Medicines Evaluation Committee

Review of Non-prescription Analgesics

An update

April 2003
Medicines Evaluation Committee

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Prepared for the Medicines Evaluation Committee by David B Newgreen
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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>AGRD Volume 2</td>
<td>Australian Guidelines for the Registration of Drugs, Volume 2</td>
</tr>
<tr>
<td>APAP</td>
<td>N-acetyl-p-aminophenol; paracetamol</td>
</tr>
<tr>
<td>APF</td>
<td>Australian Pharmaceutical Formulary and Handbook</td>
</tr>
<tr>
<td>ARTG</td>
<td>Australian Register of Therapeutic Goods</td>
</tr>
<tr>
<td>CFS</td>
<td>Coroner’s Facilitation System</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration (of the United States of America)</td>
</tr>
<tr>
<td>NAC</td>
<td>N-acetylcysteine</td>
</tr>
<tr>
<td>NAPQI</td>
<td>N-acetyl-p-benzoquinoneimine</td>
</tr>
<tr>
<td>NDPSC</td>
<td>National Drugs and Poisons Schedule Committee</td>
</tr>
<tr>
<td>NSAID</td>
<td>Non-steroidal anti-inflammatory drug</td>
</tr>
<tr>
<td>PBS</td>
<td>Pharmaceutical Benefits Scheme</td>
</tr>
<tr>
<td>RCH</td>
<td>Royal Children’s Hospital (Melbourne)</td>
</tr>
<tr>
<td>Review</td>
<td>Review of Non-Prescription Analgesics</td>
</tr>
<tr>
<td>S2</td>
<td>Schedule 2, Pharmacy Medicine</td>
</tr>
<tr>
<td>S3</td>
<td>Schedule 3, Pharmacist Only Medicine</td>
</tr>
<tr>
<td>S4</td>
<td>Schedule 4, Prescription Only Medicine</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>Update</td>
<td>Review of Non-Prescription Analgesics, An Update</td>
</tr>
<tr>
<td>VAED</td>
<td>Victorian Accident and Emergency Dataset</td>
</tr>
<tr>
<td>VEMD</td>
<td>Victorian Emergency Minimum Dataset</td>
</tr>
<tr>
<td>VIMD</td>
<td>Victorian Minimum Dataset</td>
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ACKNOWLEDGMENTS

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TERMS OF REFERENCE FOR THE UPDATE OF THE REVIEW OF NON-PRESCRIPTION ANALGESICS

1. Extend the data obtained in the Review of Non-prescription Analgesics to determine the current extent of the problem in Australia with respect to the incidence of hepatotoxicity and liver transplants following paracetamol overdose and in particular whether there is reliable evidence that liver toxicity occurs in some individuals within or close to recommended therapeutic dosage regimens.

2. Obtain data on ibuprofen overdoses and inappropriate dosing in children.

3. Consider the current situation with regard to analgesics with a view to updating the Review of Non-prescription Analgesics particularly in the areas of children’s doses and labelling requirements for paracetamol and ibuprofen.

4. Consider the US mandatory label statement for paracetamol “ALCOHOL WARNING: If you consume more than 3 alcoholic drinks every day, ask your doctor whether you should take acetaminophen or other pain relievers/fever reducers. Acetaminophen may cause liver damage” in the light of any information that has become available since 1998.

5. Consider the US mandatory label statement for aspirin and other NSAIDs “If you consume 3 or more alcoholic drinks every day, ask your doctor whether you should take [name of NSAID] or other pain relievers/fever reducers. [Name of NSAID] may cause stomach bleeding”.

6. Consider the UK mandatory warning statement “Immediate advice should be sought in the event of an overdose, even if you (your child) feel well, because of the risk of delayed, serious liver damage”.

7. Consider the additional UK mandatory warning statement “Do not take with other paracetamol-containing products”.

8. Consult with stakeholders and professional persons or bodies as necessary following agreement with the OTC Medicines Section.

9. Make recommendations to the TGA and MEC on the above.

10. Return all documentation to the TGA on completion of the project.

11. Other issues following agreement with the OTC Medicines Section.

The TGA’s OTC Medicines Section will arrange all literature searches through the TGA Library.
SUMMARY

International concern about the effects of overdose with paracetamol continues unabated. Indeed, the literature on the subject continues to expand rapidly. In Australia, admissions to hospitals for poisoning have risen and paracetamol continues to be a leading agent. Most admissions are the result of deliberate self-poisoning rather than overdosing because of ignorance, or due to accidental consumption by children. Numbers of liver transplants and deaths from paracetamol poisoning continue to be exceedingly low in Australia when compared with the number of people who use the drug safely and suitably. But there is no cause for complacency. Paracetamol is a drug and as such has unwanted effects even though these are not usually experienced when it is used in the recommended manner. The public and general retailers must see paracetamol and other medicines accordingly, not to be “enterprised, nor taken in hand, unadvisedly, lightly, or wantonly” as if they were ordinary items of commerce.

The Update has considered the legislative changes in the United Kingdom and the studies published since the law was changed. The Update believes there should be a statement that medical advice must be promptly obtained after an overdose and secondly, that the symptoms of liver damage are delayed. The delayed effect is unusual in medicines that are readily available. The public should be so informed in clear but not alarmist terms. The Update has not, however, proposed further restrictions on the sale of paracetamol.

On the question of paracetamol use by chronic alcohol users, the Update recommends against the adoption of the warning that is mandatory in the United States. The data are not strong enough and there would be complications arising from people substituting other analgesics which are likely to give greater problems when used with alcohol, even though the effects are not especially marked in non-prescription analgesics. In a sense, the existence of paracetamol probably offers a protective effect if an alcohol drinker uses it instead of aspirin and the NSAIDs. While there is a somewhat stronger case, for different reasons, for an alcohol warning for aspirin and the NSAIDs, the Update does not believe, on the available data, that such a recommendation is warranted.

While each of the three main non-prescription analgesics – paracetamol, aspirin and ibuprofen – can be considered individually, the controls on them must not be seen in isolation. Restrictions on one will result in substitution with another and the advantages and disadvantages of the substitution must be contemplated by public health authorities.

The Therapeutic Goods Administration asked the Update to consider several issues about ibuprofen in children. Few problems have been uncovered in connection with overdose. Nonetheless, there are circumstances when it should not be used or at least used with particular caution and paracetamol, provided it is taken strictly in accordance with the directions, remains the first line of treatment in Australia for the approved indications.

In October 2002, the Medicines Control Agency of the United Kingdom proposed a revision of the labelling of aspirin that would exclude directions for use in children.
under 16 years of age. The Update saw the practicality of the British proposal and has recommended it for consideration in Australia, notwithstanding that there are some deficiencies in the argument.

The Review of Non-Prescription Analgesics of 1998 made a number of recommendations about education, especially of health professionals. These are repeated.

This report was first issued as a ‘draft for comment’ in February 2003. The report was reconsidered by the Medicines Evaluation Committee on 3 April 2003 and recommendations 1, 4 and 11 amended in the light of comments that had been received. A summary of comments is included as Appendix 4 (Page 67).

April 2003
RECOMMENDATIONS

Recommendation 1

Recommendation 1 was deleted following consideration of comments from stakeholders at the Medicines Evaluation Committee meeting on 3 April 2003.

Recommendation 2

In the event that additional strengths of ibuprofen oral liquids are marketed, the Australian Pharmaceutical Advisory Council, through the respective professional bodies, remind pharmacists and their staff, medical practitioners, nurses and health centre sisters that there is more than one strength of ibuprofen oral liquids and ensure that purchasers are made aware of the dose.

Recommendation 3

No change to the present guidelines on the use of paracetamol in children in relation to dose in mg/kg, maximum dose per day (not exceeding 2,400mg, unless on medical advice), frequency and duration.

Recommendation 4

The TGA, in consultation with stakeholders, initiate a campaign to educate consumers and health professionals on the safe use of analgesics in general and paracetamol in particular.

Recommendation 5

The American warning label about paracetamol and alcohol should not be adopted in Australia.

Recommendation 6

Recommendations 4.1 and 4.2 of the Review be implemented. These Recommendations were:

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 users.

4.2 In the course of their detailing to medical practitioners and pharmacists, sponsors’ representatives mention that paracetamol dosages and the duration of treatment may need modification if the patient is a moderate to heavy habitual alcohol drinker.
Recommendation 7

The American warning label about aspirin, the NSAIDs and alcohol should not be adopted in Australia.

Recommendation 8

The editor of the Australian Prescriber be requested to arrange for, and publish, a review article about the relationship between aspirin and the NSAIDs and the consumption of alcohol and gastric bleeding.

Recommendation 9

The Medicines Evaluation Committee and the National Drugs and Poisons Schedule Committee consider the inclusion of: (i) a statement such as “Immediate advice should be sought in the event of an overdose, even if you (your child) feel(s) well, because of the risk of delayed, serious liver damage”; followed by (ii) the telephone number of the national poisons information centre; on all primary packs and immediate containers of medicines that contain paracetamol.

Recommendation 10

The Medicines Evaluation Committee and the National Drugs and Poisons Schedule Committee consider the inclusion of the statement: “Do not take with other paracetamol-containing products, unless advised by your doctor or pharmacist” on all primary packs and immediate containers of medicines that contain paracetamol.

Recommendation 11

SUSDP warning Statements Nos. 34 and 35 should be abbreviated while retaining the essential messages that consumers should keep to the recommended dose and not take analgesics for more than a few days at a time without medical advice.

Recommendation 12

Pharmacy organisations remind pharmacists: (i) of the mention in the Australian Pharmaceutical Formulary and Handbook 18th edition about cautionary and advisory label No.19; and (ii) to ensure that pharmacy assistants routinely advise purchasers of “cold and flu” products that contain paracetamol not to take additional paracetamol.

Recommendation 13

The National Drugs and Poisons Schedule Committee be again asked to consider updating and rationalising the cautionary and advisory statements applicable to non-prescription medicines that contain aspirin or the NSAIDs, as mentioned in the Review, and having regard to the recent action in the United Kingdom.
INTRODUCTION

The 1998 Review

In 1997, the Therapeutic Goods Administration commissioned the preparation of a Review of Non-Prescription Analgesics (“the Review”). A major stimulus for the Review was the availability of different strengths and pack sizes of paediatric liquid formulations of paracetamol and the confusion in dosing that arose from them. Other reasons for the Review were to do with the proliferation of warning labels (especially on aspirin), and accidental and deliberate self-poisoning with paracetamol.

The Review was completed in February 1998 and made a number of recommendations, some related to labelling, some to children’s dosage and others to information to health professionals and consumers. Arising from the Review, industry moved quickly to implement the dosing and non-statutory labelling requirements.

Coincidental to and concurrent with the Review, major legislative changes were signalled in the United Kingdom where paracetamol had figured in many cases of deliberate self-poisoning. At the same time, the Food and Drug Administration of the United States of America introduced a mandatory warning statement on the combined use of analgesics and alcohol. The Review recommended that Australian authorities review these initiatives after they had been in operation for a year. The Review did not recommend, at the time, any specific overdose labels in connection with paracetamol pending more information. It did, however, call for improvements in the way in which warning statements were presented for aspirin because of the multiplicity of warning statements and their various sources.

The 2002 Update

At its meeting on 14 March 2002, the Medicines Evaluation Committee requested the Therapeutic Goods Administration to prepare an update (“the Update”) of the 1998 Review. The reasons for the Update arose from:

- recommendations from the 1998 Review (including consideration of the British and American actions);
- concern about paracetamol toxicity in unremarkable doses (with special reference to a coronial enquiry in New South Wales and two papers in the Medical Journal of Australia 1999; 171:472-475, 497 on paracetamol toxicity in children);
- media attention given to the above;
- the need to obtain more Australian data; and
- the large volume of recent literature, especially on paracetamol.

During the course of the Update, the Food and Drug Administration of the United States of America held a hearing in Washington DC on 19 and 20 September 2002 on non-prescription analgesics. The proceedings of the hearings have been considered. In October 2002, the Medicines Control Agency of the United Kingdom indicated that it
proposed to amend the labelling of aspirin inasmuch as it related to the warning about Reye’s Syndrome. This has been taken into account.

Because this document is an Update to the Review, frequent reference is made to the Review itself. There are therefore relatively few reference citations to the literature in the Update that had already been mentioned in the Review.

The international picture

As mentioned above, the volume of recent literature on paracetamol is staggering, given the age of the drug. There are masses of data from all around the world about telephone calls to poisons information centres, presentations to hospitals, admissions, and on morbidity and mortality. The Washington DC hearings attest to this issue. Sifting through the data has been difficult not only because of the quantity, but also because of cultural differences, prevailing laws and outcomes in cases of poisoning between the various jurisdictions. Schiødt et al (1999) have also commented on the divergence of findings between several countries. It was interesting to note that some of the surveys and studies were supported by manufacturers and a number of authors were consultants to the industry.

One review compared the use of paracetamol in deliberate self-poisoning and availability among many countries (Gunnell et al, 2000). Accessibility was classified thus:

1. Unrestricted purchase (eg Canada, USA).
2. Pharmacy-only in unrestricted quantities but small pack sizes from general retailers (eg Australia, New Zealand and formerly the UK).
3. Pharmacy only in limited pack sizes and small pack sizes from general retailers (UK and Ireland).
4. Pharmacy-only in unrestricted quantities (eg Denmark).
5. Pharmacy-only but with limits on pack size (eg, Belgium, Finland, France, Germany, Sweden and Switzerland).

What emerges is that it is not always appropriate to apply the legal requirements of one country to another. Even within one country, patterns of misuse may not be uniform. For example, despite the relatively strict regime in Sweden, there are more problems in the south of the country where the paracetamol-related suicide rates between 1987 and 1990 were similar to those of England and Wales. In the United Kingdom, problems seem to be more pronounced in the north.

In the same paper, the authors tabulated the advantages and disadvantages of the various proposals intended to reduce the number of presentations and admissions, liver transplants and fatalities. There are no easy solutions. For every initiative, there are counter arguments.

Many aspects of paracetamol use such as label content, its combination with alcohol and distribution laws therefore remain controversial. The present dilemma with paracetamol has been summed up in the boxed text (below).
While the information from other countries is interesting, Australia must look at the actual state of affairs within its borders as it finds it; namely that there are very few deaths and liver transplants in the face of large quantities of paracetamol purchased by the public with and without prescription. Nor should it be forgotten that paracetamol is a drug and as such, there is a risk in taking it, especially in doses beyond those stated on the label. It is, in most presentations, a scheduled poison within the meaning of State laws and to expect no mishaps when it is used contrary to the label is unrealistic. Life is not risk-free. Governments, the manufacturing industry and the professions all have responsibilities. And so do consumers. Provided they are given right and relevant information, consumers have a responsibility for:

- reading the labels and following the instructions;
- asking their doctors and pharmacists for further information; and
- storing the medicine safely.

Any public education campaigns should include these three simple messages. These could be augmented by posters in pharmacies and child health centres. For example, the Royal Children’s Hospital produced an in-house poster called “Paracetamol & your child...ask your pharmacist”. The theme of the poster was “...but which strength should I buy?” The poster included a reminder that strength equals milligrams per mL.

### The paracetamol situation – a summary

Deliberate self-poisoning with paracetamol remains an important problem in many countries, but with the availability of N-acetylcysteine, serious complications are uncommon and death from hepatic failure is rare. The dilemma arises from the irresponsible misuse of paracetamol in this way by a tiny minority of users, on the one hand, whereas for the vast majority, on the other hand, it is an effective and remarkably safe drug when used properly. Unfortunately, the problem will not go away. Paracetamol is ubiquitous, and the media have publicized its use for self-poisoning in some areas to such an extent that it has become almost a cult phenomenon. The rare occurrence of acute liver damage with the alleged therapeutic use of paracetamol in adults is usually related to misuse and overdose. There is also a problem with hepatotoxicity caused by the misguided administration of excessive doses of paracetamol to this age group by parents and guardians. In this context, there is a need for better education of the public in the proper use of paracetamol. More information is required about the factors that influence paracetamol hepatotoxicity in humans, particularly the effects of alcohol, other drugs, fasting, and diet.

THE ANALGESIC MARKET

Medicines containing paracetamol entered in the Australian Register of Therapeutic Goods

Table 1 analyses entries for paracetamol on the Australian Register of Therapeutic Goods (ARTG) as at June 2002 by the classifications in the left hand column. For non-prescription paracetamol-only solids and mixed analgesic solids (such as paracetamol with low dose codeine), the poison schedules are expressed as UnSch (unscheduled) or S2 (Appendix 1); and as S2 or S3, respectively. The decision to treat unscheduled and S2 classifications as if they were the same was made because it was not possible to determine from the Register whether the manufacturer produced only unscheduled packs, only scheduled packs or both.

<table>
<thead>
<tr>
<th>FORMULATION</th>
<th>EXAMPLES</th>
<th>No. on ARTG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol only/ Solid/UnSch or S2</td>
<td>Paracetamol capsules/tablets 500mg</td>
<td>124</td>
</tr>
<tr>
<td>Paracetamol only/ Liquid/ S2</td>
<td>Paracetamol oral liquids</td>
<td>79</td>
</tr>
<tr>
<td>Paracetamol only/ Suppository/ S2</td>
<td>Paracetamol suppositories</td>
<td>3</td>
</tr>
<tr>
<td>Paracetamol only/ Solid/S2</td>
<td>Paracetamol tablets for children</td>
<td>5</td>
</tr>
<tr>
<td>Mixed analgesics/ Solid/S2 or S3</td>
<td>Paracetamol with: codeine &lt;10mg</td>
<td>65</td>
</tr>
<tr>
<td>Mixed analgesics/ Solid/S3</td>
<td>Paracetamol with: codeine/doxylamine; or diphenhydramine</td>
<td>40</td>
</tr>
<tr>
<td>Mixed analgesics/ Liquid/S2</td>
<td>Paracetamol with: codeine</td>
<td>1</td>
</tr>
<tr>
<td>Mixed analgesics/ Liquid/S3</td>
<td>Paracetamol with: codeine/promethazine; or promethazine</td>
<td>6</td>
</tr>
<tr>
<td>Mixed analgesics/ Solid/S4</td>
<td>Paracetamol with: codeine 15mg-30mg; or orphenadrine; or dextropropoxyphene; or metoclopramide</td>
<td>16</td>
</tr>
<tr>
<td>Cold medicines/ Solid/S2</td>
<td>Paracetamol with: decongestants/antihistamines/ antitussives/codeine</td>
<td>128</td>
</tr>
<tr>
<td>Cold medicines/ Liquid/S2</td>
<td>Paracetamol with: decongestants/chlorpheniramine/antitussives</td>
<td>6</td>
</tr>
<tr>
<td>Cold medicines/ Liquid/S3</td>
<td>Paracetamol with: decongestants/mepyramine/antitussives</td>
<td>1</td>
</tr>
<tr>
<td>Cold medicines/ Liquid/S4</td>
<td>Paracetamol with: ephedrine/dihydrocodeine</td>
<td>1</td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td>475</td>
</tr>
</tbody>
</table>

Table 1. Paracetamol products entered on the Australian Register of Therapeutic Goods, classified by composition, physical form and poisons classification.

All paracetamol medicines intended for supply in Australia are required to be included in the ARTG but not all are available commercially. This arises because some formulations have been superseded or sponsors may have chosen not to place their goods on the market for commercial reasons. Many brands that contain only paracetamol are marketed exclusively for general sale and will not be produced in larger packs; other brands are available in multiple pack sizes, the smaller ones being
available for general sale while those above 25 are available from pharmacies only. The same ARTG number for a brand of paracetamol tablets in a particular strength applies without regard to pack size and poisons schedule. For example, Panadol tablets 500mg have the one ARTG number for packets of 12, 24, 48 and 96.

It is therefore difficult to obtain a precise picture of the number of individual line items of medicines containing paracetamol that are available on the Australian market at a particular point in time. With these caveats, the table shows the large range of medicines in Australia that contain paracetamol.

Drug selection

In a random sample weighted by age, sex and location to reflect the actual population based on Australian Bureau of Statistics data, 1618 subjects were surveyed. The analgesics were paracetamol, aspirin, the NSAIDs, others and none. Of the 1618 subjects, 1377 (85%) used an analgesic at least once a year and 241 (15%) did not use any. Regular users (1000) accounted for 62% and irregular users (377) for 23%. The rankings among the users were: 1. Paracetamol 48%; 2. NSAIDs 7%; 3. Aspirin 5%; 4. Others 2%.

Purchasing patterns

<table>
<thead>
<tr>
<th></th>
<th>All users (n=1283)</th>
<th>NSAIDs (n=255)</th>
<th>Aspirin (n=76)</th>
<th>Paracetamol (n=773)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-purchase (%)</td>
<td>79</td>
<td>74</td>
<td>76</td>
<td>80</td>
</tr>
<tr>
<td>Purchased from</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacy (%)</td>
<td>50</td>
<td>95</td>
<td>33</td>
<td>44</td>
</tr>
<tr>
<td>Supermarket (%)</td>
<td>50</td>
<td>5</td>
<td>66</td>
<td>55</td>
</tr>
<tr>
<td>How purchased</td>
<td>n=477</td>
<td>n=187</td>
<td>n=54</td>
<td>n=285</td>
</tr>
<tr>
<td>Self-select (%)</td>
<td>25</td>
<td>22</td>
<td>28</td>
<td>28</td>
</tr>
<tr>
<td>Requested (%)</td>
<td>61</td>
<td>67</td>
<td>56</td>
<td>58</td>
</tr>
<tr>
<td>Recommend (%)</td>
<td>13</td>
<td>11</td>
<td>16</td>
<td>13</td>
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</tbody>
</table>

Table 2. Source of purchase of non-prescription analgesics

The source of recommendations

<table>
<thead>
<tr>
<th></th>
<th>All users (n=1036)</th>
<th>NSAIDs (n=201)</th>
<th>Aspirin (n=177)</th>
<th>Paracetamol (n=631)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-select (%)</td>
<td>68</td>
<td>51</td>
<td>73</td>
<td>71</td>
</tr>
<tr>
<td>Doctor (%)</td>
<td>15</td>
<td>13</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>Pharmacist (%)</td>
<td>5</td>
<td>8</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Family (%)</td>
<td>5</td>
<td>8</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Friend (%)</td>
<td>2</td>
<td>11</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Pharmacist (%)</td>
<td>2</td>
<td>2</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>TV (%)</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Dentist (%)</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Media (%)</td>
<td>-</td>
<td>1</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Other (%)</td>
<td>1</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Don’t know (%)</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 3. Source of recommendation of analgesics
Pharmaceutical Benefits Scheme

Paracetamol is available under the Pharmaceutical Benefits Scheme. Significant quantities of paracetamol are supplied under the Scheme but the official figures understate the actual number because they relate only to prescriptions dispensed for patients holding concession cards such as pensioners. This arises because the products concerned, being fairly low cost items, do not attract a government contribution for the general public. The main products are uncompounded paracetamol tablets 500mg (100 tablets) and the combination of paracetamol 500mg/codeine phosphate 30mg (20 tablets). Several oral liquids are also included in the Scheme. The figures below, therefore, show only the number of PBS prescriptions to which the government contributed part or the entire price for the 12 months ending 31 March 2002.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Number</th>
<th>Govt Cost ($)</th>
<th>Total Cost ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol</td>
<td>4,275,663</td>
<td>22,368,349</td>
<td>33,343,455</td>
</tr>
<tr>
<td>Paracetamol/Codeine</td>
<td>2,751,723</td>
<td>18,623,924</td>
<td>26,305,965</td>
</tr>
</tbody>
</table>

Source: Commonwealth Department of Health and Ageing, 2002

Australian sales figures for non-prescription paracetamol (approximate) for 2001

Paracetamol (adult products) by packs (irrespective of size)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Number</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol (non-pharmacy)</td>
<td>(Unscheduled)</td>
<td>30,000,000</td>
<td>30,000,000</td>
</tr>
<tr>
<td>Paracetamol (pharmacy)</td>
<td>(Unscheduled and S2)</td>
<td>3,900,000</td>
<td>3,900,000</td>
</tr>
<tr>
<td>Paracetamol/codeine</td>
<td>(S2 &amp; S3)</td>
<td>6,000,000</td>
<td>6,000,000</td>
</tr>
<tr>
<td>Paracetamol/codeine/doxylamine</td>
<td>(S3)</td>
<td>4,000,000</td>
<td>4,000,000</td>
</tr>
<tr>
<td>Paracetamol (cold medicines)</td>
<td>(S2)</td>
<td>3,300,000</td>
<td>3,300,000</td>
</tr>
</tbody>
</table>

Paracetamol (adult products) by equivalent daily doses. This is total tablets divided by 8 ie the maximum daily dose to give an estimate of total number of potential treatment days.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Number</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol (non-pharmacy)</td>
<td>(Unscheduled)</td>
<td>73,000</td>
<td>73,000</td>
</tr>
<tr>
<td>Paracetamol (pharmacy)</td>
<td>(Unscheduled and S2)</td>
<td>73,000</td>
<td>73,000</td>
</tr>
<tr>
<td>Paracetamol/codeine</td>
<td>(S2 &amp; S3)</td>
<td>30,000</td>
<td>30,000</td>
</tr>
<tr>
<td>Paracetamol/codeine/doxylamine</td>
<td>(S3)</td>
<td>11,000</td>
<td>11,000</td>
</tr>
<tr>
<td>Paracetamol (cold medicines)</td>
<td>(S2)</td>
<td>11,000</td>
<td>11,000</td>
</tr>
</tbody>
</table>

Paracetamol (adult products) by individual tablets and capsules.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Number</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol (non-pharmacy)</td>
<td>(Unscheduled)</td>
<td>600,000,000</td>
<td>600,000,000</td>
</tr>
<tr>
<td>Paracetamol (pharmacy)</td>
<td>(Unscheduled and S2)</td>
<td>590,000,000</td>
<td>590,000,000</td>
</tr>
<tr>
<td>Paracetamol/codeine</td>
<td>(S2 &amp; S3)</td>
<td>233,000,000</td>
<td>233,000,000</td>
</tr>
<tr>
<td>Paracetamol/codeine/doxylamine</td>
<td>(S3)</td>
<td>83,000,000</td>
<td>83,000,000</td>
</tr>
<tr>
<td>Paracetamol (cold medicines)</td>
<td>(S2)</td>
<td>90,000,000</td>
<td>90,000,000</td>
</tr>
</tbody>
</table>

Paracetamol (children’s products) by packs (irrespective of size)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Number</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol (pharmacy)</td>
<td>(S2)</td>
<td>4,180,000</td>
<td>4,180,000</td>
</tr>
<tr>
<td>Paracetamol/codeine</td>
<td>(S3)</td>
<td>165,000</td>
<td>165,000</td>
</tr>
</tbody>
</table>
Paracetamol (children’s products) by equivalent daily doses

Paracetamol (pharmacy) (S2) 17,800
Paracetamol/codeine (S3) 1,665

Paracetamol (children’s products) by doses

Paracetamol (pharmacy) (S2) 137,000
Paracetamol/codeine (S3) 13,500
Source: GlaxoSmithKline

Purchase of multiple packs

Analgesics are usually purchased in Australia as single packs per occasion.

<table>
<thead>
<tr>
<th>YEAR ENDING</th>
<th>1 PACK (%)</th>
<th>2 PACKS (%)</th>
<th>3 PACKS (%)</th>
<th>&gt; 3 PACKS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18.2.2000</td>
<td>84.6</td>
<td>12.1</td>
<td>1.2</td>
<td>2.1</td>
</tr>
<tr>
<td>17.2.2001</td>
<td>87.7</td>
<td>10.5</td>
<td>1.0</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Table 4. Numbers of packs purchased at the one time. Source: AC Neilsen

Packaging

Nearly all tablets and capsules of paracetamol sold in Australia are packed in blister or similar packs. About 20 products included in the ARTG were packed in bottles fitted with child-resistant closures. These were mainly brands that were distributed through individual pharmacies or groups of pharmacies. Two exceptions are an American-based brand that is packed in 100s and is a Pharmaceutical Benefit. The other is a leading Australian brand that is commonly sold through supermarkets. It is presented as 25 gelatin coated tablets in the shape of capsules, each containing 500mg of paracetamol. Packs of this kind are significantly cheaper to produce than those that are packed in strips so providing an incentive for consumers to buy the former. This in turn may encourage other manufacturers to produce like packs in order to match the competition so resulting in greater accessibility in the home. The Review recommended that this kind of packaging should no longer be permitted for paracetamol but the two recommendations were rejected. The Update remakes the recommendations.

Recommendation 1

Recommendation 1 was deleted following consideration of comments from stakeholders at the Medicines Evaluation Committee meeting on 3 April 2003.

The original recommendation is on Page 67.
AUSTRALIAN DATA

Term of Reference No.1 states:

Extend the data obtained in the Review of Non-prescription Analgesics to determine the current extent of the problem in Australia with respect to the incidence of hepatotoxicity and liver transplants following paracetamol overdose and in particular whether there is reliable evidence that liver toxicity occurs in some individuals within or close to recommended therapeutic dosage regimens.

Many disparate sets of data are available concerning paracetamol overdose in Australia. The material below sets out the salient points obtained from a number of these that have been conducted since the Review.

The conclusions by Gow et al (1999) are consistent with other data. In short, admission numbers are increasing but the number of liver transplants and deaths remains low, especially when one takes into account the ubiquity of paracetamol and the number of doses consumed each year.

Surveys in Australia

Admissions to the Royal Children’s Hospital, Melbourne for paracetamol poisoning from 1998 - 2001

Appendix 1 of the Review was a survey on admissions to the Royal Children’s Hospital, Melbourne due to paracetamol poisoning for the period 1993 to 1997. This survey was extended for the period 1998 to 2001, thus bringing together nine consecutive years of data. Appendix 1 to the Update follows the Review format but includes the figures gained over nine years. The data obtained for the Update follows a similar pattern to those obtained for the Review with teenage girls representing the main cohort. This finding is consistent with local and overseas experience (Taylor et al, 1998; Weir, 1998; Mahadevan et al, 1999; Alander et al, 2000; Bailey et al, 2001). The survey showed an increase in annual admission rates for deliberate self-poisoning by teenage girls. Accidental poisoning, in terms of numbers of admissions to the hospital, has declined a little over the two periods surveyed but the figures are small and clear trends have not emerged.

Hospital admissions in Victoria for paracetamol poisoning from 1987/88 to 2000/01 – preschoolers

Paracetamol heads the list of substances accidentally ingested by children under 5 years of age with about 1,040 admissions out of a total of 6,859 (15%)

- Annual average number, 74.9
- Admissions
  - 1987/88  39
  - 1988/89  37
  - 1989/90  43
For the period 1996 to 2001, there were 4,081 presentations to emergency departments for poisoning in the age group 0-4 years. Paracetamol was identified in 789 (19.3%) of these. [Note: From 1996/97, private hospital figures have been incorporated into the above; these account for about 4% of admissions].

Source: Monash University Accident Research Centre

Liver transplants – Australian National Liver Transplant Unit

The most recent Annual Report of the Australian National Liver Transplant Unit includes data for the period 8 January 1986 to 31 December 2001. Of 1,201 adults assessed for liver transplant, paracetamol toxicity was the cause in 42; for children, there was one case in 177. The full report may be consulted on www.cs.nsw.gov.au/Gastro/LiverTransplant.

Admissions to Adelaide hospitals for paracetamol poisoning - 2001

Presentations to Adelaide metropolitan hospitals for paracetamol poisoning for 2001 are tabulated below.

<table>
<thead>
<tr>
<th>AGE (Years)</th>
<th>PRESENTATIONS</th>
<th>ADMISSIONS</th>
<th>SHORT STAY OBSERVATIONS</th>
<th>TRANSFERS</th>
<th>OTHER</th>
<th>DISCHARGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>62</td>
<td>8</td>
<td>10</td>
<td>1</td>
<td>-</td>
<td>44</td>
</tr>
<tr>
<td>5-9</td>
<td>4</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>10-14</td>
<td>16</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>-</td>
<td>7</td>
</tr>
<tr>
<td>15-19</td>
<td>84</td>
<td>40</td>
<td>1</td>
<td>12</td>
<td>1</td>
<td>30</td>
</tr>
<tr>
<td>20-24</td>
<td>65</td>
<td>30</td>
<td>7</td>
<td>7</td>
<td>-</td>
<td>21</td>
</tr>
<tr>
<td>25-29</td>
<td>44</td>
<td>25</td>
<td>2</td>
<td>4</td>
<td>-</td>
<td>13</td>
</tr>
<tr>
<td>30-34</td>
<td>30</td>
<td>19</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>35-39</td>
<td>32</td>
<td>16</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td>12</td>
</tr>
<tr>
<td>40-44</td>
<td>28</td>
<td>13</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>45-49</td>
<td>20</td>
<td>9</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>8</td>
</tr>
<tr>
<td>50-54</td>
<td>8</td>
<td>5</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>55-59</td>
<td>10</td>
<td>6</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>60-64</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>65-69</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>70-74</td>
<td>3</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>75-79</td>
<td>2</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>80-84</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>TOTAL</td>
<td>410</td>
<td>182</td>
<td>35</td>
<td>32</td>
<td>3</td>
<td>158</td>
</tr>
</tbody>
</table>

Source: Department of Human Services, South Australia
Hospital admissions to Victorian hospitals from 1987/88 to 2000/01 for paracetamol poisoning - adults

- 41% were 15 to 24 years of age
- 75% of admissions were for self-harm
- 20% of admission were “accidental” [deliberate therapeutic overdose]
- 65% admitted for <2 days; 31% for 2-7 days
- Admissions per year have quadrupled over 14 years [341 to 1490]
- Total number of admissions 13,638 for poisoning with paracetamol

Source: Monash University Accident Research Centre

Admissions to two Melbourne general hospitals for paracetamol poisoning, 1996/97 to 1997/98

- No significant differences between the two data sets (p = 0.05)
- Number of admissions, 442; number of individuals, 378
- 68% female; 32% male.
- 43% were 15-29 years of age
- 89% intentional overdose
- Mean Length of Stay 1.02 days
- Mean quantity ingested 25.9 tablets (men took more)
- 40% used paracetamol only; 25% took 1 extra substance
- 62% had depression, borderline personality disorder, substance abuse
- 58% had previous history of self-harm
- No deaths and no transplants
- Reasons: To die (50%), to numb emotional pain (13%), to escape (10%)


Routley et al (1999) gathered data for adult (>=15 years) poisoning from a number of Victorian sources. These were the Victorian Emergency Minimum Dataset (VEMD), the Victorian Inpatient Minimum Dataset (VIMD) [now known as Victorian Admitted Episodes Dataset (VAED)] and the Coroner’s Facilitation System (CFS). Interpretation and reconciliation of these data sets is difficult because of multiple admissions and the consumption of multiple agents. Further, some hospitals are included in the VIMD but not the VEMD; in six VEMD hospitals, the collection covered less than the three years, VEMD uses different diagnosis fields compared with VIMD and some hospitals have a poor record in capturing poisoning details.

The VEMD covering 23 hospitals for 1996 to 1998 revealed there were:

Number of person-substances: 15,001 (some patients took multiple substances)
Number of presentations: 11,861 (paracetamol: 1,970)
Number of admissions: 6,965 (paracetamol: 1,073)

In the VIMD for the 11 year period 1987/88 to 1997/98, there were 91,614 person-substances for poisoning of which 8,611 (9.4%) were for paracetamol – an annual
average of 782. A graph of the admissions shows the number of admissions for all poisonings had about doubled for the period but the number of admissions for paracetamol poisoning had about tripled for the same period. The majority (73%) of admissions were for intentional self-harm and 23% were due to excessive doses to relieve toothache or migraine.

CFS data from July 1989 to June 1995 showed paracetamol being mentioned in eight deaths; four were with paracetamol alone and the others were combinations of it with either antidepressants, amphetamines/morphine/benzodiazepines, carbon monoxide or amitriptyline/benzodiazepines/dextropropoxyphene. Whether the cause of death was paracetamol remains unclear.

Admissions to Austin and Repatriation Medical Centre – 1988 to 1995

The Austin and Repatriation Medical Centre is a tertiary referral centre that provides liver transplantation services for Victoria and Tasmania, servicing about five million people. It also services about 700,000 people from Melbourne’s north-eastern suburbs. Admission data for the eight years January 1988 to December 1995 were examined for cases of paracetamol overdose. There has been a clear upward trend in the rate of presentation. The admissions were divided into transplant referral and community patients.

Transplant referrals

- Patients presented later
- Larger overdoses, $37.7 \pm 17.6\text{g (10-78g)}$

Community patients

- 227 patients were identified; 57 were not further considered because their ingestion of paracetamol was less than 125mg/kg over 24 hours
- 170 admissions were accounted for by 152 individuals
- Age range 9 months to 83 years
- 103 females and 49 males
- 11 of the overdoses were accidental and 2 were due to excessive doses
- The mean amount was $20.7 \pm 14.0\text{g (2.5 – 107g)}$

Overall findings and conclusions

- Incidence of overdose is increasing in Australia
- Serious liver injury remains uncommon
- Annual rate of paracetamol-induced fulminant hepatic failure remained at 2/year
- <10% of local patients developed significant hepatotoxicity
- In Victoria, the incidence of fulminant hepatic failure due to paracetamol poisoning is <0.4 cases/million/year
- There were 3 deaths over a seven year period attributable to this condition; the rate being 0.07 deaths/million/year. In the UK, the corresponding rate is 2.8 deaths/million/year (before 1998)
Increased public awareness of the dangers of overdose may be a two edged sword.

Doctors should be reminded of the importance of prompt use of NAC

Source: Gow et al, 1999

Outcomes of fulminant hepatic failure managed at the Austin and Repatriation Medical Centre, 1988 to 2001

This was a survey of admissions to the liver transplant unit for the 14 calendar years from 1988 to 2001.

- 80 patients were referred to the liver transplant unit giving a referral rate of one/million/year
- 29 (36%) were admitted because of paracetamol poisoning. It was the largest single group followed by non-A non-B hepatitis (34%)
- 25 (86%) of the paracetamol group were female
- The paracetamol group was the youngest (31.3 ±12.0 years). The mean age of all patients was 37.6 ± 13.7 years
- 4 of the paracetamol group died – a suitable donor was unavailable in one case and the other 3 died within hours of admission
- The survival rate of those poisoned with paracetamol but who were not transplanted was 74%
- 9 (31%) of the paracetamol patients had unintentional overdose. All of these patients had a very poor dietary intake (due to an acute illness) during the period of paracetamol ingestion and 5 were chronic heavy alcohol users
- Hepatotoxicity under the above circumstances is well documented but is not as widely recognised at it should be in both the lay and medical communities

Source: Gow et al, 2002 (unpublished data, courtesy Dr P Angus)

Serious outcomes and “normal” doses

A number of single case reports have suggested that paracetamol toxicity can occur despite the dose being within the recommended limits and in the apparent absence of risk factors. A difficulty with single case reports where the patient has developed signs of hepatotoxicity is the unreliability of information about the details of the patient’s drug and alcohol history.

Risk factors so identified are fasting and the concurrent use of several drugs with which paracetamol is known to interact. Chronic alcohol ingestion has long been considered a risk factor but it is only recently that the case has been made a little stronger by a quantified study (Schmidt et al, 2002). Indeed, the apparent increased toxicity of paracetamol in heavy drinkers has underpinned mandatory warning labels in Canada, the United States and Germany. The subject remains controversial.

In Australia, paracetamol tablets and capsules include a maximum daily consumption figure of 8 x 500mg units (4g) daily. Labels for oral liquids for children and child strength tablets include not only dose tables based on both weight and age, but also the maximum number of doses per day and the maximum number of days of treatment
before medical advice should be obtained. All of these requirements flow from the evaluation and registration of individual products. To provide consistency across the industry, well-established labelling guidelines operate that are to be observed by sponsors when an application is made for registration of the product.

**Adults**

There have been suggestions that recommended doses of paracetamol in adults can cause hepatotoxicity in the absence of risk factors.

A major review of therapeutic misadventure attributed to paracetamol included a table setting out the clinical details of adults without excess alcohol intake who were reported to have suffered liver damage after therapeutic use of the drug (Prescott, 2000). There were 59 reports altogether but in some, doses in excess of 4g/day had been taken for misguided therapeutic use, as opposed to deliberate self-poisoning. There were many possible predisposing factors identified such as recent fasting, exposure to other drugs and chemicals, so reducing the number.

In a recent paper, this question was posed; “Is there any literature available to support that acetaminophen can cause hepatotoxicity in doses less than or equal to 4g/d on a chronic basis in adult patients without any known risk factors for acetaminophen toxicity?” (Bolesta and Haber, 2001). For the purposes of the response, the authors carried out searches of MEDLINE from 1966 to July 2001, International Pharmaceutical Abstracts (1979-May 2001) and PREMEDLINE. They confined their subjects to those:

(i) who were at least 18 years of age;
(ii) who had no known risk factors;
(iii) whose daily dose did not exceed 4g; and
(iv) whose treatment exceeded four days.

Only four cases fitted these criteria in a literature review that covered about 35 years (Johnson and Tolman, 1977; Bonkowsky et al, 1978; Bonkowsky et al, 1994; Kwan et al, 1995). In three cases, the enzymes levels returned to normal when the drug was discontinued but in one case, NAC was needed. In that case, acute renal and hepatic toxicities due to underlying chronic cardiopulmonary compromise were confounding factors. The authors thought that cases of this kind are underreported because of lack of clinical suspicion when the usual therapeutic doses are taken.

**Children**

The situation with children differs from that in adults because repeated dosing appears to be an important factor. A recent article stated: “Less well recognised but equally important is the hepatotoxic potential of multiple therapeutic doses of paracetamol in children with intercurrent illness such as diarrhoea or vomiting which may have compromised the detoxification pathways” (Cleghorn, 2002).

A 1999 paper in the *Medical Journal of Australia* focussed attention on this subject and is considered to be one of the reasons for this Update, especially as there was
considerable coverage in the newspapers (Miles et al, 1999). These authors tabulated the details of 11 patients (age ranges 6 months to 165 months) from 1985 to 1998 who had presumed paracetamol hepatotoxicity. Four died, one had severe brain damage and the remaining six recovered. Miles et al noted a distinct clinical pattern; the patients presented with a non-specific prodromal illness, often with fasting and/or vomiting. A feature that was observed was the disproportionately low rise in bilirubin levels when compared with the expected increase in transaminase levels. To the extent that one can rely on information supplied by relatives, two cases indicated that the daily dose was especially low, being 20mg/kg/day for 21 days in one case and 7 days in the other. In one of these, the plasma paracetamol level suggested a much larger dose than the 20mg/kg/day oral dose that was quoted. A response to this paper mentioned that five of the children were receiving >90mg/kg/day, the dose was unknown in four cases and there was a discrepancy in the apparent dose and the blood levels. The study implied an association between therapeutic dosing and fulminant hepatic failure (Daly et al, 2000).

The original authors disputed this response and suggested that paracetamol ingestion continued after the onset of liver damage and the blood levels reflected hepatic metabolism (O’Loughlin et al, 2000).

Two further Australian cases where hospitalised children had received less than 150mg/kg per day and developed hepatotoxicity were reported in the same edition of the MJA (Hynson & South, 1999). In one case, a four-year old 20kg girl had received about 2,400mg of paracetamol over 72 hours followed by 2,800mg (140mg/kg) over the next 17 hours. The second case was a 43kg boy who initially received 3,000mg (70mg/kg) over 24 hours rectally. This was followed over the next five days with a maximum daily dose of 4,650mg (108mg/kg) in any 24 hour period. NAC was required in the first case but not in the second. Previous papers had reported similar findings but how to determine which children were susceptible, and which were not, remains unanswered (Pershad et al, 1999; Morton and Arana, 1999; Heubi et al, 1998; Alonso et al, 1995). Because the safety of repeated doses of paracetamol in sick children has been questioned, James et al (2001) measured hepatic transaminases in 100 hospitalised children and adolescents who received at least six doses (10-15mg/kg) over 48 hours. Not surprisingly, in view of the dose and duration of treatment, no irregularities were found.

A recurring theme in the American literature is that supratherapeutic doses are inadvertently administered because of using more than one product that contains paracetamol (American Academy of Pediatrics, 2001). A risk profile has been compiled to identify children who are more likely to develop hepatotoxicity (Kearns et al, 1998). The factors are: (i) the dose ≥90mg/kg/day; (ii) the child is sick; (iii) under two years of age; (iv) treatment exceeds one day; (v) the co-administration of other products that contain paracetamol; (vi) the co-administration of various enzyme inducers; (vii) incorrect product selection; and (viii) off-label uses.

Prescott (2000) tabulated and analysed 89 reports of liver damage after therapeutic use of paracetamol in children. His appreciation is that the most striking finding was that most of the children had been given excessive doses, a finding that would follow from the above risk factors.
The Condobolin Case

A case was widely reported in the media of a 13 year old boy who died after receiving prolonged doses of paracetamol. The Coroner conducted an inquest into his death.

Summary of the case

The patient was a 13 year old boy weighing 104kg (height 166cm). He lived at Condobolin, a town in New South Wales, about 475 km west of Sydney. For treatment of damaged femoral heads, he was sent to the New Children’s Hospital in Sydney where he was operated on. A second operation was needed four days later. For the treatment of pain, he was given Panadeine Forte (paracetamol 500mg with codeine phosphate 30mg) and discharged to the local hospital where he was given paracetamol and Panadeine Forte. About 12 days after the first operation, he developed a chest infection for which flucloxacillin was prescribed for two days. He was diagnosed as having liver failure and was returned to Sydney and died three days later. Overall, he was given 32g of paracetamol over 14 days (av 2.3g/day) and on the last day received 6g.

Expert evidence from a staff specialist in gastroenterology at a Sydney teaching hospital called on the New South Wales Department of Health to establish an expert committee to examine “the use and abuse” of paracetamol, to prevent acute liver failure. The expert told the court that there should be stronger warnings on the box about reviewing treatment after 48 hours. He was quoted as saying that “in the United States, due to several large litigation cases, the manufacturer has had to put on the bottle that it [paracetamol] may cause liver failure”. [Note: It is true that American labels refer to liver toxicity but they do so only in the context of concurrent alcohol consumption].

An investigation into the case indicated that test results from a pathology centre more than 100 kilometres away, were delayed when they were faxed to the hospital and were not received by staff (O’Rourke, 2002).

Media reports

After the coronial inquiry in February 2002, but before the Coroner’s finding was handed down, the media reported in August 2002 that the Coroner would be recommending that all paracetamol sales should be from pharmacies. A spokesman for the Royal Australasian College of Physicians was quoted as advocating more safety information on the labels (O’Rourke, 2002).

Arising from this report, a correspondent to a newspaper said that he failed to see how the removal of paracetamol from supermarkets would be of much use “as a result of a medically administered fatal dose” (Ward, 2002). This attracted a response from a Melbourne pharmacist who criticised the brevity of the warnings on television advertisements for paracetamol and that supermarket checkout staff should not be giving any advice about medicines because they are not trained to do so (Lowe, 2002). There were also responses from official medical and pharmacy organisations and from the industry organisation (Kelly, 2002; Anon (g), 2002). The responses included suggestions for more prominent labelling that referred to the possibility of liver damage.
in overdose; the need for supervision at the time of sale and the issue of an alert to medical professionals in New South Wales.

One headline sensationalised the case saying: “Coroner sin-bins painkiller after boy’s death” (O’Rourke, 2002).

Coroner’s recommendations

The Senior Deputy State Coroner, Ms Jan Stevenson, made the following recommendations to the New South Wales Minister for Health:

1. The convening of an expert committee to review the current use and abuse of Paracetamol, to establish realistic guidelines to prevent potential liver failure in children;
2. The issue of an alert, advising practitioners of the death of Wade Dunn and potential medical problems which may arise where a patient prescribed Paracetamol is not within “normal” parameters;
3. The introduction of a standard form for use when transferring a patient between hospitals (whether such hospital is or not in the same Area Health Services). Such a form to contain core information such as medication, dosage and frequency of medication, pathology results, and other such information, such to aid the continued treatment of the patient;
4. Area Health Services to remind practitioners, especially in country or remote areas, to fully utilize the advice available from Base Hospitals/Specialist Hospitals where a potential exists in diagnosis of a patient, especially where such patient is a child;
5. Consideration be given to restricting the sale of paracetamol products to Pharmacies.

The Coroner also made a recommendation to the New South Wales Minister for Fair Trading:

6. Consideration be given to restricting the advertising of paracetamol products due to the potentiality of overuse of such products and the ensuing health risks especially to children.

The Update comments on the Recommendations as follows:

1. Therapeutic Guidelines Analgesic 2002 and its previous editions have advice on the use of paracetamol in both paediatric and adult circumstances. The AGRD Volume 2 has for many years included information to manufacturers on label content.

2. The Review made a number of recommendations about education of practitioners.

3. Not within the Update’s Terms of Reference.

4. Not within the Update’s Terms of Reference.

5. The Terms of Reference do not specifically require the Update to comment on the availability of paracetamol but some comment is considered appropriate. If the Coroner’s recommendation were implemented, all paracetamol products would be in Schedule 2 or perhaps Schedule 3 to the Standard for the Uniform Scheduling of Drugs
and Poisons, and therefore available only from pharmacies. Various authors have also favoured this course of action over the years. Examination of the records of patients who have overdosed for therapeutic reasons or due to deliberate self-poisoning are usually insufficiently detailed to determine whether the paracetamol was obtained (a) from a pharmacy on a doctor’s prescription or; (b) from a pharmacy without a prescription or; (c) from a general retail outlet such as a supermarket or; (d) from a combination of sources. Further, the quantity actually consumed is often not known with any certainty. There is no Australian evidence to suggest that this proposal, if implemented, would change morbidity and mortality statistics. It may or it may not; the hypothesis has not been tested.

In a subsequent newspaper article, the Coroner was quoted thus: “If you are buying something among the chocolate biscuits and floor wipes, you are not going to be worried about it” (Moynihan and Allen, 2002). A similar observation was made in the UK by a representative of an organisation that specialises in misuse of non-prescription medicines (BBC News). The President of the Pharmaceutical Society of Australia said that availability through supermarkets could reduce the likelihood that consumers appreciated the potentially lethal nature of paracetamol and supported a public benefit review into whether the potential for harm outweighs the convenience of availability in supermarkets (Anon (g), 2002). It is also not known if the Australian public perceives paracetamol, when purchased from a supermarket, as an ordinary item of commerce to be regarded as akin to chocolate biscuits or floor wipes or, alternatively, as a drug that is totally safe. If these beliefs are suspected of being held (Stiel, 2000) – and the Review and Update have heard them from several sources – they should be tested objectively.

Such a change in poisons classification, and therefore availability, may, however, encourage ordinary consumers (and deliberate self-poisoners), to use aspirin as a substitute – a drug that has problems of its own and for which, unlike paracetamol, a specific antidote is not available. If the exemption that allows small packs of paracetamol to be supplied from general retail outlets were repealed, the same should apply to aspirin. The Update notes that despite the major problems in the UK, the authorities have not totally restricted the sale to pharmacies.

6. There are advertising controls already in place. The introduction of Recommendation 6 (and Recommendation 5) would effectively place paracetamol in Schedule 3 to the Standard for the Uniform Scheduling of Drugs and Poisons. The Review (at page 15) noted: “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”. The reasoning presumably is that “they” (the government) would not allow something to be advertised
in this manner if it were dangerous. While this attitude may be suspected, firm Australian data are not available to determine how the public perceives the safety of paracetamol. Overseas data, however, indicate that adolescents overestimate dangerous doses of it (Myers et al, 1992; Gilbertson et al, 1996; Huott and Storrow, 1997; Harris et al, 1997).

It is difficult to see how Recommendations 5 and 6 could develop from this case because the paracetamol, either as a single substance or in combination with codeine, was prescribed by a medical practitioner or administered by nurses to a patient in two hospitals. Had paracetamol been a Schedule 4 poison, it is hard to accept that the outcome would have been any different.

The coronial report also states that the boy had been given flucloxacillin. Reports, especially in Australia, have mentioned idiosyncratic hepatotoxicity due to this antibiotic (Turner et al, 1989; Devereaux et al, 1995). That flucloxacillin might have been implicated in the case was not mentioned in the report. The contribution of the boy’s obesity is unclear. There are theoretical grounds to suggest that in obesity, CYP2E1 is induced so increasing the production of NAPQI (O’Shea et al, 1994) but a more specific prospective study using IV paracetamol in obese men and women indicated that the half-life and metabolic clearance were not affected (Abernethy, 1982).

The coronial report states that the boy was eating well before 22 March 2000. From this date, there are references to nausea, elevated temperature, vomiting and irritability but there is no reference to his food intake from this time. In view of the observations made in the study mentioned above (Gow et al, 2002) and that fasting is a probable risk factor in paracetamol poisoning - despite doses being in the therapeutic range – the contribution of a reduced diet to the outcome may have been significant. In a review of the relationship between glutathione depletion and paracetamol toxicity, Lauterberg (2002) has cited several case reports which point to a connection. Doubt has been cast on this association, however, because caloric restriction in obese subjects for up to three weeks has been shown not to alter the disposition of paracetamol nor does it increase its toxicity.
IBUPROFEN – OVERDOSES and INAPPROPRIATE DOSING

Term of Reference No.2 states:

Obtain data on ibuprofen overdoses and inappropriate dosing in children.

Overdoses

There have been many individual case reports and series of accidental and deliberate self-poisoning with ibuprofen (Hall et al, 1992; McElwee et al, 1990; Veltiri and Rollins, 1988; Hall et al, 1986). While numerous symptoms have been mentioned, the overall record reveals few fatalities. Gastrointestinal upset, dizziness and mild sedation are the effects usually noted but in more serious cases, metabolic acidosis, renal failure and coma are the most frequently observed. There are also reports of hepatic failure and seizure (Laurent et al, 2000; Oker et al, 2000). Generally, overdoses respond well to supportive treatment.

A major clinical trial on 27,065 febrile children under two years of age was carried out to compare the incidence of serious adverse effects with paracetamol (12mg/kg), ibuprofen (5mg/kg) or ibuprofen (10mg/kg). No placebo group was included. Treatment consisted over 6 to 10 doses over a median three days. Despite the self-acknowledged limitations of the data, the conclusion reached was that incidence rates of serious adverse effects requiring hospitalisation were low and did not vary significantly with the choice of antipyretic (Lesko et al, 1999).

Appendix 2 to this Update is a survey of admissions due to paracetamol poisoning to the Royal Children’s Hospital, Melbourne. The files on admissions due to NSAIDs for 1998 to 2001 were also extracted from the hospital’s files. There were 14 cases, many of which were multiple drug overdoses by adolescent girls. There were two cases involving ibuprofen. One was a child who took several Brufen tablets (ibuprofen 400mg, a Prescription-Only Medicine) and one who took four ibuprofen tablets 200mg. There were no sequelae.

In 2001, there were 203 enquiries directed to the Victorian Poisons Information Centre at the hospital in connection with exposures to ibuprofen. For the same period, there were 1059 about paracetamol. The Centre has adopted the following practice in response to queries when ibuprofen has been taken incorrectly. If the child has taken less than 200mg/kg, the Centre tells the parent to keep the child at home and only take the child to hospital if significant nausea, vomiting, diarrhoea or drowsiness develops in the four hours following ingestion. The most common situation is children helping themselves to Nurofen Suspension (100mg/5mL) but they rarely swallow enough to require medical assessment. If the child has taken more than 200mg/kg, medical assessment is recommended.
Multiple strengths of oral liquids

There are seven ibuprofen oral liquids entered on the ARTG. Six contain 100mg/5mL and are supplied as suspensions and syrups. There is also one product containing 40mg/mL in drop form. The concentration of the drops with respect to ibuprofen is therefore double that of the other formulations. The drops are intended for use in infants so that a sufficient dose can be given in a small volume. The Update also notes that the one product registered in the form of drops has a different brand name from the syrups and suspensions. This contrasts with the paracetamol situation where the one brand name is used across all strengths in a particular manufacturer’s range.

There is little evidence to suggest that there is a problem with inappropriate dosing with ibuprofen in children. Perhaps the overwhelming popularity of paracetamol accounts for the difference, or that ibuprofen is regarded as second choice for the usual indications and that it has not been available without a prescription for all that long. Another factor may be that no preparations of ibuprofen, unlike paracetamol, are available outside of pharmacies and are therefore perceived by the public more as a drug than as a supermarket line even though paracetamol oral liquids are only available from pharmacies.

The Review directed considerable space to the problems that arose from the potential confusion with the different strengths of paracetamol oral liquids on the Australian market and recommended that no new strengths be registered. It is true that ibuprofen does not have the delayed, serious effect on the liver with an intervening silent period that characterises paracetamol among the non-prescription analgesics. However, if more strengths of ibuprofen oral liquids were on the market, excessive doses may be administered out of confusion or ignorance. Ibuprofen oral liquids are all Schedule 2 poisons and it follows that pharmacists and their staff, as well as medical practitioners and nurses, should be made aware that the ibuprofen oral drops contain twice the concentration of ibuprofen than the syrups and suspensions. There do not appear to be any arguments based on convenience or posology in favour of adding another strength of ibuprofen to the two now registered in Australia.

On the basis of the evidence at present and the different toxicity profiles between paracetamol and ibuprofen, the Update is not in a position to make a formal recommendation that strengths of ibuprofen oral liquids, other than the present 20mg/mL and 40mg/mL, should not be registered.

Recommendation 2

In the event that additional strengths of ibuprofen oral liquids are marketed, the Australian Pharmaceutical Advisory Council, through the respective professional bodies, remind pharmacists and their staff, medical practitioners, nurses and health centre sisters that there is more than one strength of ibuprofen oral liquids and ensure that purchasers are made aware of the dose.
CHILDREN’S DOSES AND LABELLING REQUIREMENTS FOR PARACETAMOL AND IBUPROFEN

Term of Reference No.3 states:

Consider the current situation with regard to analgesics with a view to updating the Review of Non-prescription Analgesics particularly in the areas of children’s doses and labelling requirements for paracetamol and ibuprofen.

Paracetamol

A major part of the Review was devoted to medicines for children that contained paracetamol. The Review recommended:

- the dose should be 15mg/kg body weight, instead of the 12.5mg/kg dose previously recommended in Australia;
- the total daily dose should not exceed 60mg/kg body weight per day i.e. up to four doses; and
- the label should state that the medicine should not be administered for more than 48 hours without medical advice.

These recommendations were quickly implemented across the industry.

Dosing recommendations vary from country to country. The table shows the dosing regimens in four countries:

<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>DOSE (mg/kg)</th>
<th>MAXIMUM FREQUENCY</th>
<th>MAXIMUM (mg/kg/day)</th>
<th>DURATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>15</td>
<td>4 hourly but not more than 4 times a day</td>
<td>60</td>
<td>48 hours</td>
</tr>
<tr>
<td>Canada*</td>
<td>Quoted in age groups</td>
<td>4 hourly up to 5 times/day</td>
<td></td>
<td>5 days</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>10</td>
<td>4-6 hourly</td>
<td>60</td>
<td>3 days</td>
</tr>
<tr>
<td>United States</td>
<td>10-15</td>
<td>5 times/day</td>
<td>50-75</td>
<td>Fever, 3 days Pain 5 days</td>
</tr>
</tbody>
</table>

*In Canada, doses are quoted from 0 months to 12 years in a range of 40mg to 480mg, respectively, to maximum daily doses of 200mg and 2,400mg, respectively.

Despite these differences, the total daily maximum amount is about the same in all four countries.

Higher doses – 90mg/kg/day and above – are used in hospitals and single doses of 30-40mg/kg are sometimes used for acute post-operative pain and also before a
tonsillectomy. A manufacturer submitted to the Update that it was concerned at the practice of doubling the dose on the label of paracetamol oral liquids, sometimes on the advice of general practitioners and perhaps pharmacists. Some general practitioners and pharmacists may not be aware that recommended doses have increased significantly over the past ten years and doubling them is inappropriate and potentially dangerous. For this reason, the manufacturer supported education of general practitioners, pharmacists and nurses.

In a realistic and common sense appreciation of dosing and related matters in children, Cranswick and Coghlan (2000) have stated, as have many other authors, that when paracetamol is used in the recommended doses, it has few side effects and is remarkably well tolerated. They point out that it is reasonable to administer paracetamol to febrile children who are in pain, are miserable, or are uncomfortable but the decision to treat fever must be made case by case. These authors support the advice on Australian labels that medical advice should be sought after 48 hours if the child’s condition deteriorates or fails to improve. They also advise that doctors must educate parents on what signs to look for in the febrile child and place less emphasis on fever reduction. Similar views have recently been expressed, also in Australia (Purcell, 2002; Anon (e), 2002; Woodhead, 2002(b)). Moreover, there is no evidence that treatment of fever reduces the risk of febrile convulsions. Paracetamol continues as the first line therapy of choice in children at the Royal Children’s Hospital, Melbourne (Anon (a), 2002).

The most recent edition of Therapeutic Guidelines Analgesic 2002 (Therapeutic Guidelines Ltd, North Melbourne, 2002) states: “A dose of 10mg/kg is no more effective than placebo for minor pain in children. The recommended dose in children is 15mg/kg orally, every 4 hours or 20mg/kg rectally, every six hours. Maximum daily dose is 90mg/kg up to a maximum of 4g (60mg/kg/day maximum for infants aged <6 months)”. The same text also states: “Though rare, hepatotoxicity with paracetamol does not occur below doses of 150mg/kg/day. However, toxicity has been reported rarely with therapeutic doses when administered over several days in children who have other concurrent illnesses such as fever, vomiting and diarrhoea. Caution should be taken with repeated doses of paracetamol over several days in children who may be febrile and dehydrated”.

The Update has not seen any data that would suggest any change in the recommended dose rate of 15mg/kg at the frequencies and for the duration already in the AGRD Volume 2. The Update notes that Therapeutic Guidelines Analgesic 2002 includes a maximum daily dose of 90mg/kg whereas Australian manufacturers limit the number of doses to a maximum of four daily resulting in a maximum of 60mg/kg daily. Given the purposes to which paracetamol is put in the home and in the interests of safety, the Update considers that the present figure of 60mg/kg daily should remain unchanged for the purposes of the AGRD Volume 2.

**Recommendation 3**

No change to the present guidelines on the use of paracetamol in children in relation to dose in mg/kg, maximum dose per day (not exceeding 2,400mg unless on medical advice), frequency and duration.
Labels of children’s medicines containing paracetamol

In Australia, the labels for children’s medicines that contain paracetamol are governed by:

- The labelling Order made under the Therapeutic Goods Act 1989. These are general requirements applicable to all medicines for human use;
- The Standard for the Uniform Scheduling of Drugs and Poisons. The SUSDP has general requirements for the signal heading and several warning statements that relate to non-prescription analgesics (see Labelling of Analgesics);
- Australian Guidelines for the Registration of Drugs, Volume 2. The AGRD Volume 2 includes a supplement on the posology of specific analgesics for non-prescription use.

Examination of immediate containers and cartons of oral liquids intended for children show that there are many messages directed to parents or care givers. Further, there is a sentence on children’s paracetamol medicines not to continue treatment for more than 48 hours. Reference to 48 hours was required well after the SUSDP statement was applied in the 1980s so there are two messages that say much the same thing except that the more recent is more specific in relation to paracetamol and the duration of treatment. Elsewhere, the Update refers to two extra statements based on the British model but queries whether the present statements in the Standard for the Uniform Scheduling of Drugs and Poisons should continue in the interests of clarity and simplicity. The Update recommends manufacturers seek professional advice about label design so that the information is delivered in the most effective and uncluttered manner. The Review included samples of some American labels that were so detailed that the font size had to be reduced to accommodate all of the information. This is an obvious disincentive to reading the entire label. Extra information could be included in package inserts (see Appendix 2 for a British example for paracetamol) but in Australia, package inserts are not commonly used for unscheduled and Schedule 2 medicines. Whether consumers would read them, no matter how well they are presented, is unclear.

Labels cannot talk nor can they answer questions. For these reasons, the supply of children’s medicines should remain in Schedule 2 of the SUSDP so that pharmacists and staff can reinforce the written information provided by the manufacturer. The Update repeats Recommendations 2.5, 2.7 and 3.1 of the Review. The methods of implementing these recommendations should be referred to the Australian Pharmaceutical Advisory Council.

Recommendation 4

The TGA, in consultation with stakeholders, work to raise the awareness of consumers and health professionals of the key issues related to the safe use of analgesics in general and paracetamol in particular.

This recommendation was amended following further consideration by the Medicines Evaluation Committee on 3 April 2003. The original recommendation is on Page 69.
Ibuprofen

Doses in children

Similar dosing schedules for ibuprofen in children are shown in standard Australian references:

- *Therapeutic Guidelines Analgesic 2002*: 8-10mg/kg eight hourly, orally, to a maximum of 40mg/kg/day. The rectal dose is given as 20mg/kg 12 hourly.
- *Australian Medicines Handbook*: 5-10mg/kg three or four times a day.
- *Australian Pharmaceutical Formulary and Handbook 18th ed*: 5-10mg/kg six to eight hourly as needed.
- *Royal Children’s Hospital Pharmacopoeia*: Pain and fever. Oral 5-10mg/kg/dose 3-4 times a day.
- *AusDI*: **Usual paediatric dose**
  Antirheumatic (nonsteroidal anti-inflammatory) –
  Infants up to 6 months of age: Safety and efficacy have not been established.
  Children 6 months to 12 years of age: Oral, initially 30 to 40mg per kg of body weight a day in three or four divided doses, although 20mg per kg of body weight per day may be sufficient for patients with mild disease. After a satisfactory response has been achieved, dosage should be reduced to the lowest dose needed to control disease activity.
  Antipyretic –
  Infants up to 6 months of age: Safety and efficacy have not been established.
  Children 6 months to 12 years of age: oral, 5mg per kg of body weight for fevers up to 39°C and 10mg per kg of body weight for higher fevers. Dosage may be repeated, if necessary, at intervals of four to six hours or more.

**Usual paediatric prescribing limits**
  Antirheumatic –
  Oral, 50mg per kg of body weight per day.
  Antipyretic –
  Oral, 40mg per kg of body weight per day
  [Note: No dose is quoted in AusDI for relief of pain]

Other standard works state:

- *Martindale. The Extra Pharmacopoeia*: 20-30mg/kg/daily in divided doses.
  UK recommendations:
  6-12 months 150mg daily
  1-2 years 150-200mg daily
  3-7 years 300-400mg daily
  8-12 years 600-800mg daily
  Not recommended in children less than 7kg.
  USA recommendations:
  Fever: 5-10mg/kg. Pain: 10mg/kg
  6-8 hourly up to a maximum of 40mg/kg daily.

Oral NSAIDs are usually only started once the child is eating and drinking adequately, and prescribed for a set time period, eg three days. *Therapeutic Guidelines Analgesic 2002* then gives the contraindications for the use of NSAIDs. These are:
Known hypersensitivity or allergy to NSAIDs
Peptic ulcer disease
Bleeding diatheses or potential for bleeding perioperatively or postoperatively
Severe asthma, especially if aspirin-sensitive or corticosteroid-dependent
Nasal polypitis
Renal dysfunction, hypovolaemia, diuretic therapy

Guidelines for ibuprofen

The AGRD Volume 2 includes guidelines for sponsors of products that contain ibuprofen. These were published in February 2001 after consultation with industry. Since then, some deviation from the guidelines has been necessary and the Update is asked to comment. The commentary below refers only to the differences between the February 2001 draft and a new draft, referred to here as “old” and “new”, respectively. Note that the guidelines relate to ibuprofen for both adult and child formulations.

Indications

Old: Did not include migraine headache.

New: Migraine headache inserted.

Comment: There should be no objection to this insertion.

Old: “As fever is a normal and beneficial response to infection, no elaboration to the words ‘reduces fever’ will be accepted except with regard to the duration of treatment and with regard to the relief of discomfort associated with fever”.

New: “As fever is a normal and beneficial response to infection, no elaboration to the words ‘reduces fever’ will be accepted except with regard to the duration of treatment or relief of discomfort associated with fever or to give examples in which fever may occur”.

Comment: The Review argued that fever was very much a secondary indication and mentioned the expression “fever phobia”. The Update reaffirms the Review’s recommendation about not elaborating on the words ‘reduces fever’. The Update considers that by giving examples, parents or carers will be encouraged to use antipyretics more often than they are needed.

Warning statements

Old: A statement targeted to oral ibuprofen is included.

New: The advice is divided into two parts. One part applies to both orally administered and topically applied ibuprofen. The other is for orally administered ibuprofen.

Comment: The new format recognises the recent availability of topical ibuprofen. The wording is technically correct but would not the public be the better informed if the
advice referred to “blood thinners” instead of “anticoagulant medication”? As well as ibuprofen, there are two NSAIDs (naproxen and mefenamic acid) that are available in Schedule 2 for the relief of pain associated with dysmenorrhoea. Diclofenac 25mg is now available as a Schedule 3 medicine and there may be others in future. The Update suggests that a class warning statement might now be considered. The last sentence of the warning advises consumers to ask their doctor before using ibuprofen if they are taking certain drugs “or other medicines for pain relief”. Sponsors should seek advice from experts in communicating technical messages to the public.

Dose

Old: For children, the guideline said: “The recommended dose is 10mg/kg/dose or 20-40mg/kg body weight per day in divided doses according to the severity of the condition. Doses should be given every 6-8 hours as necessary with no more than 4 doses in 24 hours. Medical advice should be sought before giving ibuprofen liquids to infants under 12 months of age. Paediatric dosage recommendations based on 10mg/kg per dose – the dose (in mL) is based on a strength of 100mg/5mL”. Then follows a table setting out a range of ages, a range of average weights in kg and the dose for each group in mL.

New: “Doses should be given every 6-8 hours as necessary with no more than 4 doses in 24 hours. Where dosage instructions for children under 12 months of age are included on the labelling, the dosage instructions must include statements advising that the product should not be given to infants under 6 months, and that it should only be given to infants aged 6-12 months following the advice of a doctor”. Then follows a table showing the same age ranges and average weights but the doses are given in milligrams. The text continues: “Doses should be expressed where possible in whole numbers and should be presented with age, weight and volumes (in mL) unless otherwise justified. The recommended dose should be able to be measured using commonly available metric measuring devices. There may be instances, therefore, where the dose needs to be slightly different from the recommended milligram doses given above, depending on the ibuprofen concentration of the product. Sponsors intending to supply measuring devices with the product should consult Australian Standard AS 2224.2 – 1986. Calibrations on measuring devices should be in metric units and correspond with the doses shown on the label where possible to minimise the need for calculation and guesswork”.

Comment: The Update considers that the guideline should state the general dosing information as in the Old version. Most of the authorities quoted above give a range (unlike paracetamol where there is only one concentration, being 15mg/kg) of 5-10mg/kg per dose rather than a fixed dose of 10mg/kg, as in the old version. If, however, there was a range of 5-10mg/kg and a range of body weights for given age groups, extra complications would be introduced. On the basis of safety and simplicity, the new table’s single dose column closely follows a compromise of 7.5mg/kg and translates neatly to metric-type volumes of 2.5, 5, 7.5, 10 and 15 mL for the common 100mg/5mL products.

The new guideline recognises the introduction of an ibuprofen oral liquid that contains 40mg/mL. The word “exclusively” should be inserted before “metric units”. The
Review expressed its concern about the continued availability in Australia of various medicine measures (cups, syringes and droppers) that had teaspoonful measures as well as metric measures.
PARACETAMOL AND ALCOHOL

Term of Reference No.4 for the Update states:

Consider the US mandatory label statement for paracetamol “ALCOHOL WARNING: If you consume more than 3 alcoholic drinks every day, ask your doctor whether you should take acetaminophen or other pain relievers/fever reducers. Acetaminophen may cause liver damage” in the light of any information that has become available since 1998.

Biochemistry

In therapeutic doses, about 95% of paracetamol undergoes hepatic detoxification by conjugation to form glucuronides and to a lesser extent, sulphates. About 5% is metabolised to the hepatotoxic metabolite N-acetyl-p-benzoquinonimine (NAPQI) through the cytochrome P450 enzyme system. The NAPQI so formed is inactivated by glutathione which in turn is excreted in the urine as thiol metabolites. Doses as low as 0.5 to 3g of paracetamol reduce the levels of hepatic glutathione (Slattery et al, 1987).

In an experiment using healthy volunteers, Chien et al (1998) found that clearance of NAPQI was reduced by 72% when 500mg of paracetamol was given simultaneously with alcohol.

In an overdose, the glucuronide/sulphate pathways become saturated. Cytochrome P450 converts unconjugated paracetamol to NAPQI. Glutathione stores are also exhausted. This protective mechanism is overwhelmed so reducing the inactivation of NAPQI. The end result is liver damage.

The presence of other substances such as rifampicin and phenytoin can affect the metabolism of paracetamol. The role of alcohol is particularly complicated as the doses of both alcohol and paracetamol and the drinking pattern of the subject all have to be taken into account. Fasting is also influential as it further lowers glutathione reserves. And, as alcoholics often have an inadequate diet, more marked changes can be expected when all three factors – excess paracetamol, excess alcohol and fasting – are present.

A controversial subject

The controversy about paracetamol and alcohol is shown by these quotations from recent papers:

- “It is now generally accepted that after an overdose (italics added) of acetaminophen (INN, paracetamol), persons with chronic alcoholism are at increased risk of acetaminophen-induced hepatotoxicity”. (Thummel et al, 2000).
- “There is little evidence that a history of chronic alcohol use worsens liver damage or outcome in this circumstance” [when paracetamol is ingested in large doses for suicidal or therapeutic reasons]. (Riordan and Williams, 2002).
- “Although the possibility that chronic alcoholics are at increased risk of paracetamol hepatotoxicity can by no means be excluded, the available evidence
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does not support claims for a major toxic interaction between ethanol and paracetamol in man. Further studies are required but until these issues are resolved, all patients who take alcohol in excess must continue to be considered at high risk following an overdose of paracetamol and be treated with N-acetylcysteine accordingly”. (Prescott, 2000).

- “Because the minimum safe dose of acetaminophen is not known in the setting of chronic alcohol use, it seems prudent in such situations to avoid acetaminophen altogether, especially during brief periods of abstinence”. (Tanaka et al, 2000).
- “A comprehensive systematic review of the medical literature located no case of hepatic injury that could be reasonable (sic) attributed to the therapeutic use of APAP in an alcoholic patient”. (Palmer et al, 2002).

The relationship between chronic exposure to alcohol and paracetamol ingestion has received different emphases in Australia and the United Kingdom on the one hand and the United States on the other. These issues were mentioned in the Review and were reflected in mandatory label changes from 1998 to American products that contained paracetamol (FDA, 1998). Neither the United Kingdom nor Australia has included alcohol-specific warnings, either by law, or as a condition of registration.

Makin and Williams (2000) examined the records of 560 patients treated for paracetamol-induced severe hepatotoxicity from 1987 to 1993 in the Liver Failure Unit of King’s College Hospital. Most patients had deliberately overdosed while 7% had taken excessive doses in pursuit of analgesia. After excluding several cases because of unreliable data, patients were allocated to into four groups in terms of alcohol consumption, adjusted for men and women. These were:

(i) non-drinkers;
(ii) light drinkers (males <30g/day, females <20g/day);
(iii) moderate drinkers (males <60g/day, females <40g/day); and
(iv) heavy drinkers (males >60g/day, females >40g/day).

This information (and that of paracetamol consumption) was obtained from the subject or next of kin and every attempt was made to check the veracity of the data.

The results of their survey showed that 70% were either non-drinkers or light drinkers, 8% were moderate drinkers and 22% were heavy drinkers. An analysis of the data showed that there was no difference in the apparent severity of hepatotoxicity or outcome following overdosing for therapeutic reasons or a deliberate overdose. There was no evidence that heavy drinkers from either group developed more severe hepatotoxicity. These findings were consistent with several earlier series. A criticism of this survey was that the independent influence of chronic alcohol intake was not studied, so leaving open the possibility of confounding between variables (Schiødt et al, 2002). This objection does not seem all that strong because among the moderate and the heavy drinkers, chronic use is bound to be present.

The American authors, Kuffner and Dart (2001) criticised the FDA label. They said that in the absence of accurate, consistent data, physicians have relied on retrospective and anecdotal evidence that has perhaps lead to greater restrictions on paracetamol use than is necessary for patients who consume alcohol. A study that these authors and their
associates conducted in 2001 divided 230 alcoholic patients who were enrolled in a
drug detoxification program into two groups to receive either paracetamol 1000mg
alone or a placebo for two consecutive days. The aim of this randomised, double-blind,
placebo-controlled study was to determine whether alcoholics are at increased risk for
hepatic injury when they take paracetamol in therapeutic doses (Kuffner et al, 2001).

Study variables were AST, ALT and INR measurements. At days 2 and 4, no
differences were noted in these variables between the groups. This study drew criticism
because the conclusions might pose a potential public health hazard (Oviedo and Wolfe,
2002). The critics said that Kuffner et al should not have concluded that, because there
were no increases in enzyme levels, no hepatotoxicity occurred and that liver toxicity
has been greatly overstated. There was also objection to the duration of the trial (only
two consecutive days) because people commonly use paracetamol for prolonged
periods and the authors were remiss in not quoting a study that showed that a single
500mg dose of paracetamol given in conjunction with ethanol infusion resulted in an
increase in NAPQI (Thummel et al, 2000).

Kuffner and Dart (2001) and Dart, Kuffner and Rumack (2000) reviewed the literature
for paracetamol use in alcoholics and found that the most stringently controlled studies
have not demonstrated a greater risk for alcoholics. They concluded on the basis of
experimental evidence and literature review that “current clinical evidence does not
support a need to reduce the dose of acetaminophen given to patients who use alcohol,
nor does the evidence support prohibiting the use of acetaminophen entirely in these
patients”.

Kuffer (2001) observed that the patients who drink alcohol and who avoid paracetamol
are at increased overall risk because of the replacement of paracetamol with the
NSAIDs.

In their analysis of the literature of the effect of chronic alcohol exposure on
paracetamol-related hepatotoxicity in the clinical setting following paracetamol
overdose (from either deliberate self-poisoning for suicidal or parasuicidal intent or
overdose for therapeutic reasons), Riordan and Williams (2002) concluded that there is
little evidence that a history of chronic alcohol use worsens liver damage or outcome in
cases of paracetamol overdose.

Palmer et al (2002) undertook a large review of the literature in English and another
nine languages of alcoholics who took one or more therapeutic doses of up to 4g of
paracetamol. It produced 669 subjects. Prospective studies yielded 620 patients who
received paracetamol with no evidence of successive liver injury, including 172 who
received multiple maximal therapeutic doses. Retrospective studies provided 49 patients
with liver injury attributed to paracetamol but these were compromised by at least one
serious deficiency, these being (i) conflicting data; (ii) incomplete evaluation of other
diagnoses; and (iii) a major plausible alternative diagnosis.

Acute v chronic alcohol consumption with paracetamol overdose

The distinction between acute and chronic alcohol consumption in the face of single
paracetamol overdose was the subject of a Danish study of 645 consecutive patients
admitted from 1994 to 2000 (Schmidt et al., 2002). This study confirmed that the time to start NAC was the most important prognostic factor; i.e. the risk of developing hepatotoxicity increases with time elapsing before administering NAC. These authors recognised that numerous uncontrolled case reports have suggested that the hepatotoxicity increases with “chronic alcoholism”; Prescott (2000), however, had previously discounted this view on the basis of its anecdotal nature and that late presentations in such cases explain the prevailing view. The Danish authors believe that their study provides the first systematic evidence that chronic alcohol abuse is an independent risk factor but acknowledges that chronic alcoholics are often late presenters. Examination of the data, however, reveals a somewhat selective nature of the patients.

Support for the above finding was a recent study with 209 consecutive patients with single dose paracetamol overdose in Denmark. In this 1993-1996 series, 57 (27.3%) were chronic alcohol users and 45 (21.5%) had acute alcohol intake. Hepatic coma developed in 44 (21.1%) of the patients, nearly half of whom died; with chronic alcohol users were over-represented. The relative risks for hepatic coma and death were 5.3 (95% CI, 2.2-12.4) for the chronics and 1.4 (95% CI, 0.5-3.9) for the acutes (Schiodt et al., 2002). In this series, chronic intake of alcohol independently increased the morbidity in patients with paracetamol overdose, whereas acute alcohol intake did not affect the clinical course.

Three positions have emerged:

1. Alcohol does not enhance paracetamol toxicity when paracetamol is taken in therapeutic doses or excessive doses.
2. Alcohol does not enhance paracetamol toxicity when paracetamol is taken in therapeutic doses but it may in overdoses.
3. Alcohol does enhance paracetamol toxicity when paracetamol is taken in therapeutic doses and therefore excessive doses

The FDA’s warning about paracetamol, alcohol and the liver

In November 1997, the FDA gave notice that it intended to make mandatory a warning statement that had to appear on containers of medicines that contained paracetamol. This action followed from a number of case reports and several series that pointed to an increased risk of hepatotoxicity where paracetamol was taken in conjunction with alcohol, especially by heavy drinkers. The issue was complicated by legal and media interventions along with a concurrent trade war, not only between competing brands of paracetamol, but also among competing brands of analgesics.

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

Despite this warning, there is still no mention about the delay (“the silent period”) between ingestion and the appearance of toxic symptoms, nor is there any mention of an excessive dose of paracetamol.
Canadian warning

Canada also introduced an “alcohol warning”. It states: *Chronic heavy alcohol users may be at increased risk of liver damage when taking more than the recommended dose of acetaminophen.*

Although the subject matter of the Canadian statement is similar to the American, it does not quantify the amount of alcohol in terms of the number of drinks nor does it direct drinker/consumers to their medical practitioners. The description “heavy alcohol user” is a man or woman who consumes more than 60g (75mL) or 40g (50mL), respectively, of ethanol daily. For example, a man consuming four 375mL cans of beer containing 4.9%v/v ethanol, very nearly meets this definition. Further comment on the Canadian version is set out below.

Should there be a paracetamol/alcohol warning statement on Australian products?

The 1998 Review considered the relationship between alcohol and paracetamol consumption. The Review concluded that a similar warning was not warranted in Australia but that the FDA’s requirement be re-examined after it had been in operation for one year. If such an initiative were prescribed in Australia, clear and consistent advice would need to be given to consumers by medical practitioners, pharmacists and manufacturers.

Interestingly, neither the United Kingdom nor the Republic of Ireland – despite their tightening of the regulations governing the labelling, packaging and supply of analgesics – have thought it necessary to include an “alcohol warning”.

The matter remains unresolved. There is no definitive answer to the question. At this stage, however, the Update does not recommend the compulsory adoption of a statement along the lines of that used in the USA. The Review mentioned the different controls of availability of medicines in that country when compared with Australia and the litigious nature of American society. Follow-up studies to that of Schmidt *et al* (2002) and Schiødt *et al* (2002) will be required before a warning of this kind should be considered in Australia. If a paracetamol-alcohol warning label were contemplated for Australia, the Canadian wording more accurately reflects the present state of knowledge because it:

- refers to chronic heavy alcohol users;
- uses the word “may”; and
- links the use of alcohol to overdoses of paracetamol.

The American label does not do these things. Should a statement of this kind be considered, suitable testing among consumer groups would be necessary.

The Update considers that the matter should be managed within professional circles by way of education.

A problem arises with sponsors whose American principals direct their Australian subsidiaries to include the American statement. If such a statement were included
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Voluntarily as a safety issue, it would create an inconsistency and be at odds with the advice the Review received in 1998 in that aspirin might be substituted and be less appropriate in the circumstances described on page 26 of the Review.

**Recommendation 5**

The American warning label about paracetamol and alcohol should not be adopted in Australia.

**Recommendation 6**

Recommendations 4.1 and 4.2 of the Review be implemented. These Recommendations were:

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 users.

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

Term of Reference No.5 states:

Consider the US mandatory label statement for aspirin and other NSAIDs “If you consume 3 or more alcoholic drinks every day, ask your doctor whether you should take [name of NSAID] or other pain relievers/fever reducers. [Name of NSAID] may cause stomach bleeding”.

FDA regulatory action

In 1998, regulations came into effect in the United States of America requiring the above statement to be shown on labels of non-prescription products containing aspirin or the NSAIDs with ibuprofen and naproxen being the most prominent (Federal Register 1998;63(205):56789-56802). Notice of the intention to make the rule was made in late 1997 and the FDA asked manufacturers to voluntarily adopt the sentence. A similar statement was not among the amendments in relation to analgesics that were introduced in the United Kingdom in 1998.

Alcohol, aspirin, NSAIDs and peptic ulcer disease

The relationship between the consumption of either aspirin or the NSAIDs with peptic ulcer disease is well established. About one-third of gastric ulcers are caused by NSAIDs. Distinctions can be made on the dose and duration of treatment and on the particular NSAID, with ibuprofen being generally regarded as the least likely of the class to be implicated. Alcohol, when in high concentration, can cause gastritis, especially in heavy drinkers. Aspirin, in the presence of hydrochloric acid, can produce severe gastric bleeding in dogs and this effect is much enhanced by alcohol. It is caused by an impairment of the mucosal barrier to back diffusion of intraluminal hydrogen ions into the mucosa.

In a laboratory experiment, 60 normal volunteers were divided equally into six groups taking ibuprofen (600mg), aspirin (75mg) or placebo with or without alcohol (approx 35mL ethanol in orange juice). Four doses were given over 24 hours. Each subject was endoscoped and the gastric mucosa examined. Aspirin caused the most damage, followed by ibuprofen and the placebo. Alcohol increased the damage in all groups but not to any significant extent. Interestingly, the effect was slightly more pronounced with ibuprofen (Lanza et al, 1985).

Henry et al, (1993) in a five year study, looked at the risks on using non-aspirin NSAIDs in the presence of alcohol or aspirin. A combination of aspirin with regular and significant intakes of alcohol, NSAIDs and smoking were significantly associated with an adverse outcome. Additive risks were shown when NSAIDs were combined with aspirin or when either aspirin or the NSAIDs were taken with significant amounts of alcohol. These authors concluded that the risks of non-aspirin NSAIDs when taken with aspirin or alcohol were unclear. When this study was conducted, the non-prescription NSAIDs were less widely used in Australia than today. They were
Schedule 4 (Prescription Only Medicine) until 1989 when low strength ibuprofen (200mg) was transferred from Schedule 4 to Schedule 3 (Pharmacist Only Medicine). Despite the transfer to non-prescription status, ibuprofen could not be advertised to the public and it was available only after an interview with a pharmacist. Ibuprofen was transferred to Schedule 2 (Pharmacy Medicine) in 1996, the effect of which was to allow advertising. Were this study carried out today, the result might be different because of the down-scheduling of ibuprofen, which, unlike aspirin, continues to be in Schedule 2 and hence available only from pharmacies.

A major case control study (1224 patients and 2945 neighbour controls) carried out between 1987 and 1996 in the USA and between 1989 and 1992 in Sweden attempted to assess the risk of acute major gastrointestinal bleeding among users of aspirin and ibuprofen at various levels of alcohol consumption (Kaufman et al, 1999).

In the case of aspirin, there was a significant positive association with the regular use of aspirin at doses >325mg but trends of relative risk could not be established at levels of <1 to 20 drinks per week. At high levels of alcohol consumption, precise data were not available but overall, the relative risk estimate among all current drinkers combined was 7.0 (CI 5.2-9.3); among ex-drinkers, it was 9.0 and among never-drinkers, it was 5.1. For doses of aspirin < or = 325mg, the relative risk for both occasional and heavier drinkers, the risk estimates were lower.

For ibuprofen, the study did not state the dose or the duration of treatment. One unusual results was recorded; the study found an estimated relative risk of 4.4 (CI 1.8-11) for patients who drank less than one drink per week but this estimate was markedly less at higher levels of alcohol consumption. The overall relative risk estimate for regular ibuprofen use among all drinkers combined was 2.7 (CI 1.6-4.4)

An analysis and editorial comment of the Kaufman study and previous literature agreed that heavy drinkers who take aspirin are at greater risk of gastrointestinal bleeding but the Kaufman data do not equivocally support an additive effect of aspirin and alcohol on the risk of bleeding (Pfau and Lichtenstein, 1999). The group at greatest risk is that comprising patients who use higher doses of aspirin or other NSAIDs on a regular or daily basis and who drink at least three to five alcoholic beverages every day.

For ibuprofen, “regardless of the doses, kind, or frequency of NSAIDs taken, no significant difference is reported to exist overall between NSAID users who describe any current drinking, those who are ex-drinkers, or patients who reported never drinking alcohol”. The data do not support an additive or synergistic effect of alcohol with aspirin or alcohol with ibuprofen. The editorial concluded: (i) there is no proof that mild to moderate alcohol use increases the risk of upper gastrointestinal bleeding in patients who are using aspirin or NSAIDs, especially if the NSAIDs are used on an as-needed basis; (ii) at risk patients need to be identified; and (iii) patient education is critical in that there is a potential danger of daily heavy consumption of alcohol in patients who are taking, or who must take, NSAIDs.

A study in Saskatchewan using health insurance data sought to determine if the combination of alcohol and the NSAIDs posed a greater risk than either alone; in other words, was the action additive or synergistic? (Neutel and Appel, 2000). The study
suggested, on the basis of the odds ratio, that alcohol abuse (italics added) with ibuprofen or naproxen (6.5) was greater than the expected odds ratio if the two were added (4.5). Higher odds ratios were obtained if other NSAIDs were substituted. If the ibuprofen and naproxen data were obtained from health insurance figures, these drugs would very likely have been prescribed at higher doses than those used in non-prescription circumstances. This would indicate lower odds ratios for non-prescription NSAIDs. These authors pointed out that the FDA warning deals with concurrent use of three or more drinks per day and not directly with long-term alcohol abuse. Although concurrent alcohol use appears to increase the risk of GI bleeding as an independent factor, it may not have the same impact as alcohol abuse induced damage. Neutel and Appel thought that the warning might be extended to include a caution about long term excessive alcohol use as well as current use.

Canadian labels or package inserts do not include a statement about alcohol with the NSAIDs.

A recent American paper considered the risks of gastrointestinal bleeding due to non-prescription NSAIDs (Blot and McLaughlin, 2000). The survey was carried out by seeking information from gastroenterologists who were asked to complete forms for up to 10 recent cases involving GI bleeding and 10 procedure-matched patients without GI bleeding who were the controls. Demographic data and analgesic, tobacco and alcohol use were obtained from 627 “bleeding” patients and 590 “non-bleeding” controls. Both aspirin and ibuprofen were linked to increased risks of GI bleeding in both drinkers and non-drinkers with aspirin/alcohol combining in a nearly additive manner but ibuprofen/alcohol being multiplicative. Having said that, the authors admitted that the data were too sparse to evaluate adequately additive effects compared with multiplicative effects. Drinking alcoholic beverages was associated with a statistically significant two-fold increase in risk of GI bleeding (95% CI 1.4-2.7) with the increase occurring among both smokers and non-smokers. In an acknowledgment of the limitations of their survey, the authors caution that no definitive statements about adverse effects can be drawn. There was no information on the kinds of alcoholic drinks and there were missing data on how much alcohol was consumed. Rather, the information obtained from the survey was more useful in generating, or refining, the hypothesis that OTC levels of NSAIDs can increase the risk of GI bleeding and that alcohol further intake increases that risk. The findings are, however, supportive of the Saskatchewan study.

Should an alcohol statement be required on labels of medicines that contain aspirin or the NSAIDs?

From the data available and from what is known about the effects of alcohol on the gastrointestinal tract, one could reasonably conclude that alcohol is a risk factor for people taking aspirin or the NSAIDs. But is it to the extent of mandating the text of the statement that is used in the United States? The risk is presumably higher if a prescription NSAID is taken but there is no requirement in that country (or in Australia) for an extra label to be added to containers of NSAIDs dispensed in pursuance of a prescription. Further, people who purchase ibuprofen are more likely to require it on an as-needed basis, rather than chronically. Or is there an unstated commercial reason; namely, that if an alcohol warning has to go on paracetamol, it must also be placed on...
aspirin and the NSAIDs so that none of these analgesics is perceived as having a marketing advantage over the others in a highly competitive environment? In other words, either all of the OTC analgesics must have an alcohol warning (for different pharmacological reasons), or none of them should have it. Despite the different pharmacology and toxicology of the particular drugs, the OTC analgesic business has many of the characteristics of a perfectly competitive market: minimally perceived differences in the product, large numbers of buyers and sellers, matched prices, similar presentations, ready availability and similar uses.

Therefore, any product differentiation such as the absence of a negative statement will be an advantage to the competitor and advertised as such.

Examination of Product Information (PI) documents fails to show significant mention of alcohol for the prescription-only NSAIDs. Alcoholism is sometimes mentioned as a risk factor known to be associated with gastrointestinal ulceration. But under the standard headings of Contraindications, Precautions and Drug Interactions in PIs, there is nothing remotely resembling the American warning. The Australian Pharmaceutical Formulary and Handbook 18th edition does not make any recommendation to pharmacists about adding a supplementary label in connection with the use of alcohol when NSAIDs have been prescribed.

On the basis of the available data, there may be a case for heavy drinkers who are chronic users of aspirin at any dose to take heed of the warning that forms the American statement. These patients are likely to be in the older age group and whose consumption of aspirin is in small daily does for inhibition of platelet aggregation. Presumably the recommendation to take aspirin in a low daily dose would be on the initial advice of a medical practitioner who is in a position to balance the risks facing a particular patient. It does not follow, however, that an American-style warning is justified on Australian packages given the data and that Australia does not have the financial barriers to accessing medical services that are present in the United States and a graded system on controls on availability of medicines.

A further complication is the peculiar relationship between alcohol consumption and Alka Seltzer. The Update has not researched this subject.

**Recommendation 7**

The American warning label about aspirin, the NSAIDs and alcohol should not be adopted in Australia.

**Recommendation 8**

The editor of the *Australian Prescriber* be requested to arrange for, and publish, a review article about the relationship between aspirin and the NSAIDs, the consumption of alcohol and gastric bleeding.
ADDITIONAL UNITED KINGDOM WARNING STATEMENTS

Term of Reference No. 6 states:

Consider the UK mandatory warning statement “Immediate advice should be sought in the event of an overdose, even if you (your child) feel well, because of the risk of delayed, serious liver damage”.

Term of Reference No. 7 states:

Consider the additional UK mandatory warning statement “Do not take with other paracetamol-containing products”.

These statements formed part of several measures introduced in the United Kingdom on 16 September 1998 to reduce the incidence of morbidity and mortality arising from paracetamol poisoning. As none of the studies considered the contribution of the warning statements in isolation, it is necessary to review the effects of the initiatives taken as a whole. The Terms of Reference do not require the Update to make any recommendations on availability but passing reference is made to it.

The extent of the problem

Compared with other countries, the United Kingdom had disproportionately more hospital admissions, more liver transplants and more deaths associated with paracetamol. Briefly, the figures quoted were:

- In 1997, 562 death certificates had referred to paracetamol as the underlying cause of death, with aspirin and ibuprofen being implicated in 51 and two cases, respectively. (Anon (d), 2000)
- About half of all cases of liver failure were ascribed to paracetamol (O’Grady, 1999).
- Paracetamol was implicated in 40% of cases on deliberate self-poisoning (Fagan and Wannan, 1996)
- Paracetamol was the most common cause of fulminant liver failure (ibid).
- There were about 70,000 admissions due to deliberate self-poisoning with paracetamol yearly (ibid).
- In Scotland, from 1991 to 1993, the incidence of deliberate self-poisoning with paracetamol was estimated to be 73.3 (males) and 91.7 (females) per 100,000 per year (McLoone and Crombie, 1996. (In Virginia USA, the corresponding rate was 21.4/100,000 per year (Bond and Hite, 1999)).
- When the restrictions were announced in September 1997, the Medicines Control Agency announced that paracetamol overdose accounts for 30,000 to 40,000 hospital admissions and 100 – 150 deaths each year.

No definitive answer has been provided for the reason for the high rates of morbidity and mortality in the United Kingdom but various factors have been mentioned or
speculated on about why people use paracetamol for suicide (Gazzard et al., 1976). These include the wide use of bottles of loose tablets in addition to the more expensive strip or foil packs; the popularity of combinations of paracetamol with dextropropoxyphene (Rutherford, 2001); late presentations to hospital; the belief among the young that paracetamol is a sedative and that British poisons information centres, unlike those in Australia, do not accept enquiries from the public. There is, however, a high awareness of the dangers of a paracetamol overdose in the United Kingdom (Brandon, 2002, personal communication), although this was not always the case (Gazzard et al., 1976).

The legislative remedy

Proposals were made as far back as 1976 to reduce the number of cases of paracetamol poisoning in the UK (Gazzard et al., 1976). In 1988, the Birmingham coroner proposed that paracetamol products should be labelled with a warning saying immediate medical advice should be sought if an overdose was suspected. Industry opposed the suggestion because previous market research had shown that one third of users would stop taking the drug and that the warning might lead to more deaths. The Department of Health had decided that the benefits for the few had been outweighed by the harm that such changes would cause (Anon (c), 1988).

In an effort to reduce the incidence of morbidity and mortality, new regulations came into full operation on 16 September 1998, after having been signalled one year earlier. The British government hoped the new rules would reduce the number of deaths by around 10% (BBC News). The quantity restriction followed that of France where the maximum size is limited to 8 gram of paracetamol. The regulations:

- reduced to 16 the number of paracetamol-containing tablets or capsules available from general retail outlets (in Australian terms, an unscheduled substance);
- reduced to 32 the number of paracetamol-containing tablets or capsules available from pharmacies (similar to Schedule 2 arrangements in Australia);
- permitted pharmacists to supply up to 100 tablets or capsules without a prescription, at the pharmacists’ discretion and in justifiable circumstances (similar to Schedule 3 arrangements in Australia);
- required labels or leaflets to have the sentence: “Immediate advice should be sought in the event of an overdose, even if you (your child) feel well, because of the risk of delayed, serious liver damage”;
- required labels to have the sentence: “Do not take with other paracetamol-containing products”;
- required the use of blister or strip packaging.

The restrictions were not extended to effervescent forms, granules, powders, suppositories and liquids as these were seldom implicated in overdose.

Similar restrictions, where appropriate, were applied to salicylates.
Initial criticism of the legislation

The UK restriction related to the number of tablets in a pack but not to the number of packets that could be sold at any one time. A person could purchase any number of packets at the one shop and neither the seller nor the buyer committed any offence. Even the strapping together of two or more packets of 16 was within the law.

The Proprietary Association of Great Britain felt that the new regulations would do little to address the problem. The Association’s secretary said: “If someone wants to purchase more than sixteen, all they have to do is go to several different shops and do just that. So we don’t think it is going to work as a restrictive practice”. A spokesman for Overcount – an organisation that specialises in addiction and misuse of over-the-counter medicines – said new labelling which will appear on the packets warning of the risks of taking too many tablets could lead some people to attempt an overdose. The spokesman said: “For the person that’s (sic) contemplating an overdose that is a cry for help – the pseudo-overdose – they may actually be drawn to deliberately choose this product”. He also questioned the training and supervision of sale staff in supermarkets and garage forecourts, many of whom seemed unaware of the problems and continue to sell several packets in the one sale. “You have to question why drugs, even in quantities of 16, are being sold at places like garages, supermarkets and shops” (BBC News).

The effects on general practice and the destruction in public confidence in paracetamol were condemned when the proposals were announced (O’Connell, 1997). General practitioners see the development of self-reliance on the part of patients as an integral part of a GP’s work which the new regulations would undermine (Hobson, 1997).

Jowett (1998) objected on the basis of cost increases and that, because self-poisoning is usually impulsive, the restrictions were unwarranted. The reduction to 16 tablets was described as “token” and “unhelpful”. He was also concerned at the possibility of transferring the problem to other substances so creating an overdose cocktail. Jowett felt that the prevention of repetitive overdose should receive attention.

Irish initiatives

The Republic of Ireland introduced an apparently more restrictive regime after the Irish Medicines Board recommended the sale of emergency supplies of 12 tablets only, to be available for general retail sale, and 24 tablets at a pharmacy. The labels had to include the sentences: “Contains paracetamol” and “Immediate medical advice should be sought in the event of overdosage because of the risk of irreversible liver damage” (Anon (f), 1997). The Irish response, in terms of the number of tablets, followed that of Finland in 1976. Interestingly, the introduction of the restrictions in 1997 was only a recommendation until given statutory effect in October 2001 (Laffoy et al, 2001).

Results of surveys

Robinson et al (2000). Admissions to five general hospitals in Belfast for paracetamol poisoning for the two six-month periods – January to June 1998 (590 patients) and January to June 1999 (594 patients) – were studied. While precise data on the number of tablets actually taken could not be stated, there was a reduction in the serum concentration of paracetamol at 4-6 hours post ingestion. There were also reductions in the overall amounts of antidote used and the number of severe paracetamol overdoses. The incidence of severe liver failure, however, was unchanged.

Turvill et al (2000) of the Royal Free Hospital in London, audited all overdoses presenting to it from September 1995 to August 1999 and calculated the total number of paracetamol overdoses that occurred. There was a 21% reduction in all paracetamol overdoses and a 64% reduction in severe overdoses. These resulted in a saving of about 200 in-patient days. Benzodiazepine overdoses remained constant over the period studied.

Prince et al (2000) examined the records of patients admitted to a liver unit in the north of England before and after September 1998 and also patients registered in the UK for liver transplant between October 1995 and December 1999. The severity of the overdose remained constant throughout the study period. They noted that 25% of referrals were at high risk of paracetamol toxicity because of alcoholism or use of anticonvulsants. Based on monthly referral rates, there was a reduction of severe paracetamol hepatotoxicity both locally (median 2.5 to 1) and nationally (median 3.5 to 2). Interestingly, the annual rate of referrals to the local centre was already falling in the three years before September 1998 but it fell more sharply after September 1998.

These authors cautioned that the legislation could have a deleterious effect if more dangerous substances such as the tricyclic antidepressants were to replace paracetamol.

A Welsh survey (Thomas & Jowett, 2000) of 116 and 112 overdose patients admitted six months before and six months after the amendment found that the number of paracetamol cases had dropped from 52 to 40, a fall from 44.8% to 35.7%. The quantity taken was known for 44 patients in the before group and 35 in the after group. Of the before group, 68% had taken more than 16 tablets while in the after group, the figure was 51%; these were reflected in the reduction in the number who required NAC from 16 cases to 9 cases. There was, however, an increase in the use of other agents, often as part of a mixture, including tricyclic antidepressants. Although there was a reduced demand on liver units, the overall unwanted workload on general physicians remained the same.

Following the introduction of the new requirements in Ireland, Donohoe & Tracey (2000) examined 2020 cases (1044 in 1997 and 976 in 1998) of acute deliberate paracetamol poisoning. More than 50% of cases involved 24 or less tablets with no significant difference between the years. The number involving more than 48 tablets declined but was not statistically significant. They
concluded that the incidence of overdose did not change after a voluntary reduction in the pack size was recommended in the Republic of Ireland.

- Hawton et al (2001) carried out a prospective study to examine the effect of the legislative changes on paracetamol-induced mortality; cases of liver toxicity after paracetamol overdose, as reflected in the numbers of liver transplants, referrals to liver units and abnormal liver function tests; the number and nature of cases of paracetamol overdose; and sales. The scope of this study is such that it is summarised in some detail.

Mortality study:

*Data source:* England and Wales  
*Composition of data:* Number of suicides, undetermined deaths and deaths resulting from poisoning attributable to paracetamol and the salicylates.  
*Periods:* Penultimate 12 months before the change, 12 months before the change and 12 months after the change.  
*Results:* A reduction in the number of paracetamol-related deaths from 262 to 241 to 203 (21%) for the above periods. The figures for salicylate deaths halved.

Admissions to liver units and transplants:

*Data source:* Five liver units in England  
*Composition of data:* Numbers of admissions to liver units and numbers of liver transplants.  
*Periods:* The 24 months before and the 12 months after the change. [Note: unlike the mortality figures (above), this part of the study did not divide the pre-legislative period into two lots of 12 months].  
*Results:* There was a 30% reduction in admissions to the liver units; numbers listed in four of the units for transplants more than halved (no data were supplied from the fifth unit); there were 66% fewer patients requiring liver transplants due to paracetamol poisoning.

<table>
<thead>
<tr>
<th>Transplant Unit</th>
<th>No. patients (24 months before/12 months after)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birmingham</td>
<td>132/18</td>
</tr>
<tr>
<td>Leeds</td>
<td>146/57</td>
</tr>
<tr>
<td>London (King’s College Hospital)</td>
<td>244/99</td>
</tr>
<tr>
<td>London (Royal Free Hospital)</td>
<td>39/9</td>
</tr>
<tr>
<td>Newcastle</td>
<td>58/18</td>
</tr>
</tbody>
</table>

(after BMJ 2002;325:678)

Non-fatal poisoning:

*Data source:* Seven general hospitals in England  
*Composition of data:* Number of presentations (but not admissions).  
*Periods:* The 12 months before and after the legislation.
Results: The absolute number of presentations decreased by 11% but the proportion of paracetamol presentations relative to others was unchanged. The proportion of overdoses in which more than 32 tablets were taken decreased by 17% and the average number of tablets taken in paracetamol overdoses decreased by 7%.

Sales:

Data source: Intercontinental Medical Statistics
Composition of data: Sales to pharmacies and other outlets in the United Kingdom (excluding Boots brand name products).
Results: There was a decrease in the number of tablets per packet sold but an increase in the number of packets resulting in little change in the total number of uncompounded paracetamol tablets sold. The data are unclear on any differentiation between pharmacy and general retail sales and sales of the 100 pack were excluded. There were substantial reductions in sales of a number of compounded paracetamol products, compounded salicylate products, combined paracetamol and salicylates and uncompounded salicylates.

- Newsome et al (2001). This survey took place in Scotland. The authors compared data from patients admitted to the Scottish Liver Transplantation Unit for the periods 1992-1998 (before the new regulations) and 1998-2001 (when the new regulations were in operation). The authors found no differences in the monthly referral rate for patients with paracetamol-induced acute liver failure, including those cases meeting King’s College Poor Prognosis Criteria. The only significant change in demographic data was a fall in time from overdose to hospital presentation, being 32.2 hours to 13.1 hours. This study differed from the previous ones in that it covered a longer period (30 months versus 12 months). The study showed an association between paracetamol poisoning and social deprivation. The authors said that alternative strategies to decrease paracetamol poisoning are needed in Scotland.

- Sheen et al (2001) used serum concentrations as an indicator of paracetamol toxicity and found there was no change in Tayside, Scotland after the new regulations were in operation.

- Laffoy et al (2001) collected data from Irish hospitals for the number of admissions for paracetamol overdose between 1993 and 1999. There was a 29% increase over the period with a drop of only 1.9% since the recommendations of the Irish Medicines Board were introduced in 1997. Other findings were that females had twice the admission rate of males; the proportion of intentional overdoses rose from 54.4% to 72.3%; about 50% of intentional overdose admissions were in the 15-24 age group; children under the age of 5 years accounted for about 20% of admissions.

These authors also had no difficulty in purchasing multiple packs (2 x 24 or 4 x 12) in 100 Dublin supermarkets, mini-markets, smaller shops/newsagents and petrol stations. The Board’s conditions were ignored because: (i) sales in excess
of the guidelines (12 tablets) are easily made; (ii) large supermarkets sell packs of 24; (iii) supermarkets display large quantities and a variety of paracetamol products; and (iv) stocks are not limited to emergency supplies.

Unlike the UK, where the change in overdose behaviour was attributed to the introduction of blister packs and reduced availability, the same did not happen in Ireland where blister packs are used routinely. It was concluded that the reduced availability was the likely contributing factor in the improvements seen in the UK.

Subsequent literature comments

Shortly after the new legislation came into force, Cranney et al (1998) expressed the view that the reforms would not work. They noted that 32 tablets were enough to commit suicide, noting that the new regulations did not prevent the easy acquisition of tablets. They bought eight packets of 16 from four different supermarkets within half an hour. Unit costs had roughly doubled (due to packaging); some patients would go to doctors to obtain paracetamol on the NHS so increasing the cost of the scheme and create extra work for general practitioners. The vast majority of people would be inconvenienced. They considered that the proposal had “laudable aspirations but are a paternalistic folly”. Liddell (2001) observed a person attempt to buy four packets at a supermarket and be told that there was a limit of two at the checkout but more could be purchased at the cigarette counter. [Note: A small supermarket in Queensland was observed to stock packets of paracetamol behind the manned cigarette counter instead of on the self-service shelves (Routley V, personal communication, 2002) but the purpose was connected with the extortion threats rather than supervising purchases for therapeutic reasons (Petrie A, personal communication, 2002)]. Norman et al (2001) found it was possible in London to purchase much in excess of the restricted numbers in pharmacies, supermarkets and corner shops. These authors also found that it was possible to buy large quantities from vending machines which do not limit the amount sold.

The price of a dose of paracetamol has increased by 91 per cent and there is serious inconvenience to the public as a packet of 32 tablets represents four day’s treatment for one person with a chronic painful condition. One correspondent asserted that pharmaceutical firms and packaging companies were the only beneficiaries of the amendment even if no lives were saved (Wakeford, 2000). Some pharmacists were refusing to supply more than 32 tablets, irrespective of the reasons, even though they may do so at their discretion in justifiable circumstances (Walton, 2000).

The Turvill and Prince papers were the subject of a critique by Poulin (2000) who agreed that both studies showed clinically and statistically significant decreases in the numbers of overdoses and transplants, but did not provide definitive evidence of causation. Neither study differentiated between unintentional and intentional poisoning, nor did either report on paracetamol mortality and completed suicide. In noting the high rate of paracetamol poisoning in the UK, Poulin said that there exists in the UK an entrenched mass awareness of paracetamol as a vehicle for suicide which may be difficult to reverse. Despite the criticism of the studies, Poulin concluded that the new measures were well-founded and do not seem unduly harsh.
The negative results of the Robinson study (above) were considered unsurprising because the median ingested dose did not reach a level of 12g. doses below which rarely cause hepatic failure. In an attempt to reconcile the conflicting results of Robinson on the one hand, and of Prince et al and of Turvill et al on the other, Sheen and MacDonald (2000) believe that there should be a stricter definition of paracetamol overdose to take into account only those subjects who claim to have taken an overdose and who have a measurable serum level. These authors said that in view of the modest results found in the Turvill study, limiting paracetamol to prescription-only should be considered.

The Hawton study was criticised because one year is too short a time to assess the full impact of the legislation (Dargan and Jones, 2001; Scott, 2001). There were specific criticisms concerning the assessments of the acute liver patients and that there has been little change in blood paracetamol concentrations and the mean number of tablets taken per overdose. Sheen and MacDonald (2001) observed that the Hawton study used figures from England and Wales only. In Scotland, where the mortality rates are twice that of England and Wales, the number of self-poisonings has remained unaffected. Anecdotal evidence of admissions to the Royal Infirmary of Edinburgh indicated that the restrictions were not working. A public education campaign focusing on the potential dangers of overdosing and improved labelling by avoiding small print, were suggested (Payne, 2000).

Isbister and Balit (2001) observed the omission of the effect of the legislation on accidental poisoning in children and that with only one year of data, the results were not significant for the larger transplant units alone.

Natoff (2000) queried whether the objective of reducing admissions had really been achieved but Brandon (2000) explained that the restrictions were not necessarily intended to reduce the number of overdoses but to reduce the severity of impulse overdoses taken in the home.

Other observations

In a commentary, the Paracetamol Information Centre (an industry-funded organisation) believes that the legislation has achieved its intention to reduce impulse overdoses which are usually made using whatever is to hand in the home. Those seriously intent on suicide would probably not be deterred and that there is little that is effective in preventing a serious suicide attempt. The Centre said that the legislation caused considerable inconvenience to the public in general and to those suffering from chronic pain, especially by reduced accessibility and increases in cost. However, the Centre now believes that the restrictions strike a reasonable balance between availability and a reduction in self harm (Paracetamol Information Centre, 2002).

Comment

Despite the many criticisms of the methodologies and especially the short time of testing the outcomes following the changes, it would be difficult to assert that the four changes when taken together, (limitations on availability, use of blister packs and two
new warning labels) did not have some beneficial influence. The Irish evidence points indirectly to the first of these – limits on availability – as being the major factor because the Irish previously used blister packs rather than bottles. Nothing has been said about the warning statements other than reference to an earlier finding that stronger warnings on labels are unlikely to have much impact (Hawton et al, 1996; Fagan and Wannan, 1996). The Scottish data, however, hints at the possible beneficial effect of the label (in relation to the delayed effect) by showing that the time between consumption and hospital presentation fell from 32 hours to 13 hours.

Also omitted is whether the publicity, of itself, given to the new controls had an influence by raising public awareness that an OTC medicine taken in overdose could have catastrophic consequences. The doubling of the price has likewise not been mentioned as a possible factor.

**Analysis of UK, Irish, Canadian and American warnings**

Both the UK and Irish statements refer to liver damage but the Irish statement makes no reference to the all important property of the delayed symptoms. Moreover, the irreversibility of the damage to the liver may not occur. Nor does it follow that all overdoses will produce liver damage. The UK statement directs people to obtain immediate advice in the event of an overdose but from whom? Poisons information centres in the UK are not accessible to the general public unlike those in Australia although the Update understands that the National Health Service now operates a call centre for public use.

As well as “Immediate medical advice should be sought in the event of an overdose, even if you (your child) feel well, because of the risk of delayed, serious liver damage”, there is a second abbreviated statement: “Immediate medical advice should be sought in the event of an overdose, even if you feel well”. The first statement must appear on the primary pack if there is no package insert. If there is a package insert, the first statement must be included in it, provided the second statement also appears on the container.

**The North American experience**

Although the Terms of Reference Nos. 6 and 7 mention only the UK warning statements, the Update considers desirable some comment on the North American experience, especially that of the USA in light of recent hearings by the Food and Drug Administration.

In 1977, the FDA’s Advisory Review Panel recommended to the FDA the following warning to be placed on the labels of paracetamol products: *Do not exceed recommended dosage because severe liver damage may occur.* An extra recommended statement, applicable to chronic users, read: *Do not exceed recommended dosage or take for more than 10 days, because severe liver damage may occur.*

By 1988, a tentative final monograph was published concerning non-prescription analgesics and comments were invited in relation to the Advisory Review Panel’s proposals.
Arguments in favour of warning statements were:

1. Consumers have a “right to know” about toxic effects.
2. There is increasing use of acetaminophen.
3. Fatalities and liver damage have occurred in children.
4. The warning may discourage consumers from exceeding the recommended daily dosage.
5. There are no unique signs of paracetamol toxicity such as tinnitus that occurs with salicylate poisoning.
6. The symptoms of toxicity do not appear for several days.
7. Reference to liver damage would raise awareness of the problem.

Arguments against the proposed statements were:

1. There were insufficient data to justify their inclusion.
2. People would be discouraged from ever using the product.
3. Suicidal persons would be encouraged to misuse paracetamol products.
4. Naming an organ that may be injured from an acute overdose or from excessive use would place the responsibility of recognising organ damage on the consumer, who would be assuming the role of a physician.
5. It would cause alarm and anxiety in people who used it rationally.
6. In OTC doses, there was no evidence of hepatotoxicity and it was sufficient to simply state that in the event of accidental overdosage, the message should be to seek professional assistance or contact a poisons information centre.
7. It was inappropriate for children’s products because there is a lack of documented fatalities in children from acute overdose.

By 1993, the FDA’s Non-Prescription Drug Advisory Review Committee considered the need for warnings on analgesics and agreed that they should relate to alcohol and be organ-specific i.e. Paracetamol-Liver and NSAID/Aspirin-Stomach. Several months later, however, the Committee withdrew its recommendation about organ specificity but the FDA decided to adopt both aspects of the warning.

The FDA then appears to have decided on a compromise position because, although accepting of the arguments about not mentioning particular organs, it shared the Committee’s concern about the delayed appearance of toxic symptoms – “the silent period”. The wording decided on by the FDA was: Prompt medical attention is critical even if you do not notice any signs or symptoms. In case of accidental overdose, seek professional assistance or contact a poison control center immediately.

In September 2002, the FDA organised a hearing to discuss paracetamol hepatotoxicity. Public submissions were sought and included among them was a vigorous submission by an organisation called the Public Citizens Health Research Group. This group criticised the FDA for not having accepted the 1977 recommendations to strengthen the labelling and for ignoring recent data from the UK. [Note: In FDA papers relevant to the FDA Nonprescription Drugs Advisory Committee meeting for 19-20 September 2002, the small number of non-American papers and omission of the recent UK studies were striking]. In support of the need to tighten controls, the Group said that paracetamol deaths had doubled from 76 in 1995 to 141 in 1999 with death certificate
data producing an estimated average number of deaths per year at 458. The Group proposed the following plan:

1. Labels and advertisements should mention liver toxicity, the early symptoms, and warn against the simultaneous consumption of other medicines that contain paracetamol. There should also be articles in the medical and lay press.
2. Reducing the total daily maximum dose of 4g (to an unstated amount).
3. Reducing the maximum tablet strength to 325mg.
4. Standardising the concentration of liquid formulations.
5. Removing irrational combinations from the market.
6. Further study on whether paracetamol should be co-formulated with NAC.

The British Medical Journal reported that the FDA had avoided a debate on tough new measures to reduce overdoses from painkillers in order to avoid offending the pharmaceutical industry (Moynihan, 2002). According to the article, there will be no extra controls on paracetamol other than stronger warnings on the label. Drug company representatives were said to be delighted with the Committee’s decision. The hearing was described as being “eight hours of what were at times confused, uncertain and vague deliberations”. Discussions about the UK initiatives were prevented.

In 1998, the Review made several recommendations concerning education; the Update reiterates these recommendations and also proposes consideration of further warnings on labels. It does not agree with Points 2 and 3 of the above plan; a drug needs to be given in an adequate dose without the need to take too many tablets. Moreover, a 325mg strength tablet (Dolamin) was once available in Australia but was later discontinued. For Point 4, the Review addressed this issue by recommending that no new strengths of oral liquids should be registered. Point 5 is not relevant to Australia because all formulations are subject to individual product evaluation and Point 6 is of doubtful value as reference to any standard pharmacology text about the properties of NAC will reveal. Finally, the Australian regulatory framework has certain safeguards that are absent in the USA, namely a poisons schedules regime and a product registration system that follows an individualised evaluation of each application.

In Canada, regulations mandate a number of warning statements. That relevant to overdose reads: In case of accidental overdose, even if there are no symptoms, contact a doctor or Poison Control Centre at once.

The Update notes that neither the Canadian nor the American statements make specific references to delayed toxicity, although they vaguely allude to it. Whether someone who had overdosed on paracetamol would connect the absence of symptoms in the short term with a later, possibly serious, outcome is debatable. The North American statements refer to accidental overdose but do not mention a deliberate overdose after which the person may have second thoughts about his or her act and its possible consequences. There is no reference to the liver in a general context but there is in a separate warning statement in connection with the consumption of alcohol.

Each label states that an overdose may be hazardous but neither says why.
How relevant is the situation in the UK and Ireland to Australia?

As mentioned in the 1998 Review, the number of deaths due to paracetamol poisoning in Australia is proportionately very much less than in the UK. This has not changed although the number of admissions in Australia has gradually increased over the last ten years or so.

Should there be changes to availability and labelling of paracetamol in Australia?

Terms of Reference Nos. 6 and 7 require consideration of the mandatory UK warning statements but do not extend to questions of availability. For the purpose of completing the discussion of the UK situation, some comment is, however, made.

Availability

All problems with paracetamol would disappear by banning its supply in the manner of Dr John Snow removing the handle of the Broad Street pump in 1854. The Update could find only one authority who proposed this course of action (Carter, 1996). The closest state of affairs that could be equated with the banning of paracetamol arose in 2000 in Australia when an extortionist tampered with paracetamol capsules by contaminating a particular brand with strychnine. The product was withdrawn by the manufacturer. A threat was later made against the market leader which withdrew and destroyed its entire range. A subsequent analysis was carried out on calls to the New South Wales Poisons Information Centre and presentations to the Hunter Valley Toxicology Service (Balit et al, 2002). These authors showed that for the period of withdrawal, the number of telephone calls to the Centre concerning paracetamol and aspirin remained unchanged but the number of calls about ibuprofen increased significantly. Hospital presentations were largely unchanged in the cases of paracetamol and ibuprofen but increased with aspirin. They concluded that “restrictions of paracetamol-containing products may inadvertently increase poisoning with potentially more toxic agents”. Not surprisingly, the market leader for ibuprofen objected because the conclusion was not linked to any long term outcomes and might give the impression that overdoses of ibuprofen could leave the patient with ongoing morbidity (Steans, 2002). Further criticisms were that the study did not provide convincing evidence concerning the effects of paracetamol sales restrictions on population health and that the clinical significance of a statistically significant increase in calls about ibuprofen and aspirin was questionable (Gunnell, 2002). The study, however, was not designed to elicit this information. It indicated that in the absence of one drug, the public will use a substitute.

Reclassifying paracetamol as a Prescription Only Medicine (Sheen and MacDonald, 2000; Sheen et al, 2002) or as a Pharmacy Medicine or a Pharmacist Only Medicine has also been advocated (Anon (g), 2002; Sparrow, 2002). Doubts have been cast on the efficacy of these reclassifications because of the possibility of substituting more lethal methods. The elderly would also be disadvantaged and might use NSAIDs instead with a greater risk to their health (Griffith et al, 2001). Further, evidence from Denmark (where paracetamol is only available from pharmacies but without quantity limits) shows that the drug is a common cause of fatal overdose (Gunnell et al, 2000).
Several British and Irish commentators (above) have noted the availability of multiple small packs in shops and criticised the lack of control at the checkout counter and the availability of paracetamol from vending machines. A correspondent to a Melbourne newspaper believed that it was not an appropriate role for a checkout operator in a supermarket to intervene in the purchase of more than one packet of analgesics because they are not trained to do so (Lowe, 2002).

1. The warning about the delayed toxic effect on the liver

The present Australian labelling of analgesics is discussed elsewhere in this Update. Mention was made earlier in this chapter about the belief in the British literature that stronger warnings were unlikely to achieve any benefits and may even encourage the very act that it is intended to prevent; namely, the impulsive consumption of large doses of paracetamol. In like vein, an eminent jurist said: "The only reason why all our rock ledges and cliff tops are not festooned with signs is that nobody believes that they would actually affect the outcome of litigation and would probably make things worse" (Spigelman, 2002). It is obvious, however, to everyone that if you jump off a rock ledge or a cliff top, you will injure or kill yourself. But it is not so obvious to everyone that you can get into serious trouble by taking an excessive dose of a medicine that is freely available and widely advertised. Paracetamol is different in its toxicology from most other non-prescription drugs in that the symptoms of poisoning – when it occurs – are delayed for about three days with an absence of other noticeable symptoms, or, as O’Grady (1997) describes it – “the sting in the tail”. To the public, this sequence of events is understandably unexpected and unusual. If you take a drug in overdose, you expect something to happen within a few hours, not several days later.

A possible disadvantage is that, in providing more information, there may be the unwanted result of providing more incentive for inappropriate use, particularly given the long window of opportunity to use the overdose as an attention seeking device.

Because paracetamol is different from most other drugs in this respect, the Update considers that the public is entitled to this information and should be so warned. This is not a novel idea and it is worth quoting the final paragraph of an early paper on the subject: “The results of this survey [where only 12 out of 107 self-poisoners knew that an overdose of paracetamol could be hepatotoxic] suggest that if the effects of an overdose of paracetamol had been known the patients would not have taken the drug. Hence the public should be told this fact, possibly as follows. Firstly, specific propaganda could be incorporated into a wide programme of education aimed at reducing the current misuse of medicines. Secondly, the usual wording on the packaging against exceeding the recommended dose could be revised, though this would have to avoid frightening the normal therapeutic user” (Gazzard et al, 1976).

Similarly, the New Zealand Medicines Classification Committee was reported as stating at its 27th meeting in May 2002: “Members felt strongly that in recent times there had been a move away from shielding patients from risk information. They agreed that there was a move towards fully informed consumers and that consumers have a right to be informed of possible dangers as well as benefits. The recommendation [to Medsafe, the New Zealand counterpart to the Therapeutic Goods Administration in Australia] was a move to inform consumers in positive terms”.

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Doubtless, the person bent on taking his or her own life with paracetamol – or anything else – is not going to be dissuaded by a warning label along the British or Irish lines. It may, however, have an advisory and preventative role in cases of the impulsive gesture, the overdose for a therapeutic reason, (such as migraine headache, toothache, or persistent fever in children) or accidental overdose in the case of a child.

The Review declined to make any recommendation on the matter in 1998 but the rising number of admissions to hospitals points to the need for the community to be advised of the peculiar problem with paracetamol. One company – an American manufacturer that uses jars with a child resistant closure instead of strip packs – has already included on its Australian labels a sentence similar to the abbreviated UK statement and the one used in the USA. Its label states: “Do not use with other products containing paracetamol. In case of accidental overdose, seek medical attention immediately. Prompt medical attention is critical for adults as well as children even if you do not notice any signs or symptoms”.

For the above reasons, the Update is attracted to a statement along the lines of that now used in the United Kingdom. The sentence is fairly long and advice should be sought from experts in written communication, and from consumers themselves, about delivering the substance of this message is the most understandable way. It follows that surveys should be conducted to see if there are any changes in the cause, number and severity of admissions.

**Recommendation 9**

The Medicines Evaluation Committee and the National Drugs and Poisons Schedule Committee consider the inclusion of: (i) a statement such as “Immediate advice should be sought in the event of an overdose, even if you (your child) feel(s) well, because of the risk of delayed, serious liver damage”; followed by (ii) the telephone number of the national poisons information centre; on all primary packs and immediate containers of medicines that contain paracetamol.

2. The warning about using more than one paracetamol medicine

The second of the new UK warnings states: “Do not take with other paracetamol-containing products. Under Australian law, the names of all active ingredients and the quantity per dosage unit must be shown on the main label. In the case of some products, the generic name – paracetamol – forms part of the brand name and sometimes appears in large print along with the name of the sponsor. One product that is sold by brand name includes the word “Paracetamol” in a font size substantially bigger than the minimum size prescribed by law. Given the large number of products on the market that contain paracetamol (as shown by the table on page 4) the admonition presumes that consumers will read that part of the label that refers to composition.

There is at least one paracetamol product on the Australian market that states: “Do not use with other products containing paracetamol”.
When would a consumer use – rightly or wrongly – two different products at the same time that contain paracetamol? The following situations arise in practice:

1. One circumstance might arise from using two different brands of paracetamol such as one having been prescribed by a doctor and another having been purchased without a prescription. The Update was informed by a pharmacist that he overhead an elderly woman ask a checkout operator in a supermarket if she could take a popular brand of paracetamol for arthritis. The operator read the label and said yes. When the customer asked if she could take it with Panamax® (paracetamol 500mg), the pharmacist decided to intervene.

2. A second case might involve the use of paracetamol tablets in addition to one of the many cold medicines that contain paracetamol as part of a multicomponent formulation. As these are Schedule 2 poisons, pharmacy staff would be expected to advise prospective purchasers that it is not necessary to take paracetamol tablets as well. Data are not available indicating that there is a problem in this respect although logic might suggest an increased likelihood, especially as consumers’ attention is probably directed to the trade name and the purpose for which the medicine is intended rather than the names of the ingredients. The Pharmaceutical Society of Australia issues a policy document on the handling of Schedule 2 and Schedule 3 poisons in the pharmacy.

3. Where two separate paracetamol products could be safely and effectively taken together is for migraine. Patients with migraine often create their own pharmacological ladder by starting with the least potent drug until they find the formulation or combination of drugs that suit them best. For example, some prefer one tablet containing paracetamol 450mg/codeine phosphate 9.75mg/doxylamine succinate 5mg (a pharmacist-only medicine) plus one paracetamol 500mg tablet instead of two tablets of the combination. For migraine and a variety of other painful conditions, some patients find that one tablet containing paracetamol 500mg/codeine phosphate 30mg (a prescription-only medicine) plus one paracetamol 500mg tablet affords sufficient analgesia without the need to take extra codeine had two tablets of the first mentioned formulation been taken.

4. Prescriptions under the Pharmaceutical Benefits Scheme for both paracetamol tablets 500mg (100 tablets) and paracetamol 500mg/codeine phosphate 30mg (20 tablets) are by no means unusual. In these cases, it is important that doctors and pharmacists inform patients about the dosing arrangements in order to avoid doubling up on the consumption of paracetamol.

The UK statement would be appropriate in most circumstances but could be modified, by the addition of the words, *unless advised by your doctor or pharmacist.*
Recommendation 10

The Medicines Evaluation Committee and the National Drugs and Poisons Schedule Committee consider the inclusion of the statement: “Do not take with other paracetamol-containing products, unless advised by your doctor or pharmacist” on primary packs and immediate containers of medicines that contain paracetamol.

There are already several warnings required on non-prescription analgesics, as described in a later chapter. These warnings are of a general nature and although the information is appropriate, the public’s appreciation of them is unknown. If the new statements were mandated and the present statements remain, there is a danger of cluttering the label and reducing the font size to such an extent that consumers may not bother reading the messages that are really important. The Review (at pages 70-73) included actual size examples of American labels to illustrate the problem.

Recommendation 11

SUSDP warning Statements Nos. 34 and 35 should be abbreviated while retaining the essential messages that consumers should keep to the recommended dose and not take analgesics for more than a few days at a time without medical advice.

This recommendation was amended following further consideration by the Medicines Evaluation Committee on 3 April 2003. The original recommendation is on Page 74.
LABELLING of ANALGESICS

Mandatory requirements

Australian labels for all medicines that are included in a poisons schedule have changed since the 1998 Review and are similar to those used in New Zealand. For a Schedule 2 poison, the signal heading and cautionary statement that appeared as the first lines on the main label before June 2000 were:

- **CAUTION S2**
  - USE STRICTLY AS DIRECTED
  - KEEP OUT OF REACH OF CHILDREN

The word “CAUTION”, the surrounding frame, and the words, “Keep out of reach of children” had to be in red capital letters. The symbol “S2” could be outside the frame.

The present signal heading reads:

- **PHARMACY MEDICINE**
  - KEEP OUT OF REACH OF CHILDREN

The use of red type is no longer mandatory.

The new heading emphasises the distribution of the medicine instead of the two caveats, “Caution” and “Use strictly as directed”. The latter imperative is certainly relevant in the case of paracetamol but whether such changes are of any significance to the public remains untested.

In the case of Schedule 3 poisons, the old label was identical to that for Schedule 2, except for the schedule number itself (“S3”). The new label is headed by the expression:

- **PHARMACIST ONLY MEDICINE**
  - KEEP OUT OF REACH OF CHILDREN

Paracetamol

Paracetamol attracts one of the following warning statements as required by the Standard for the Uniform Scheduling of Drugs and Poisons. Small packs of solid dose paracetamol are unscheduled but the warnings below are nonetheless required as one of several conditions that enable such packs to be sold from any retail outlet.

- **Statement No. 34** WARNING – This medication may be dangerous when used in large amounts or for a long time (period).

- **Statement No. 35** CAUTION – This preparation is for the relief of minor and temporary ailments and should be used strictly as directed.
CAUTION – This preparation is for the relief of minor and temporary ailments and should be used strictly as directed. Prolonged or excessive use without medical supervision could be harmful.

These statements had their origins in the 1970s when the problems of long term kidney damage caused by the excessive consumption of aspirin were recognised in Australia. The same statements were also applied to medicines containing paracetamol. These statements were incorporated into individual State laws during the 1980s. Despite the similarity of indications for their use, the toxicological profiles of the two drugs are very different. In light of our knowledge about paracetamol-induced hepatotoxicity, the above statements might be considered insufficient and/or too general. They could be replaced with statements to make specific reference to the delayed and potentially serious adverse effects on the liver when excessive doses are taken and/or for a period beyond that set out on the label. One sponsor submitted that the present warnings are far too vague because the terms “large amount”, “long time”, “period”, “prolonged or excessive use” are unquantified and do not give consumers any guidance.

The SUSDP and the Labelling Order made under the Therapeutic Goods Act 1989 require the name of any poison or the name of any active component, respectively, to appear on the main label, together with the quantity per unit. A minimum font size is prescribed. Thus, any products that contain paracetamol, whether as the sole active agent or in combination with other drugs, must disclose this information on that part of the label that is presented to the consumer. Moreover, the disclosure must be on both the immediate container and the carton, if there is one.

Under Australian law, most medicines (except in prescribed circumstances) for supply in Australia must be entered on the Australian Register of Therapeutic Goods, otherwise their supply is unlawful. As a condition of registration, guidelines in the form of the Australian Guidelines for the Registration of Drugs Volume 2 must be observed by sponsors. For paracetamol medicines intended for children, the guidelines for labelling include:

- a children’s dosage table (doses being calculated on the basis of 15mg/kg body weight);
- a statement that the medicine should not be given for more than 48 hours without medical advice; and
- a statement that not more than four doses should be given daily.

In the case of tablets and capsules of 500mg strength, there is a statement limiting the maximum number per day to eight (4g). In view of the specificity of the above, the continued use of the SUSDP statements is now questioned, especially for children’s formulations of paracetamol.
Dispensed medicines that contain paracetamol

When a medicine containing paracetamol is dispensed on the prescription of a medical or dental practitioner, the labelling is determined by laws governing the practice of pharmacy, as well as those regulating drugs. The signal headings and the warning statements are not statutorily required in this circumstance, but as a matter of good professional practice, pharmacy-based computer software includes the maximum daily dose caveat as well as the specific directions prescribed by the medical practitioner or dentist. When a drug with sedating properties, such as codeine, forms part of the product, the appropriate SUSDP warning statement must be placed on the container, unless it is already printed on the container by the manufacturer.

- The *Australian Pharmaceutical Formulary and Handbook* (APF) has a set of ancillary cautionary and advisory labels, in the form of brightly coloured stickers, which pharmacists may add to containers. The 18th edition has a new label (No.19) in the series and it is applicable to paracetamol. It reads: “This preparation contains PARACETAMOL. Consult your doctor or pharmacist if you are taking other products containing PARACETAMOL”.

  The commentary states: “This label is necessary for all products containing paracetamol because of the diversity of combination products whose brand names do not signify the presence of the medicine. It is also appropriate for use on combination products containing paracetamol available over the counter. The usual recommended adult total daily dose of paracetamol is 4 grams”. The APF, in its counselling notes, recommends that: (i) doses should not be removed from the original packaging until the dose is required; (ii) patients should be counselled to seek medical advice before taking other paracetamol-containing products; and (iii) the maximum daily adult dose is 4g.

Recommendation (ii) of the APF counselling notes (above) should extend to pharmacists as there are legitimate occasions when two separate products – each containing paracetamol – can be safely and appropriately used together. The situation that pharmacists and their staff should emphasise is that people should not take paracetamol tablets at the same time as they take “cold and flu” tablets whose formulation includes paracetamol. There are many brands of “cold and flu” products on the market and they are popular with the public. Not all of them contain paracetamol. The Update’s experience is that many consumers think all “cold and flu” preparations are much the same even though formulations vary markedly.

A similar statement is mandatory in the United Kingdom and Canada. In a submission to the FDA hearing on 19 September 2002, McNeil Consumer & Specialty Pharmaceuticals advised that a large drug database company that supplies pharmacies began distributing supplementary labels stating:

- This medicine contains ACETAMINOPHEN. Taking more than recommended may cause serious liver problems.
- Do not take other ACETAMINOPHEN containing products at the same time without first checking with your Doctor. Check all medicine labels carefully.
Despite the statistical and scientific material presented at the hearing, emotion took over when a woman gave evidence to the FDA’s panel (Stolberg, 2002). Her healthy 23 year old son died of paracetamol poisoning because he inadvertently took several different products containing this drug for the relief of wrist pain. She said, “You cannot allow more innocent men, women and children to suffer. Death is not an acceptable side effect”. Hopefully, Australia’s poison scheduling arrangements and the professional practice that accompany them should prevent or at least minimise such mishaps occurring in this country.

Paracetamol is included in many products that are indicated for the relief of the multiple symptoms of cold and flu as well as being the principal ingredient of analgesic medicines. Concern has already been expressed about consumers inadvertently consuming excessive doses of paracetamol. This occurs when people deliberately take too much because (i) the recommended dose has not relieved the pain or (ii) several different products that contain paracetamol are taken concomitantly. If ibuprofen were included similarly in cold and flu treatments (and some are already on the market), a similar situation could develop, giving rise to adverse gastrointestinal effects. To some extent, the exclusion of the NSAIDs in any form from the non-pharmacy retail market may offer some protection provided the necessary counselling is provided by pharmacists and staff when ibuprofen or any other NSAID is requested. The same counselling neither would, nor should, nor could, be expected to occur if ibuprofen and the other NSAIDs were available in supermarkets.

**Recommendation 12**

Pharmacy organisations remind pharmacists (i) of the mention in the Australian Pharmaceutical Formulary and Handbook 18th edition about cautionary and advisory label No.19; and (ii) to ensure that pharmacy assistants routinely advise purchasers of “cold and flu” products that contain paracetamol not to take additional paracetamol.

**Aspirin and the non-prescription NSAIDs**

*Rationalising of labels*

The Review made detailed recommendations about rationalising the labels for non-prescription medicines that contained aspirin or the NSAIDs. The recommendations arose out of industry concern about the variety of warning and advisory statements that came from official sources. Some of the statements were statutorily imposed through the SUSDP and given effect through State laws; these apply to new and existing products. Others were requirements imposed on a product’s inclusion in the ARTG; these apply by way of the AGRD Volume 2 to that product and subsequent products only; still other statements were proposed by the Australian Drug Evaluation Committee.

The Update observes that the recommendations made in the Review on this matter were not implemented. For example, a packet of a 24 tablets of generic aspirin 300mg made for a leading retailer makes no mention of stomach ulcers but packets of two leading brands had this information. Ibuprofen also carries such a warning.
Aspirin and Reye’s Syndrome – new UK labelling

The whole question of the association between aspirin and Reye’s Syndrome remains controversial. The incidence of the syndrome has certainly declined throughout the world corresponding to the time warning statements have been required but causality has not been proven.

A newspaper report quoted official United Kingdom sources as stating that aspirin would be banned for children less than 16 years of age (Beaumont, 2002). “ban” is inappropriate; governments cannot “ban” something unless they legislate to remove it totally from the market. On the advice of the Committee on Safety of Medicines, the Medicines Control Agency has proposed a statement that will say that aspirin should not be given to children under 16 years age except on medical advice. The Committee has advised that the earlier agreed warning “Do not give to children under 12 years and avoid up to and including 15 years of age if feverish” should be simplified to “Do not give to children aged under 16 years, unless on the advice of a doctor”. The Committee also concluded that given the availability of a range of analgesic products for this age group not associated with Reye’s, there was simply no need to expose those under 16 to the risk – however small.

In addition, there would be changes to package inserts. It is unclear what has precipitated this action at this time. One possibility is that the present wording is unclear; another is that consumers shied away from paracetamol in the wake of the publicity associated with deaths due to paracetamol and turned to aspirin as a substitute.

The Reye’s warning used in Australia states: “Consult a doctor before giving this medication to children or teenagers with chicken pox, influenza or fever” (SUSDP, Appendix F, Part 1 – Warning Statement No.37).

For unscheduled preparations, the same warning must be in capital letters not less than 1.5mm in height followed by:

CAUTION – DO NOT GIVE TO CHILDREN UNDER TWO YEARS OF AGE EXCEPT ON DOCTOR’S ADVICE.

The present UK warning would be confusing to many people. The Australian version is clearer and allows for aspirin to be used for pain in febrile youngsters with or without medical advice. Further, it impliedly allows aspirin to be used in febrile states subject to medical advice. Whether it is reasonable to remove all reference to all indications in all non-medically directed circumstances in the absence of supporting evidence, as proposed in the UK, is a fair question.

The Review addressed the complications of the labelling of aspirin medicines and called for a rationalisation. It was also noted that its use in chronic juvenile arthritis had been superseded by the NSAIDs and that there was no longer any need for a dose to be stated for children under 12 years of age. It is still used in hospitals after some forms of cardiac surgery and in rare conditions where it would be used under specialist direction. It would seem that aspirin has had its day as a routine analgesic and antipyretic in children. There are alternatives to aspirin for children with pain or fever and a new
message, consistent with that proposed in the UK, would be shorter and simpler; label clutter would also be reduced. The Review suggested a new full replacement text. In light of the recent British action, Recommendation 6.5 of the Review (at page 50) might be varied by amending the fifth dot point to read:

- in children under 16 years of age.

**Recommendation 13**

The National Drugs and Poisons Schedule Committee be again asked to consider updating and rationalising the cautionary and advisory statements applicable to non-prescription medicines that contain aspirin or the NSAIDs, as mentioned in the Review, and having regard to the recent action in the United Kingdom.
Appendix 1 – SUSDP SCHEDULE 2 ENTRY FOR PARACETAMOL

PARACETAMOL for therapeutic use except:

(a) when included in Schedule 4;

(b) in individually wrapped powders or sachets of granules each containing 1000 mg or less of paracetamol as the only therapeutically active constituent other than effervescent agents, when:
   (i) in a primary pack containing not more than 12 such powders or sachets;
   (ii) labelled with the statement:
        WARNING - This medication may be dangerous when used in large amounts or for a long period; or
        CAUTION - This preparation is for the relief of minor and temporary ailments and should be used strictly as directed. Prolonged use without medical supervision could be harmful; and
   (iii) not labelled for the treatment of children under 7 years of age; or

(c) in tablets or capsules each containing 500 mg or less of paracetamol as the only therapeutically active constituent other than effervescent agents, when:
   (i) packed in blister or strip packaging or in containers with child-resistant closures;
   (ii) in a primary pack containing not more than 25 such tablets or capsules;
   (iii) the primary pack is labelled with the statement:
        WARNING - This medication may be dangerous when used in large amounts or for a long period; or
        CAUTION - This preparation is for the relief of minor and temporary ailments and should be used strictly as directed. Prolonged use without medical supervision could be harmful; and
   (iv) not labelled for the treatment of children under 7 years of age.
Appendix 2 – SURVEY OF PARACETAMOL-INDUCED ADMISSIONS TO THE ROYAL CHILDREN’S HOSPITAL 1998 - 2001

The Review included the results of a survey carried out for the period 1993 to 1997 of admissions to the Royal Children’s Hospital, Melbourne for paracetamol poisoning. An extension of that survey for the period 1998 to 2001 has been added for the purposes of the Update giving nine continuous years of data.

Results

For the calendar years 1998 – 2001 (shaded), there were 127 admissions of adolescents and children because of deliberate self-poisoning, accidental overdose arising from improper storage or dosing errors. Some adolescents were admitted more than once.

<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 or UNKNOWN ANTIDOTE</th>
<th>Av.LoS (DAYS)</th>
<th></th>
</tr>
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<tr>
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<td>6</td>
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<td>5</td>
<td>3</td>
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</tr>
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<td>1</td>
<td>9</td>
<td>8</td>
<td>14</td>
<td>12</td>
<td>1</td>
<td>1.9</td>
</tr>
<tr>
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<td>3</td>
<td>4</td>
<td>5</td>
<td>12</td>
<td>9</td>
<td>9</td>
<td>2.2</td>
</tr>
<tr>
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<td>3</td>
<td>2</td>
<td>3</td>
<td>11</td>
<td>6</td>
<td>4</td>
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</tr>
<tr>
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<td>3</td>
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<td>5</td>
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<tr>
<td>TOTAL</td>
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<td>68</td>
<td>12</td>
<td>18</td>
<td>25</td>
<td>57</td>
<td>44</td>
<td>22</td>
<td>2.0 (av)</td>
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<td>10</td>
<td>10</td>
<td>7</td>
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<td>15</td>
<td>46</td>
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<td>52</td>
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Table 1. 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 (unshaded) and 1998 – 2001 (shaded).

Reasons for admission by sex and age group

Table 2 analyses the 127 admissions for the years 1998 – 2001.

Self-poisoning

The data for the Update period shows an increase in the number of admissions per year from 24.6 to 31.8 with an overall mean of 27.8 for the nine years surveyed. The increase is accounted for by the disproportionate increase in the number of adolescent girls who self-poison, some repeatedly. Annual admission rates for this cohort over the two periods studied were 13.6 and 21.5, respectively. The rate for adolescent boys has
declined slightly. There were 4 cases of primary school age children overdosing on paracetamol.

Reliable information about how much was taken is difficult to gauge. In some cases, the records did not yield any useful information. From the figures examined, those adolescents who self-poisoned took an average of about 16g (32 tablets). There was no indication, except where Prescription Only Medicines were implicated, of the source of the medicines ie. the files did not show whether the paracetamol was purchased from a pharmacy or a general retailer.

**Accidental poisoning**

The number of admissions for accidentally self-administered poisoning among pre-schoolers has declined slightly from a mean of 7 to 6.3. The mean number of subjects who received the wrong dose or for too long declined from 1.6 to 1.0

<table>
<thead>
<tr>
<th>Preparations involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incorrect storage accounted for 25 of the admissions in the preschool age group; oral liquids were consumed in 13 cases and solid dose forms in 11 cases.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Preparations involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combinations of paracetamol, either as a co-formulation or with other products (including alcohol) were involved in 61 admissions (48%) and the single substance in 65 instances (51%). The former figure is higher than that recorded recently where 31% of subjects used more than one drug concomitantly – usually sedatives and other analgesics (Schmidt and Dalhoff, 2002).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Preparations involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>In one case, the identity of the paracetamol product was unknown. There were insufficient data to determine if the pack size was a factor in admission rates.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Preparations involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment and intervention</td>
</tr>
<tr>
<td>Activated charcoal was administered in 46 cases as the sole antidotal intervention; N-acetylcysteine (NAC) was given intravenously in 47 cases (37%), charcoal having been</td>
</tr>
</tbody>
</table>

Table 2. Reasons for admission by age and sex in cases of admission due to paracetamol poisoning at the Royal Children’s Hospital, 1998 – 2001.
previously given in many of these. Either no treatment or treatment unknown was recorded in 30 cases.

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 11 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 in this series. One “near miss” involved a 15 year old male took an estimated 350 Panadol tablets. He was commenced on NAC 17 hours after the ingestion. There had been a situational crisis involving a theft of money. He was remorseful. He was in hospital for 8 days and his liver was expected to fully recover after six months.

Discussion

The files showed fairly standard patterns; large files were indicative of deliberate self-poisoning, sometimes repeatedly, by adolescent girls who usually had concurrent psychological or psychiatric disorders. Thin files were single admissions due to accidental overdose caused by toddlers taking incorrectly stored medicines or being administered their medicine too frequently or for too long or in the wrong dose.

The case notes of the adolescents revealed sad histories. The terms “suicidal ideation”, “depression”, “self-mutilation”, “substance abuse”, “psychoses”, “borderline personality disorder” occur repeatedly. There are also instances of impulsive behaviour where the patient had not intended to take her own life and was remorseful after the event. These findings are consistent with findings in other parts of the world. Adolescents with psychiatric problems often minimise the dangerousness of paracetamol in overdose and therefore frequently choose it for suicidal gestures arising from arguments with parents, cultural differences and break ups in relationships. An American study yielded an intriguing discrepancy, in that some subjects took the tablets in order to sleep (as opposed to killing themselves) but that less than 5% of high school students surveyed thought paracetamol would be useful for insomnia. This research confirmed earlier work of the gross underestimation of paracetamol’s lethality in overdose: 50% thought 100 or more tablets were needed to cause death and 36% thought it would take 250 or more. The authors believed that self-poisoning with paracetamol is likely to remain the most common form of suicidal behaviour in view of its heavily advertised reputation of being safe and its over-the-counter status (Harris et al., 1997). An equivalent Australian study would be valuable to see if it matches overseas results given the differences in availability and packaging.

The number of admissions for preschool age children has fallen a little over the nine years studied. Three North American studies show some interesting international comparisons. During a 5½ year period, 110 patients were admitted to the Hospital for Sick Children, Toronto, Canada. Only four were pre-schoolers; three had acute
overdoses and one had chronic poisoning as a result of a therapeutic error. The remainder were adolescents; 102 had acute intentional overdose and four had staggered intentional overdose. NAC was given to 53 of the adolescents. There were no deaths or liver transplants (Bailey et al., 2002). These authors compared their findings with several American studies where the situation, in respect of chronic paracetamol poisoning due to therapeutic error, was more serious (Rivera-Penera et al., 1997; Heubi et al., 1998). Some reasons for the differences were offered. These included differing perceptions of the significance of fever; confusion in strengths of oral liquids; labelling (Canada has doses for children < 2 years of age, the USA does not); and access to free health care in Canada.

A case where the dose was close to the therapeutic dose deserves further comment. Before admission, the 8 year old female had non-specific symptoms of vomiting, fever and headaches. She had received doses of Panadol (formulation details unknown) for 4-5 days up to about 2g/day. On transfer to the RCH, her ALT had risen from 609 to 2690 units/L. NAC was given. The liver was not encephalopathic but there were signs of impending liver failure – low grade jaundice, peripheral oedema and minimal ascites. The ALT peaked at 8024 and the Prothrombin time was markedly prolonged to 77.5 seconds. She was in hospital for 5 days and recovered fully. There was no underlying liver disease or autoimmune disease.

The specialist did not think the parents had exceeded the dose and wondered if the child had not metabolised the drug. Another explanation might be reduced food intake when the child was feverish. The old rule of “stuff a cold and starve a fever” might be positively dangerous if paracetamol is used to lower temperature.

The two cases reported by Hynson and South (1999) were not included in this survey as the two patients were admitted under different circumstances. This raises the question of overdose with therapeutic intent that takes place under medical supervision, including hospitals, which go unreported.
Appendix 3 – EXAMPLE OF A BRITISH PACKAGE INSERT FOR PARACETAMOL

**What do Panadol Tablets do?**

Panadol Tablets contain paracetamol, which is an analgesic (pain killer) and antipyretic (helps to reduce body temperature when you have a fever).

**What are Panadol Tablets used for?**

Panadol Tablets are suitable for headache, migraine, backache, rheumatic and muscle pain, neuralgia, toothache, period pain. Panadol Tablets also relieve discomfort in colds, influenza, sore throats and help reduce temperature.

Panadol Tablets are also recommended for the relief of pain due to non-serious arthritis.

**Check before you take these tablets**

**IMPORTANT:**

- Do not take with any other paracetamol-containing products.

**Panadol Tablets should not be taken:**

- if you are sensitive to paracetamol or to any of the other ingredients listed above.

---

### What is in the pack?

Each Panadol Tablet contains the active ingredient Paracetamol Ph Eur 500 mg.

The tablets also contain starch, polyvidone, potassium sorbate (E202), talc and stearic acid. The film coating contains hydroxypropyl methylcellulose and triacetin. The printing ink contains ethanol, propylene glycol, shellac, brilliant blue FCF (E133), sodium lactate and dimethyldiphenylsiloxane.

Panadol Tablets come in a carton containing 12, 16 or 32 tablets.

### Who makes Panadol Tablets?

The product licence holder is SmithKline Beecham Consumer Healthcare, Brentford, TW8 9BD, U.K. and all enquiries should be sent to this address.

The manufacturer is SmithKline Beecham (Dungarvan), Co. Waterford, Ireland.
Please see your doctor before you take Panadol Tablets:

- if you are taking metoclopramide or domperidone - used to treat nausea and vomiting.
- if you are taking cholestyramine - used to treat high cholesterol.
- if you have severe liver or kidney disease.
- if you are taking anticoagulants (drugs to thin the blood e.g. warfarin) and you need to take a painkiller on a daily basis over a long period. However, you can take occasional doses of Panadol Tablets.
- If your headaches become persistent, see your doctor.

If you are pregnant or breast feeding:

Please see your doctor before you take Panadol Tablets if you are pregnant. You can take Panadol Tablets whilst breast feeding.

How to take Panadol Tablets:

Adults, including the elderly:
Take 2 tablets every 4 hours as required. Do not take more frequently than every 4 hours. Do not take more than 8 tablets in 24 hours.

Children (6-12 years):
Give 1/2 to 1 tablet every 4 hours as required. Not more than 4 tablets should be given in 24 hours. Do not give to children for more than 3 days without consulting a doctor.
Do not give to children under 6 years of age.
Do not exceed the stated dose.

If symptoms persist, consult your doctor.
Check with your doctor if you suffer from non-serious arthritis and need to take painkillers every day.

What should you do if you take too many Panadol Tablets?
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.

Will Panadol Tablets suit you?
Most people taking Panadol Tablets find they cause them no problems. However, occasionally some people may get allergic reactions, such as skin rash. In all the years paracetamol has been used there have been very rare reports of blood disorders, but these were not necessarily caused by paracetamol. These effects should go away once you stop taking the medicine.

If you are concerned about these effects, or if Panadol Tablets affect you in any other way, stop taking them and talk to your doctor or pharmacist.

Further Information
Do not use this medicine after the "Use by" date shown on the pack.

Remember: Keep all medicines safely away from children.

Panadol is a trade mark.
Leaflet revised July 2000

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SmithKline Beecham Consumer Healthcare, Brentford, TW8 9BD, UK, 40.229C L609026/03
Appendix 4 - Summary of comments from stakeholders

**Recommendation 1**

Recommendations 6.10 and 6.11 of the Review should be implemented

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”.

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.

NDPSC  
Not supported – lack of complementary legislation, need for appropriate non-blister / strip packaging, possibility of innovation where CRC necessary.

TGC  
Not supported – consistency with other products, lack of evidence that blister / strip packaging is more effective than CRC, lack of evidence that blister / strip packaging would reduce suicide rates

ASMI  
Not supported:
- UK situation cannot be considered equivalent to Australia;
- CRC pack not cheaper than blister / strip as stated in report;
- Would send negative message about effectiveness of CRC and be inconsistent with retaining CRC for liquid paracetamol products;
- ASMI proposes a limit of not more than 100 tablets or capsules per pack for pharmacy-only products.

Herron  
Not supported:
- Problem is not paracetamol but depression and suicide;
- No clear evidence that bottles promote increased rate or extent of overdose of abuse;
- Bottle is more expensive than strip / blister (contrary to statement in report);
- Incentive for consumer is convenience and portability.
Recommendation 2

In the event that additional strengths of ibuprofen oral liquids are marketed, the Australian Pharmaceutical Advisory Council, through the respective professional bodies, remind pharmacists and their staff, medical practitioners, nurses and health centre sisters that there is more than one strength of ibuprofen oral liquids and ensure that purchasers are made aware of the dose.

ASMI Supported.

Suggests further development of the ibuprofen guideline to be consistent with the paracetamol guideline

Recommendation 3

No change to the present guidelines on the use of paracetamol in children in relation to dose in mg/kg, maximum dose per day (not exceeding 2,400mg, unless on medical advice), frequency and duration.

ASMI Supported.
Recommendation 4

Recommendations 2.5, 2.7 and 3.1 of the Review should be referred to the Australian Pharmaceutical Advisory Council (APAC) for implementation. These Recommendations were:

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.

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 of 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.

3.1 Professional organisations and departments of health remind (a) 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.

ASMI

Supported in principle:
- Advocates a “consultative forum” under APAC consisting of ASMI, NPS and TGA;
- Seeks TGA’s continuing support in developing the Industry Code of Practice for Labelling.

Herron

Supported:
- Education of pharmacists, GPs and nurses needed to stop recommending “double dosing” of liquid paracetamol
- Community education advocated to increase awareness of help line services such as ‘Lifeline’.

Pharmaceutical Society

Broader public health messages needed rather than just relying on health professionals.
All paracetamol oral liquid preparations should have a suitable measuring device in the box containing the bottle.

Pharmacy Guild

Understanding is that APAC’s role does not include implementation, therefore difficult to see how this recommendation can be implemented by APAC.

PHARM

PHARM is an advisory committee only – implementation will have to be done by other stakeholders.
Recommendation 5

The American warning label about paracetamol and alcohol should not be adopted in Australia.

ASMI  Supported.

Herron  Supported.

Recommendation 6

Recommendations 4.1 and 4.2 of the Review be implemented. These Recommendations were:

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 users.

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

ASMI  Supported in principle:

- Advocates a “consultative forum” under APAC consisting of ASMI, NPS and TGA (as in Recommendation 4 above);
Recommendation 7

The American warning label about aspirin, the NSAIDs and alcohol should not be adopted in Australia.

ASMI  Supported

Recommendation 8

The editor of the *Australian Prescriber* be requested to arrange for, and publish, a review article about the relationship between aspirin and the NSAIDs and the consumption of alcohol and gastric bleeding.

ASMI  Advocates a “consultative forum” under APAC consisting of ASMI, NPS and TGA (as in Recommendation 4 and 6 above).

Herron  Supported

Pharmaceutical Society  Extend to include:
- NPS to include information in their clinical detailing;
- PSA to include articles in its professional journal; and
- Pharmacy schools to include in their curriculum.
Recommendation 9

The Medicines Evaluation Committee and the National Drugs and Poisons Schedule Committee consider the inclusion of: (i) a statement such as “Immediate advice should be sought in the event of an overdose, even if you (your child) feel(s) well, because of the risk of delayed, serious liver damage”; followed by (ii) the telephone number of the national poisons information centre; on all primary packs and immediate containers of medicines that contain paracetamol.

ASMI Supported with qualifications:
- Expert advice on wording of message
- Refer the issue to the ‘performance based labelling’ project.

Herron Agree in principle but:
- Omit the word “overdose”
- Include PIC phone number on all medicines

Sanofi-Synthelabo “Agree completely” but concerned that there is no room on labels of PANAMAX ELIXIR for additional warnings

Pharmacy Guild Supported
Recommendation 10

The Medicines Evaluation Committee and the National Drugs and Poisons Schedule Committee consider the inclusion of the statement: “Do not take with other paracetamol-containing products, unless advised by your doctor or pharmacist” on all primary packs and immediate containers of medicines that contain paracetamol.

ASMI Questions the effectiveness of this recommendation:
- Lack of objective evidence to support it;
- May be confusing to consumers (actives already declared on the label);
- Should be considered as part of the Labelling project;
- If implemented, it is more applicable to combination products, not single-active products.

Herron Supported – suggest alternative wording “Do not take other paracetamol containing products without seeking medical advice”.

Pharmaceutical Society Suggests that paracetamol content could be highlighted on labels to minimise the potential for duplication.

Pharmacy Guild Supported

Sanofi-Synthelabo “Agree completely” but concerned that there is no room on labels of PANAMAX ELIXIR for additional warnings
**Recommendation 11**

The Medicines Evaluation Committee and the National Drugs and Poisons Schedule Committee consider that if the two new statements (or suitable variants of them) are agreed to, consideration should be given to omitting Warning Statements Nos. 34 and 35 from the labels of medicines that contain paracetamol.

**ASMI**

Refer to Labelling project as per Recommendations 9 and 10:
- SUSDP statements 34 and 35 require a thorough review;
- Statements apply to other analgesics – need for consistency;
- Warning statements need to include a reference to prolonged use of analgesics.

**Herron**

Suggests deleting 34 but retaining the last sentence of 35 (“prolonged or excessive use without medical supervision could be harmful”).

**Recommendation 12**

Pharmacy organisations remind pharmacists: (i) of the mention in the Australian Pharmaceutical Formulary and Handbook 18th edition about cautionary and advisory label No.19; and (ii) to ensure that pharmacy assistants routinely advise purchasers of “cold and flu” products that contain paracetamol not to take additional paracetamol.

**ASMI**

Supported in principle:
- Should be related to a ‘consultative forum’ as proposed in Recommendations 4, 6 and 8.

**Pharmacy Guild**

Prefers Recommendation 10 warning on all labels – ancillary labelling is only required if the product is dispensed.
Recommendation 13

The National Drugs and Poisons Schedule Committee be again asked to consider updating and rationalising the cautionary and advisory statements applicable to non-prescription medicines that contain aspirin or the NSAIDs, as mentioned in the Review, and having regard to the recent action in the United Kingdom.

**ASMI**  Supported in principle:
- Should be referred to the Labelling Project
- Membership concerned about lack of evidence for extending restriction on use to all children under 16 years.

**Pharmaceutical Society**  Stronger label warnings regarding the relationship of aspirin and stomach bleeding could be justified.
REFERENCES and FURTHER READING


Anon (b). Pharmacy-only paracetamol recommended. Aust J Pharm 2002; 83:805


Anon (g) Paracetamol overdose death. Aust Pharm 2002; 21(9):638.


Bonkowsky HL, Kane RE, Jones DP et al.. Acute hepatic and renal toxicity from low doses of acetaminophen in the absence of alcohol abuse or malnutrition: evidence for increased susceptibility to drug toxicity due to cardiopulmonary and renal insufficiency. Hepatology 1994; 19:1141-1148.
Review of Non-prescription Analgesics – An update

British Broadcasting Corporation. Suicide fears limit paracetamol sales. news.bbc.co.uk/hi/health/newsid_172000/172674.stm
Cameron MG. Deaths from low dose paracetamol poisoning. Lower threshold has probably not overburdened hospital services in Gloucester. BMJ 1998; 317:1656.
Carter D. Why does a top surgeon want to ban paracetamol? Daily Mail, 1 October 1996.
Review of Non-prescription Analgesics – An update


Griﬃth DL, Diggory P, Jones V et al. Availability of paracetamol. www.bmj.com/cgi/eletters/322/7285/553#13140


Gow PJ, Jones RM, Dobson JL, Angus PW. Aetiology and outcome of fulminant hepatic failure managed at an Australian liver transplant unit. *Personal communication*


Hynson JL, South M. Childhood hepatotoxicity with paracetamol doses less than 150mg/kg per day. *Med J Aust* 1999; 171:497.
Review of Non-prescription Analgesics – An update


Jowett NI. Limitation of the counter sales of paracetamol. Restrictions to 16 g will not prevent overdose and is unhelpful for patients with chronic disease. BMJ 1998; 317:1657.


Kelly J. Plea to restrict pain pill. Herald Sun, 12 September 2002


Liddell K. Sales restrictions flouted. Pharm J 2001; 266:819.


Lowe I. Why I protect the public from pain-killers. The Age, 15 August 2002.[incorrectly cited as Love I]


McAliskey DP. Deaths from low dose paracetamol poisoning. Several issues were not considered in the article. BMJ 1998; 317:1655.


Moynihan R. FDA fails to reduce accessibility of paracetamol despite 450 deaths a year. BMJ 2002;325:678.


O’Connell S. Proposals will have negative effects. BMJ 1997; 314:751.


O’Rourke C. Doctor urges alert on Panadol use. Sydney Morning Herald, 19 February 2002..


Paracetamol Information Centre. Legislation restricting pack sizes of pain relievers has been successful in reducing overdoses. www.pharmweb.net


Pfau PR, Lichtenstein GR. NSAIDs and alcohol: never the twain shall mix? Am J Gastroenterol 1999; 94(11):3098-3100


Rivera-Penera T, Gugig R, Davis J et al. Outcome of acetaminophen overdose in pediatric patients and factors contributing to toxicity. J Pediat 1997; 130:300-304


Review of Non-prescription Analgesics – An update


Scott A. Pack size legislation. [www.bmj.com/cgi/eletters/322/7296/1203#14998](www.bmj.com/cgi/eletters/322/7296/1203#14998) 7 Jun 2001.


Sheen CL, MacDonald TM. Severity of overdose after restriction of paracetamol availability. Study’s results conflict with those of other papers. *BMJ* 2001; 322:553-554.


Sparrow A. Doctor calls for paracetamol to be taken off shelves. [www.abc.net.au/pm/s646689.htm](www.abc.net.au/pm/s646689.htm)


Spiller HA. Persistently elevated acetaminophen concentrations for two days after an initial four-hour non-toxic concentration. *Vet Human Toxicol* 2001; 43:218-291.


Thomas MR, Jowett NI. Restricting paracetamol sales have not reduced admissions with self-poisoning. [www.bmj.com/cgi/eletters/321/7266/926#10324](www.bmj.com/cgi/eletters/321/7266/926#10324) 20 Oct 2000


Review of Non-prescription Analgesics – An update


Wakeford R. But at least someone benefits. [www.bmj.com/cgi/eletters/321/7266/926#10245](www.bmj.com/cgi/eletters/321/7266/926#10245) 13 Oct 2000.


Woodhead M. (a) Paracetamol moves may be harmful. *Aust Doctor* 2002; 20 September.

Woodhead M. (b) In the heat of the moment. *Aust Doctor* 2002; 25 October, p.24