td>
<td>38</td>
<td>1.65</td>
</tr>
<tr>
<td>35-39</td>
<td>18</td>
<td>78</td>
<td>4.33</td>
<td>10</td>
<td>24</td>
<td>2.40</td>
</tr>
<tr>
<td>40-44</td>
<td>12</td>
<td>21</td>
<td>2.51</td>
<td>4</td>
<td>5</td>
<td>1.25</td>
</tr>
<tr>
<td>45-49</td>
<td>11</td>
<td>15</td>
<td>1.50</td>
<td>4</td>
<td>9</td>
<td>2.25</td>
</tr>
<tr>
<td>50-54</td>
<td>3</td>
<td>8</td>
<td>2.67</td>
<td>2</td>
<td>3</td>
<td>1.50</td>
</tr>
<tr>
<td>55-59</td>
<td>1</td>
<td>3</td>
<td>3.00</td>
<td>2</td>
<td>3</td>
<td>1.50</td>
</tr>
<tr>
<td>60-64</td>
<td>3</td>
<td>4</td>
<td>4.00</td>
<td>2</td>
<td>3</td>
<td>1.50</td>
</tr>
<tr>
<td>65-69</td>
<td></td>
<td>3</td>
<td>8</td>
<td>2.67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>70-74</td>
<td>3</td>
<td>22</td>
<td>7.33</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>75-79</td>
<td>3</td>
<td>51</td>
<td>17.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>399</td>
<td>771</td>
<td>1.93</td>
<td>264</td>
<td>400</td>
<td>1.52</td>
</tr>
</tbody>
</table>

### Separations for poisoning by analgesics (ICD9 code 965.4) with external code E950.0 (suicide and self-inflicted injury) by sex, age group and average length of stay

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Female</th>
<th></th>
<th></th>
<th>Male</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Separations</td>
<td>Bed Days</td>
<td>ALoS</td>
<td>Separations</td>
<td>Bed Days</td>
<td>ALoS</td>
</tr>
<tr>
<td>10-14</td>
<td>57</td>
<td>143</td>
<td>2.51</td>
<td>8</td>
<td>17</td>
<td>2.13</td>
</tr>
<tr>
<td>15-19</td>
<td>264</td>
<td>686</td>
<td>2.60</td>
<td>69</td>
<td>150</td>
<td>2.17</td>
</tr>
<tr>
<td>20-24</td>
<td>132</td>
<td>281</td>
<td>1.98</td>
<td>69</td>
<td>184</td>
<td>2.67</td>
</tr>
<tr>
<td>25-29</td>
<td>96</td>
<td>189</td>
<td>1.97</td>
<td>36</td>
<td>89</td>
<td>2.47</td>
</tr>
<tr>
<td>30-34</td>
<td>58</td>
<td>104</td>
<td>1.79</td>
<td>37</td>
<td>74</td>
<td>2.00</td>
</tr>
<tr>
<td>35-39</td>
<td>54</td>
<td>95</td>
<td>1.78</td>
<td>22</td>
<td>102</td>
<td>4.64</td>
</tr>
<tr>
<td>40-44</td>
<td>33</td>
<td>67</td>
<td>2.03</td>
<td>20</td>
<td>42</td>
<td>2.10</td>
</tr>
<tr>
<td>45-49</td>
<td>29</td>
<td>105</td>
<td>3.62</td>
<td>11</td>
<td>21</td>
<td>1.91</td>
</tr>
<tr>
<td>50-54</td>
<td>13</td>
<td>30</td>
<td>2.31</td>
<td>11</td>
<td>40</td>
<td>3.64</td>
</tr>
<tr>
<td>55-59</td>
<td>5</td>
<td>8</td>
<td>1.60</td>
<td>3</td>
<td>12</td>
<td>4.00</td>
</tr>
<tr>
<td>60-64</td>
<td>3</td>
<td>19</td>
<td>6.33</td>
<td>2</td>
<td>2</td>
<td>1.00</td>
</tr>
<tr>
<td>65-69</td>
<td>4</td>
<td>8</td>
<td>2.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70-74</td>
<td>1</td>
<td>13</td>
<td>13.00</td>
<td>1</td>
<td>30</td>
<td>30.00</td>
</tr>
<tr>
<td>75-79</td>
<td>1</td>
<td>3</td>
<td>3.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>80-84</td>
<td>2</td>
<td>7</td>
<td>3.50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;=85</td>
<td>2</td>
<td>6</td>
<td>3.00</td>
<td>1</td>
<td>12</td>
<td>12.00</td>
</tr>
<tr>
<td>Total</td>
<td>754</td>
<td>1744</td>
<td>2.31</td>
<td>290</td>
<td>775</td>
<td>2.67</td>
</tr>
</tbody>
</table>
### Separations for poisoning by analgesics (ICD9 code 965.4) with external code E850.4 (accidental poisoning) by sex, age group and average length of stay

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Female Separations</th>
<th>Female Bed Days</th>
<th>Female ALoS</th>
<th>Male Separations</th>
<th>Male Bed Days</th>
<th>Male ALoS</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>1</td>
<td>1</td>
<td>1.00</td>
<td>4</td>
<td>7</td>
<td>1.75</td>
</tr>
<tr>
<td>1-4</td>
<td>76</td>
<td>81</td>
<td>1.07</td>
<td>88</td>
<td>97</td>
<td>1.10</td>
</tr>
<tr>
<td>5-9</td>
<td>1</td>
<td>10</td>
<td>1.00</td>
<td>2</td>
<td>3</td>
<td>1.50</td>
</tr>
<tr>
<td>10-14</td>
<td>22</td>
<td>35</td>
<td>1.59</td>
<td>15</td>
<td>36</td>
<td>2.40</td>
</tr>
<tr>
<td>15-19</td>
<td>64</td>
<td>117</td>
<td>1.83</td>
<td>17</td>
<td>40</td>
<td>2.35</td>
</tr>
<tr>
<td>20-24</td>
<td>43</td>
<td>124</td>
<td>2.86</td>
<td>14</td>
<td>25</td>
<td>1.79</td>
</tr>
<tr>
<td>25-29</td>
<td>14</td>
<td>44</td>
<td>3.14</td>
<td>10</td>
<td>13</td>
<td>1.30</td>
</tr>
<tr>
<td>30-34</td>
<td>22</td>
<td>44</td>
<td>2.00</td>
<td>5</td>
<td>6</td>
<td>1.00</td>
</tr>
<tr>
<td>35-39</td>
<td>12</td>
<td>12</td>
<td>1.00</td>
<td>6</td>
<td>6</td>
<td>1.00</td>
</tr>
<tr>
<td>40-44</td>
<td>11</td>
<td>11</td>
<td>1.38</td>
<td>5</td>
<td>10</td>
<td>2.00</td>
</tr>
<tr>
<td>45-49</td>
<td>5</td>
<td>5</td>
<td>1.25</td>
<td>4</td>
<td>14</td>
<td>3.50</td>
</tr>
<tr>
<td>50-54</td>
<td>2</td>
<td>3</td>
<td>1.50</td>
<td>4</td>
<td>78</td>
<td>19.50</td>
</tr>
<tr>
<td>55-59</td>
<td>1</td>
<td>22</td>
<td>22.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60-64</td>
<td>1</td>
<td>1</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>65-74</td>
<td>1</td>
<td>4</td>
<td>4.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>=&gt;85</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>4</td>
<td>4.00</td>
</tr>
<tr>
<td>Total</td>
<td>272</td>
<td>514</td>
<td>1.89</td>
<td>170</td>
<td>333</td>
<td>1.96</td>
</tr>
</tbody>
</table>

### Separations for poisoning by analgesics (ICD9 code 965.4) with external code E950.0 (suicide and self-inflicted injury) by sex, age group and average length of stay

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Female Separations</th>
<th>Female Bed Days</th>
<th>Female ALoS</th>
<th>Male Separations</th>
<th>Male Bed Days</th>
<th>Male ALoS</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-14</td>
<td>39</td>
<td>105</td>
<td>2.69</td>
<td>8</td>
<td>43</td>
<td>5.38</td>
</tr>
<tr>
<td>15-19</td>
<td>184</td>
<td>465</td>
<td>2.69</td>
<td>36</td>
<td>65</td>
<td>1.81</td>
</tr>
<tr>
<td>20-24</td>
<td>96</td>
<td>281</td>
<td>2.93</td>
<td>51</td>
<td>122</td>
<td>2.39</td>
</tr>
<tr>
<td>25-29</td>
<td>79</td>
<td>193</td>
<td>2.44</td>
<td>28</td>
<td>49</td>
<td>1.75</td>
</tr>
<tr>
<td>30-34</td>
<td>62</td>
<td>190</td>
<td>3.06</td>
<td>17</td>
<td>26</td>
<td>1.53</td>
</tr>
<tr>
<td>35-39</td>
<td>32</td>
<td>52</td>
<td>1.63</td>
<td>17</td>
<td>50</td>
<td>2.94</td>
</tr>
<tr>
<td>40-44</td>
<td>31</td>
<td>69</td>
<td>3.19</td>
<td>22</td>
<td>45</td>
<td>2.05</td>
</tr>
<tr>
<td>45-49</td>
<td>10</td>
<td>62</td>
<td>6.20</td>
<td>10</td>
<td>31</td>
<td>3.10</td>
</tr>
<tr>
<td>50-54</td>
<td>10</td>
<td>16</td>
<td>1.60</td>
<td>7</td>
<td>12</td>
<td>1.71</td>
</tr>
<tr>
<td>55-59</td>
<td>1</td>
<td>1</td>
<td>1.00</td>
<td>2</td>
<td>2</td>
<td>1.00</td>
</tr>
<tr>
<td>60-64</td>
<td>1</td>
<td>4</td>
<td>4.00</td>
<td>1</td>
<td>1</td>
<td>1.00</td>
</tr>
<tr>
<td>65-69</td>
<td>3</td>
<td>71</td>
<td>23.87</td>
<td>2</td>
<td>13</td>
<td>6.50</td>
</tr>
<tr>
<td>70-74</td>
<td>4</td>
<td>6</td>
<td>1.50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>75-79</td>
<td>1</td>
<td>8</td>
<td>8.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>80-84</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>12</td>
<td>12.00</td>
</tr>
<tr>
<td>Total</td>
<td>563</td>
<td>1583</td>
<td>2.86</td>
<td>202</td>
<td>471</td>
<td>2.33</td>
</tr>
<tr>
<td>Age Group</td>
<td>Female Separations</td>
<td>Male Separations</td>
<td>Female Bed Days</td>
<td>Male Bed Days</td>
<td>Female ALoS</td>
<td>Male ALoS</td>
</tr>
<tr>
<td>-----------</td>
<td>--------------------</td>
<td>------------------</td>
<td>----------------</td>
<td>--------------</td>
<td>-------------</td>
<td>----------</td>
</tr>
<tr>
<td>&lt;1</td>
<td>2</td>
<td>2</td>
<td>1.00</td>
<td>2</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>1-4</td>
<td>54</td>
<td>60</td>
<td>1.11</td>
<td>84</td>
<td>85</td>
<td>1.01</td>
</tr>
<tr>
<td>6-9</td>
<td>1</td>
<td>4</td>
<td>4.00</td>
<td>2</td>
<td>2</td>
<td>1.00</td>
</tr>
<tr>
<td>10-14</td>
<td>15</td>
<td>34</td>
<td>2.27</td>
<td>4</td>
<td>10</td>
<td>2.50</td>
</tr>
<tr>
<td>15-18</td>
<td>56</td>
<td>99</td>
<td>1.77</td>
<td>19</td>
<td>45</td>
<td>2.37</td>
</tr>
<tr>
<td>20-24</td>
<td>32</td>
<td>45</td>
<td>1.41</td>
<td>23</td>
<td>33</td>
<td>1.43</td>
</tr>
<tr>
<td>25-29</td>
<td>20</td>
<td>29</td>
<td>1.45</td>
<td>9</td>
<td>11</td>
<td>1.22</td>
</tr>
<tr>
<td>30-34</td>
<td>14</td>
<td>25</td>
<td>1.86</td>
<td>8</td>
<td>14</td>
<td>1.75</td>
</tr>
<tr>
<td>35-39</td>
<td>12</td>
<td>22</td>
<td>1.83</td>
<td>17</td>
<td>29</td>
<td>1.71</td>
</tr>
<tr>
<td>40-44</td>
<td>10</td>
<td>18</td>
<td>1.80</td>
<td>8</td>
<td>12</td>
<td>1.50</td>
</tr>
<tr>
<td>45-49</td>
<td>5</td>
<td>6</td>
<td>1.20</td>
<td>8</td>
<td>10</td>
<td>5.00</td>
</tr>
<tr>
<td>50-54</td>
<td>2</td>
<td>2</td>
<td>1.00</td>
<td>4</td>
<td>9</td>
<td>2.25</td>
</tr>
<tr>
<td>55-59</td>
<td>1</td>
<td>1</td>
<td>1.00</td>
<td>2</td>
<td>7</td>
<td>3.50</td>
</tr>
<tr>
<td>60-64</td>
<td>1</td>
<td>1</td>
<td>1.00</td>
<td>1</td>
<td>2</td>
<td>2.00</td>
</tr>
<tr>
<td>70-74</td>
<td>1</td>
<td>1</td>
<td>1.00</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>75-79</td>
<td>1</td>
<td>1</td>
<td>1.00</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80-84</td>
<td>3</td>
<td>28</td>
<td>9.33</td>
<td>3</td>
<td>2</td>
<td>2.67</td>
</tr>
<tr>
<td>Unk</td>
<td>1</td>
<td>1</td>
<td>1.00</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>230</td>
<td>379</td>
<td>1.85</td>
<td>186</td>
<td>274</td>
<td>1.47</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Female Separations</th>
<th>Male Separations</th>
<th>Female Bed Days</th>
<th>Male Bed Days</th>
<th>Female ALoS</th>
<th>Male ALoS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-4</td>
<td>1</td>
<td>1</td>
<td>1.00</td>
<td>1</td>
<td>1</td>
<td>1.00</td>
</tr>
<tr>
<td>10-14</td>
<td>26</td>
<td>78</td>
<td>3.00</td>
<td>61</td>
<td>10</td>
<td>1.87</td>
</tr>
<tr>
<td>15-19</td>
<td>159</td>
<td>344</td>
<td>2.16</td>
<td>351</td>
<td>79</td>
<td>2.26</td>
</tr>
<tr>
<td>20-24</td>
<td>105</td>
<td>221</td>
<td>2.10</td>
<td>421</td>
<td>177</td>
<td>4.21</td>
</tr>
<tr>
<td>25-29</td>
<td>68</td>
<td>131</td>
<td>1.83</td>
<td>33</td>
<td>107</td>
<td>3.24</td>
</tr>
<tr>
<td>30-34</td>
<td>53</td>
<td>117</td>
<td>2.21</td>
<td>22</td>
<td>40</td>
<td>1.82</td>
</tr>
<tr>
<td>35-39</td>
<td>52</td>
<td>96</td>
<td>1.85</td>
<td>20</td>
<td>32</td>
<td>1.60</td>
</tr>
<tr>
<td>40-44</td>
<td>39</td>
<td>77</td>
<td>1.97</td>
<td>12</td>
<td>24</td>
<td>2.00</td>
</tr>
<tr>
<td>45-49</td>
<td>21</td>
<td>86</td>
<td>4.10</td>
<td>12</td>
<td>22</td>
<td>1.83</td>
</tr>
<tr>
<td>50-54</td>
<td>7</td>
<td>18</td>
<td>2.57</td>
<td>6</td>
<td>27</td>
<td>4.50</td>
</tr>
<tr>
<td>55-59</td>
<td>2</td>
<td>11</td>
<td>1.11</td>
<td>4</td>
<td>6</td>
<td>1.50</td>
</tr>
<tr>
<td>60-64</td>
<td>2</td>
<td>2</td>
<td>4.00</td>
<td>2</td>
<td>8</td>
<td>4.00</td>
</tr>
<tr>
<td>65-69</td>
<td>4</td>
<td>4</td>
<td>1.00</td>
<td>2</td>
<td>8</td>
<td>4.00</td>
</tr>
<tr>
<td>70-74</td>
<td>3</td>
<td>10</td>
<td>3.33</td>
<td>1</td>
<td>11</td>
<td>11.00</td>
</tr>
<tr>
<td>75-79</td>
<td>5</td>
<td>45</td>
<td>9.00</td>
<td>1</td>
<td>5</td>
<td>5.00</td>
</tr>
<tr>
<td>&gt;85</td>
<td>2</td>
<td>3</td>
<td>1.50</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>546</td>
<td>1241</td>
<td>2.27</td>
<td>199</td>
<td>557</td>
<td>2.80</td>
</tr>
</tbody>
</table>
## Separations for poisoning by analgesics (ICD9 code 965.4) with external code E850.4 (accidental poisoning) by sex, age group and average length of stay

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Separations</td>
<td>Bed Days</td>
</tr>
<tr>
<td>&lt;1</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>1-4</td>
<td>123</td>
<td>127</td>
</tr>
<tr>
<td>5-9</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>10-14</td>
<td>29</td>
<td>54</td>
</tr>
<tr>
<td>15-19</td>
<td>95</td>
<td>166</td>
</tr>
<tr>
<td>20-24</td>
<td>82</td>
<td>97</td>
</tr>
<tr>
<td>25-29</td>
<td>41</td>
<td>59</td>
</tr>
<tr>
<td>30-34</td>
<td>26</td>
<td>41</td>
</tr>
<tr>
<td>35-39</td>
<td>25</td>
<td>58</td>
</tr>
<tr>
<td>40-44</td>
<td>19</td>
<td>33</td>
</tr>
<tr>
<td>45-49</td>
<td>14</td>
<td>26</td>
</tr>
<tr>
<td>50-54</td>
<td>11</td>
<td>82</td>
</tr>
<tr>
<td>55-59</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td>60-64</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>65-69</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>70-74</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>75-79</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>80-84</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>&gt;=85</td>
<td>1</td>
<td>37</td>
</tr>
<tr>
<td>Unk</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>489</td>
<td>828</td>
</tr>
</tbody>
</table>

## Separations for poisoning by analgesics (ICD9 code 965.4) with external code E950.0 (suicide and self-inflicted injury) by sex, age group and average length of stay

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Separations</td>
<td>Bed Days</td>
</tr>
<tr>
<td>1-4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>5-9</td>
<td>68</td>
<td>207</td>
</tr>
<tr>
<td>10-14</td>
<td>267</td>
<td>610</td>
</tr>
<tr>
<td>15-19</td>
<td>187</td>
<td>379</td>
</tr>
<tr>
<td>20-24</td>
<td>110</td>
<td>206</td>
</tr>
<tr>
<td>25-29</td>
<td>88</td>
<td>220</td>
</tr>
<tr>
<td>30-34</td>
<td>75</td>
<td>228</td>
</tr>
<tr>
<td>35-39</td>
<td>71</td>
<td>142</td>
</tr>
<tr>
<td>40-44</td>
<td>42</td>
<td>88</td>
</tr>
<tr>
<td>45-49</td>
<td>12</td>
<td>31</td>
</tr>
<tr>
<td>50-54</td>
<td>10</td>
<td>39</td>
</tr>
<tr>
<td>55-59</td>
<td>5</td>
<td>26</td>
</tr>
<tr>
<td>60-64</td>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td>65-69</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>70-74</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>75-79</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>&gt;=85</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>944</td>
<td>2229</td>
</tr>
</tbody>
</table>
### Separations for poisoning by analgesics (ICD9 code 965.4) with external code E850.4 (accidental poisoning) by sex, age group and average length of stay

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Female Separations</th>
<th>Female Bed Days</th>
<th>Female ALoS</th>
<th>Male Separations</th>
<th>Male Bed Days</th>
<th>Male ALoS</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>10</td>
<td>10</td>
<td>1.03</td>
<td>10</td>
<td>13</td>
<td>1.30</td>
</tr>
<tr>
<td>1-4</td>
<td>103</td>
<td>106</td>
<td>1.03</td>
<td>126</td>
<td>136</td>
<td>1.08</td>
</tr>
<tr>
<td>6-9</td>
<td>2</td>
<td>2</td>
<td>1.00</td>
<td>4</td>
<td>6</td>
<td>1.50</td>
</tr>
<tr>
<td>10-14</td>
<td>16</td>
<td>30</td>
<td>1.88</td>
<td>3</td>
<td>5</td>
<td>1.67</td>
</tr>
<tr>
<td>15-19</td>
<td>100</td>
<td>187</td>
<td>1.87</td>
<td>21</td>
<td>25</td>
<td>1.19</td>
</tr>
<tr>
<td>20-24</td>
<td>63</td>
<td>94</td>
<td>1.49</td>
<td>20</td>
<td>32</td>
<td>1.60</td>
</tr>
<tr>
<td>25-29</td>
<td>41</td>
<td>72</td>
<td>1.76</td>
<td>23</td>
<td>32</td>
<td>1.39</td>
</tr>
<tr>
<td>30-34</td>
<td>26</td>
<td>42</td>
<td>1.62</td>
<td>6</td>
<td>10</td>
<td>1.67</td>
</tr>
<tr>
<td>35-39</td>
<td>16</td>
<td>48</td>
<td>3.00</td>
<td>6</td>
<td>23</td>
<td>3.83</td>
</tr>
<tr>
<td>40-44</td>
<td>22</td>
<td>56</td>
<td>2.55</td>
<td>10</td>
<td>24</td>
<td>2.40</td>
</tr>
<tr>
<td>45-49</td>
<td>9</td>
<td>29</td>
<td>3.22</td>
<td>12</td>
<td>28</td>
<td>2.33</td>
</tr>
<tr>
<td>50-54</td>
<td>8</td>
<td>16</td>
<td>2.00</td>
<td>3</td>
<td>5</td>
<td>1.67</td>
</tr>
<tr>
<td>55-59</td>
<td>1</td>
<td>1</td>
<td>1.00</td>
<td>1</td>
<td>4</td>
<td>4.00</td>
</tr>
<tr>
<td>60-64</td>
<td>2</td>
<td>2</td>
<td>1.00</td>
<td>1</td>
<td>1</td>
<td>1.00</td>
</tr>
<tr>
<td>65-69</td>
<td>1</td>
<td>1</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70-74</td>
<td></td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1.00</td>
</tr>
<tr>
<td>75-79</td>
<td>2</td>
<td>4</td>
<td>2.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>80-84</td>
<td>1</td>
<td>4</td>
<td>4.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;85</td>
<td>1</td>
<td>2</td>
<td>2.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>414</td>
<td>696</td>
<td>1.68</td>
<td>247</td>
<td>345</td>
<td>1.40</td>
</tr>
</tbody>
</table>

### Separations for poisoning by analgesics (ICD9 code 965.4) with external code E950.0 (suicide and self-inflicted injury) by sex, age group and average length of stay

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Female Separations</th>
<th>Female Bed Days</th>
<th>Female ALoS</th>
<th>Male Separations</th>
<th>Male Bed Days</th>
<th>Male ALoS</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-14</td>
<td>78</td>
<td>229</td>
<td>2.94</td>
<td>7</td>
<td>50</td>
<td>7.14</td>
</tr>
<tr>
<td>15-19</td>
<td>262</td>
<td>737</td>
<td>2.81</td>
<td>66</td>
<td>128</td>
<td>1.94</td>
</tr>
<tr>
<td>20-24</td>
<td>160</td>
<td>347</td>
<td>2.17</td>
<td>71</td>
<td>133</td>
<td>1.87</td>
</tr>
<tr>
<td>25-29</td>
<td>118</td>
<td>206</td>
<td>1.75</td>
<td>48</td>
<td>89</td>
<td>1.85</td>
</tr>
<tr>
<td>30-34</td>
<td>90</td>
<td>288</td>
<td>3.20</td>
<td>48</td>
<td>123</td>
<td>2.56</td>
</tr>
<tr>
<td>35-39</td>
<td>79</td>
<td>201</td>
<td>2.54</td>
<td>43</td>
<td>93</td>
<td>2.16</td>
</tr>
<tr>
<td>40-44</td>
<td>83</td>
<td>205</td>
<td>2.47</td>
<td>18</td>
<td>42</td>
<td>2.33</td>
</tr>
<tr>
<td>45-49</td>
<td>34</td>
<td>85</td>
<td>2.50</td>
<td>17</td>
<td>78</td>
<td>4.59</td>
</tr>
<tr>
<td>50-54</td>
<td>23</td>
<td>66</td>
<td>2.87</td>
<td>15</td>
<td>94</td>
<td>6.27</td>
</tr>
<tr>
<td>55-59</td>
<td>7</td>
<td>37</td>
<td>5.29</td>
<td>7</td>
<td>38</td>
<td>5.43</td>
</tr>
<tr>
<td>60-64</td>
<td>4</td>
<td>9</td>
<td>2.25</td>
<td>4</td>
<td>23</td>
<td>5.75</td>
</tr>
<tr>
<td>65-69</td>
<td></td>
<td>5</td>
<td>2.00</td>
<td>21</td>
<td>40</td>
<td>4.20</td>
</tr>
<tr>
<td>70-74</td>
<td></td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1.00</td>
</tr>
<tr>
<td>75-79</td>
<td>2</td>
<td>7</td>
<td>3.50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>80-84</td>
<td>1</td>
<td>10</td>
<td>10.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;85</td>
<td>2</td>
<td>9</td>
<td>4.50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>940</td>
<td>2417</td>
<td>2.57</td>
<td>353</td>
<td>832</td>
<td>2.64</td>
</tr>
</tbody>
</table>
Appendix 3 - AMERICAN WARNING/CAUTION STATEMENTS

Paracetamol Tablets 500mg, container of 60 tablets fitted with a child-resistant closure

**WARNINGS:** Do not take this product for pain for more than 10 days or for fever for more than 3 days unless directed by a doctor. If pain or fever persists or gets worse, if new symptoms occur, or if redness or swelling is present, consult a doctor because these could be signs of a serious condition. As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product. Keep this and all drugs out of the reach of children. In case of accidental overdose, seek professional assistance or contact a poison control center immediately. Prompt medical attention is critical for adults as well as for children even if you do not notice any signs or symptoms.

Alcohol warning. If you drink three or more alcoholic beverages daily, you should ask your doctor whether you should take [product name] or other pain relievers. [Product name] may increase your risk of liver damage.

[Note: the alcohol warning label has been added in expectation of the FDA directive].
Paracetamol Drops 80mg/0.8mL, container of 15mL with child-resistant closure

WARNING: Sealed with printed bottle wrap for your protection. Keep this and all medication out of the reach of children. In case of accidental overdosage, contact a physician or poison control center immediately. Consult your physician if fever persists for more than 3 days or if pain continues for more than 5 days. Do not use with other products containing acetaminophen.
Aspirin tablets 325mg, container of 25 tablets fitted with a child-resistant closure

WARNINGS: Children and teenagers should not use this medicine for chicken pox or flu symptoms before a doctor is consulted about Reye Syndrome, a rare serious illness reported to be associated with aspirin. Do not take for more than 10 days or for fever for more than 3 days unless directed by a doctor.

If pain or fever persists or gets worse, if new symptoms occur or if redness or swelling is present, consult a doctor because these could be signs of a serious condition. Do not take this product if you are allergic to aspirin, have asthma, have stomach problems (such as heartburn, upset stomach or stomach pain) that persist or recur, gastric ulcers or bleeding problems unless directions by a doctor.

Keep this and all drugs out of reach of children. If ringing the ears or loss of hearing occurs, consult a doctor before taking anymore of this product. In case of accidental overdose, seek professional assistance or contact a poison control center immediately.
As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product.

IT IS ESPECIALLY IMPORTANT NOT TO USE ASPIRIN DURING THE LAST 3 MONTHS OF PREGNANCY UNLESS SPECIFICALLY DIRECTED TO DO SO BY A DOCTOR BECAUSE IT MAY CAUSE PROBLEMS IN THE UNBORN CHILD OR COMPLICATIONS DURING DELIVERY.

DRUG INTERACTION PRECAUTION: Do not take this product if you are taking a prescription drug for anticoagulation (thinning the blood), diabetes, gout or arthritis unless directed by a doctor.

Alcohol warning: If you drink three or more alcoholic beverages daily, ask your doctor whether you should take [product name] or other pain relievers. [Product name] may increase your risk of stomach bleeding.

[note: the alcohol warning label has been added in expectation of the FDA directive].
Ibuprofen tablets 200mg, container of 50 tablets fitted with a child-resistant closure

WARNING: ASPIRIN SENSITIVE PATIENTS, DO NOT TAKE THIS PRODUCT IF YOU HAVE HAD A SEVERE ALLERGIC REACTION TO ASPIRIN, E.G. ASTHMA, SWELLING, SHOCK OR HIVES, BECAUSE EVEN THOUGH THIS PRODUCT CONTAINS NO ASPIRIN OR SALICYLATES, CROSS-REACTIONS MAY OCCUR IN PATIENTS ALLERGIC TO ASPIRIN.

WARNINGS: Do not take for pain for more than 10 days or for fever for more than 3 days unless directed by a doctor.

If pain or fever persists or gets worse, if new symptoms occur, or if the painful area is red or swollen, consult a doctor. These could be signs of serious illness. If you are under a doctor’s care for any serious conditions, consult a doctor before taking this product. As with aspirin and acetaminophen, if you have any condition which requires you to take prescriptions drugs or if you have had any problems or serious side-effects from taking any non-prescription pain reliever do not take IBUPROFEN TABLETS without first discussing it with your doctor. If you experience any symptoms which are unusual or seem unrelated to the condition for which you took Ibuprofen, consult a doctor before taking any more of it. Although Ibuprofen is indicated for the same conditions as aspirin or acetaminophen, it should not be taken with them except under a doctor’s direction. Do not combine this product with any other Ibuprofen-containing product. As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product. IT IS ESPECIALLY IMPORTANT NOT TO USE IBUPROFEN DURING THE LAST 3 MONTHS OF PREGNANCY UNLESS SPECIFICALLY DIRECTED TO DO SO BY A DOCTOR BECAUSE IT MAY CAUSE PROBLEMS IN THE UNBORN CHILD OR COMPLICATIONS DURING DELIVERY. Keep this and all drugs out of the reach of children. In case of accidental overdose, seek professional assistance or contact a poison control center immediately.

Alcohol warning: If you drink three or more alcoholic beverages daily, ask your doctor whether you should take [product name] or other pain relievers. [Product name] may increase your risk of stomach bleeding.

[note: the alcohol warning label has been added in expectation of the FDA directive].
Appendix 4 - SUGGESTED CONTENT OF GUIDELINE FOR PARACETAMOL

Paracetamol

Indications

Sponsors may use any or all of the representative indications set out below (or similar) as appropriate to a particular product without the need to supply supporting efficacy data, subject to does and dosing frequency being satisfactory.

For the temporary relief of pain [and discomfort] associated with: headache, migraine, toothache, dental procedures, backache, muscular aches, arthritis, rheumatics, menstruation, sore throat, and symptoms of cold and flu. Reduces fever.

For childrens’ formulations, teething, earache and immunisation may be added to any of the above, as appropriate to the age group.

Sponsors may propose any other indication but may be requested to supply supporting efficacy and safety data.

As fever is a normal and beneficial response to infection, no elaboration to the words “reduces fever” will be accepted except in the context of limits to the duration of treatment.

Mandatory warning statements

The Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP) should be consulted for the content of mandatory warning statements for paracetamol.

Dose

Adult dose recommendations in single active ingredient products:

- 500 to 1000mg every four to six hours as required. Dosage should not exceed 4g per day (expressed on the label as number of units eg tablets).

Adult dosage recommendations in products containing additional active ingredients:

- Due to lack of flexibility when dosing with such products and because the majority of patients require more than 500mg of paracetamol for effective analgesia, products should be formulated so that doses of other ingredients are at safe and effective levels when at least 600mg of paracetamol is taken.

Paediatric dosage recommendations, 7 to 12 years:

- 250 to 500mg every four to six hours as required, not exceeding 2g per day.
Paediatric dosage recommendations, 1 month to 6 years, based on 15mg/kg:

<table>
<thead>
<tr>
<th>Age</th>
<th>Average body weight (kg)</th>
<th>Single dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - 3 months</td>
<td>4.1 - 5.7</td>
<td>61 - 85</td>
</tr>
<tr>
<td>3 - 6 months</td>
<td>5.7 - 7.6</td>
<td>85 - 114</td>
</tr>
<tr>
<td>6 - 12 months</td>
<td>7.6 - 9.9</td>
<td>114 - 148</td>
</tr>
<tr>
<td>1 - 2 years</td>
<td>9.9 - 12.1</td>
<td>148 - 181</td>
</tr>
<tr>
<td>2 - 4 years</td>
<td>12.1 - 16.3</td>
<td>181 - 244</td>
</tr>
<tr>
<td>4 - 6 years</td>
<td>16.3 - 20.1</td>
<td>244 - 301</td>
</tr>
</tbody>
</table>

Doses should be given every four to six hours as required with not more than four doses in 24 hours. The medicine should not be administered for more than 48 hours without seeking medical advice. Statements to these effects must appear on labels of the primary pack and the immediate container.

The total **daily** dose should not exceed 90mg/kg

The recommended dose should be able to be measured using commonly available metric measuring devices. There may be instances where the dose needs to be slightly different than the recommended milligram dose given above, having regard to the paracetamol concentration of the product.
Appendix 5 - SUGGESTED CONTENT OF GUIDELINE FOR ASPIRIN

Aspirin

Indications

Sponsors may use any or all of the representative indications set out below (or similar) as appropriate to a particular product without the need to supply supporting efficacy data, subject to does and dosing frequency being satisfactory.

    For the temporary relief of pain [and discomfort] associated with: headache, migraine, toothache, dental procedures, backache, muscular aches, arthritis, rheumatics, menstruation, sore throat, and symptoms of cold and flu. Reduces fever.

Sponsors may propose any other indication but may be requested to supply supporting efficacy and safety data.

As fever is a normal and beneficial response to infection, no elaboration to the words “reduces fever” will be accepted except in the context of limits to the duration of treatment.

Mandatory warning statements

The Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP) should be consulted for the content of mandatory warning statements for aspirin.

Dose

Adult dosage recommendations:

- 300 to 1000mg every four hours as required. Dosage should not exceed 4g per day (expressed on the label as the number of units eg tablets) for not more than 10 days.

Paediatric dosage recommendations:

- Specific doses should not be stated. Any reference to children under the dosage section on the label should state: “On medical advice”.
REFERENCES AND FURTHER READING

Aldred JE. Registration of medicines. Individual assessment or monographs? Aust Pharmacist 1988;7:8-10
Anon (a) Which? calls for paracetamol plus methionine to be more readily available. Pharm J 1994;252:562
Anon (b) Pack size and labelling changes for paracetamol and aspirin products. Pharm J 1997;259:317
Anon (c). Aspirin and paracetamol to be controlled through POM Order. Pharm J 1997;259:394
Barker JD, de Carle DJ, Anuras S. Chronic excessive acetaminophen use and liver damage. Ann Int Med 1977;87:299-301
Berlin C. In: Pediatric OTCs overlapping age directions not inherent problem. F-D-C Reports 1997;5:3
Casteels-Van Daele M. Reduction of deaths after drug labelling for risk of Reye’s syndrome. Lancet 1993;341:118-9
Chan TY. The epidemiology of acetaminophen (paracetamol) poisoning in Hong Kong. Vet Hum Toxicol 1996;38:443-4
Coleman DL. Society’s analgesic advice wrong. Pharm J 1997;259:369
Dean BS, Bricker JD, Krenzok EP. Outpatient N-acetylcysteine treatment for acetaminophen poisoning: an ethical dilemma or a new financial mandate? Vet Hum Toxicol 1996;38:222-4


Frank OR, Coulthard KP. Paracetamol for fever. *Aust Family Physician* 1988;17:771


Gunnell D, Hawton K, Murray V et al. Use of paracetamol for suicide and non-fatal poisoning in the UK and France: are restrictions on availability justified? *J Epidemiol Community Health* 1997;51:175-9


Hobson SJ. Availability of paracetamol. *Pharm J* 1997;259:645

Johnson MW, Friedman PA, Mitch WE. Alcoholism, nonprescription drugs and hepatotoxicity; the risk from unknown acetaminophen ingestion. Am J Gastroenterol 1981;76:530-3
Jones AL, Hayes PC, Proudfoot AT et al, Krenzelok EP. Should methionine be added to every paracetamol tablet? BMJ 1997;315:301-4
Jonville AP, Autret E, Majzoub S et al. [Epidemiology of pediatric paracetamol poisoning(retrospective analysis of calls received by the poison control centre of Tours)]. J Toxicol Clin Exp 1990;10:21-5
Kumar S, Rex DK. Failure of physicians to recognize acetaminophen toxicity in alcoholics. Arch Intern Med 1991;151:1189-91
LaBrecque DR, Mitros FA. Increased hepatotoxicity of acetaminophen in the alcoholic. Gastroenterology 1980;78:1310 [abstract]
Lee WM. The selling of acetaminophen. Gastroenterology 1995;109:2043-4
Lilley B, Hender E. Concerned about paracetamol overdose information. Aust Pharmacist 1997;16:110-1
O’Connell S. Proposals will have negative effects. *BMJ* 1997;314:751
O’Dell JR, Zetterman RK, Burnett DA. Centrilobular hepatic necrosis following acetaminophen-induced hepatic necrosis in an alcoholic. *JAMA* 1986;255:2636-7
Pounder DJ, McAllister P. Paracetamol is wrongly blamed. *BMJ* 1997;314:751
Rivera-Penera T, Gugig R, Davis J et al. Outcome of acetaminophen overdose in pediatric patients and factors contributing to hepatotoxicity. *J Pediatr* 1997;130:300-4
Shann F. Antipyretics in severe sepsis. Lancet 1995;345:338
Shindell S. Reduction of deaths after drug labelling for risk of Reye’s syndrome. Lancet 1993;341:119
Spender Q. Methionine should be included in all paracetamol preparations. BMJ 1997;314:751
Spooner JB, Harvey JG. Paracetamol overdosage - facts not misconceptions. Pharm J 1993;250:706-7
Strom BL. Editorial. Adverse reactions to over-the-counter analgesics taken for therapeutic purposes. JAMA 1994;272:1866-7
Thomas JD. Unlawful sales. Pharm J 1993;251:436
Taylor SJ. Provide hurdles to overdosing. BMJ 1997;314:750-1
Whitcomb DC, Block GD. Association of acetaminophen hepatotoxicity with fasting and ethanol use. JAMA 1994;272:1845-50
Whyte IM, Dawson AH, Clancy CM. Over the counter analgesic compounds. Personal communication, 1998