



## **MHRA UK PUBLIC ASSESSMENT REPORT**

### **Liquid paracetamol for children: revised UK dosing instructions have been introduced**

**November 2011**

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## PLAIN-LANGUAGE SUMMARY

**KEY MESSAGE:** The UK dosing instructions for children's liquid paracetamol products have been revised. The revised patient information will clarify the most effective dose to be given to a child according to their age.

### Background

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency responsible for regulating medicines and medical devices in the UK. We continually review the safety of medicines and vaccines in the UK, and inform healthcare professionals and the public of the latest updates through several means, including public assessment reports. This report summarises a UK review of children's paracetamol products, and the reasons why changes have been made to the dosing instructions.

Paracetamol is a widely used and effective treatment for pain and fever in adults and children aged 2 months and over, and for reducing post-vaccination fever in babies aged 2 – 3 months. Some paracetamol products can be bought over-the-counter in a pharmacy or other retail outlets, and some are prescribed.

Around 84% of children in the UK receive paracetamol by the age of 6 months. Some paracetamol products have been developed specifically for use in children age less than 16 years. They are mainly available as liquid formulations<sup>1</sup>.

In hospitals, calculating the appropriate dose of paracetamol for a child is based on the concentration of paracetamol in mg per kg of bodyweight. However, this method of calculating a dose is not always practical for parents or carers to manage at home. Therefore, the recommended dosing for liquid paracetamol given to children by a parent or carer at home is by volume (in mL), which is determined based on the child's age.

The recommended dosing tables for children's liquid paracetamol that were used previously had very wide age bands, where a 1-year old child was recommended the same dose as a 6-year old. With these recommendations, younger children may have received a dose of paracetamol that was higher than necessary. The MHRA therefore reviewed all available data to determine whether the dosing recommendations for children's liquid paracetamol needed to be revised.

On the basis of the review, the recommended doses of paracetamol for children have been changed in order to ensure that children get the most effective dose of paracetamol. The introduction of the new dosing instructions and advice, which are presented in the tables below, began in autumn 2011.

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<sup>1</sup> Brands of liquid oral paracetamol products licensed in the UK for use in children include: Calpol; Disprol; Junior Parapaed; Medinol; Medised

## Results

### NEW DOSING INSTRUCTIONS FOR CHILDREN'S LIQUID PARACETAMOL PRODUCTS:

#### Infant paracetamol suspension (120 mg/5 mL):

Child's age	Condition(s) for treatment:	How much to give?	How often (in 24 hours)?
2 – 3 months	1. Post-vaccination fever 2. Other causes of pain and fever if your baby weighs over 4 kg and was born after 37 weeks	2.5 mL	Usually once. However, if necessary, after 4–6 hours a second 2.5 mL dose may be given
<ul style="list-style-type: none"> <li>• Do not give to babies less than 2 months of age</li> <li>• Do not give more than two doses</li> <li>• Leave at least 4 hours between doses</li> <li>• If further doses are needed, talk to your doctor or pharmacist</li> </ul>			

Child's age	Condition(s) for treatment	How much to give?	How often in 24 hours?
3 – 6 months	Pain and/or fever	2.5 mL	4 times
6 – 24 months		5 mL	4 times
2 – 4 years		7.5 mL	4 times
4 – 6 years		10 mL	4 times
<ul style="list-style-type: none"> <li>• Do not give more than four doses in any 24-hour period</li> <li>• Leave at least 4 hours between doses</li> <li>• Do not give this medicine to your child for more than 3 days without speaking to your doctor or pharmacist</li> </ul>			

**Paracetamol six plus suspension (250 mg/5 mL):**

Child's age	Condition(s) for treatment	How much	How often (in 24 hours)?
6–8 years	Pain and/or fever	5 mL	4 times
8–10 years		7.5 mL	4 times
10–12 years		10 mL	4 times
<ul style="list-style-type: none"><li>• Do not give more than four doses in any 24-hour period</li><li>• Leave at least 4 hours between doses</li><li>• Do not give this medicine to your child for more than 3 days without speaking to your doctor or pharmacist</li><li>• Do not give to children under the age of 6 years</li></ul>			

- Paracetamol six plus suspension dose for children age 12 – 16 years: 10–15 mL up to 4 times a day
- Liquid paracetamol dose for adults and children aged over 16 years: 10–20 mL up to 4 times per day.

**Advice**

- The product information for all children's liquid paracetamol products is being updated with the new dosing instructions outlined above. Always follow the dosing instructions provided on the product packaging and in the leaflet in the box.
- A special spoon or syringe will be supplied with the liquid paracetamol product to ensure it is measured accurately. Do not use any other spoon or device to measure the product.
- If you have any questions regarding the new dosing instructions for children's paracetamol, please ask a pharmacist or healthcare professional

The above information has also been communicated in an article in the [July 2011 issue of Drug Safety Update](#), the monthly MHRA publication for health professionals containing the latest information and advice on medicines and vaccines safety.

# 1. INTRODUCTION

(See glossary for an explanation of terms used in this report)

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency responsible for regulating medicines and medical devices in the UK. We continually review the safety of medicines and vaccines in the UK, and inform healthcare professionals and the public of the latest updates through several means, including public assessment reports. This report discusses changes introduced to the dosing instructions for children's paracetamol products in autumn 2011, and the reasons why the changes were made.

Paracetamol is an analgesic and antipyretic treatment that is widely used in the UK, particularly in children. Its use has increased since aspirin (another analgesic) was contra-indicated in children under the age of 12 years in 1996, [a contra-indication that was further extended to children under the age of 16 years in 2003](#). A study in 2007 reported that in a group of over 14 000 babies in England, 84% had used paracetamol by age 6 months.<sup>1</sup>

Paracetamol is indicated for treatment of mild to moderate pain and as an antipyretic in children from the age of 2 months, and for the treatment of post-vaccination fever in infants age 2–3 months. It is mainly available as a liquid formulation for children in the UK in two strengths: 120 mg/5 mL and 250 mg/5 mL, (although a few brands offer variations on strength).

The therapeutic dose of paracetamol is defined on the basis of mg paracetamol per kg bodyweight. It is generally accepted that the therapeutic range for both analgesic and antipyretic activity is a plasma paracetamol level of 10–15 mg/L<sup>2</sup> which equates to a dose of 10-15 mg/kg.<sup>3</sup> In line with this, a range of studies have demonstrated that paracetamol is effective at doses between 10-20 mg/kg administered every 4–6 hours.<sup>4,5,6,7,8,9</sup>

## 1.1 Previous paediatric posology for paracetamol

In the UK, **home dosing** with paediatric paracetamol is dependent on age alone. Tables 1a and 1b show the previous recommended doses of paracetamol for children before the revisions were introduced.

**Table 1a.** Recommended dosing for infant paracetamol suspension (120 mg/5 mL) before changes introduced in 2011

AGE	DOSE	HOW OFTEN (IN 24 HOURS)?
3 months – <1 year	2.5 mL	4 times
>1 year – <6 years	5 – 10 mL	4 times

**Table 1b.** Recommended dosing for paracetamol six plus suspension (or 250 mg/5 mL)

<b>AGE</b>	<b>DOSE</b>	<b>HOW OFTEN (IN 24 HOURS)?</b>
<b>6 – 12 years</b>	<b>5–10 mL</b>	<b>4 times</b>

With the dosage regimen shown in tables 1a and 1b, some children will have received more paracetamol than necessary for their size.

We therefore reviewed evidence on the effectiveness and safety of paracetamol for children, to determine whether the paediatric dosing recommendations needed to be revised. The following report summarises the findings from the review, and presents the new dosing instructions for paediatric paracetamol that were introduced in autumn 2011.

## 2. BACKGROUND AND SUMMARY OF DATA CONSIDERED

### 2.1. Mechanism of action of paracetamol

Paracetamol has recognised analgesic and antipyretic activities, and weak anti-inflammatory activity. The antipyretic activity of paracetamol, and possibly the analgesic action, is ascribed to a central inhibition of prostaglandin synthesis in neurons and brain endothelial cells.<sup>10,11</sup>

### 2.2 Metabolism and pharmacokinetics of paracetamol

**Paediatric metabolism summary:** The major route of paracetamol metabolism is via sulphation and glucuronidation. Sulphation is the major route of paracetamol metabolism in children while glucuronidation is the major route in adults. Around 5-10% of paracetamol is oxidised by cytochrome P (CYP) enzymes (the expression and activity of which varies with age and between individuals) to form N-acetyl-p-benzoquinoneimine (NAPQI), a toxic by-product. Normally NAPQI is detoxified by conjugation with glutathione in both adults and children. If the concentration of NAPQI exceeds glutathione levels (eg, after paracetamol overdose), NAPQI binds to hepatocytes causing severe liver damage.

**Paediatric pharmacokinetics summary:** Drug clearance of paracetamol in children is thought to be lower than in adults, particularly in children age 3 years or less. The lower rate of clearance in children may be due to their lower weight, or their slower metabolism. The maximum analgesic effect of paracetamol in a child appears to occur approximately 1.5 – 2 hours after administration.

#### **All data assessed:**

##### *Adult metabolism*

Paracetamol is distributed throughout most body tissues with an apparent volume of distribution of approximately 1 L/kg bodyweight. A clinically insignificant proportion of the drug binds to plasma proteins.<sup>12</sup>

In adults, 60–90% of a therapeutic dose of paracetamol is metabolised by conjugation to form paracetamol glucuronide and sulphate. 5–10% is oxidised by mixed function oxidase enzymes (in humans mostly by cytochrome P (CYP) 2E1 [85%] but CYP3A4 also contributes [15%]) to form the highly reactive and toxic compound N-acetyl-p-benzoquinoneimine (NAPQI). This is usually immediately detoxified by conjugation with glutathione and subsequently excreted by the kidney as cysteine and mercapturate conjugates. When the concentration of NAPQI exceeds that of intracellular glutathione, NAPQI covalently binds to hepatocytes leading to necrosis. Only 1-4% of a therapeutic dose of paracetamol is excreted unchanged in the urine.

Glucuronide conjugates – the major urinary paracetamol metabolite in adults – are primarily formed in the liver.<sup>13</sup> Glucuronidation occurs via UDP-glucuronyltransferase (UGT) enzymes (mainly UGT1A6 and UGT1A9) and does not seem to be readily saturable in man even in severely poisoned patients.<sup>13</sup>

Sulphate conjugation is a major parallel route of non-toxic elimination of paracetamol, although in adults this is less important than glucuronidation<sup>13</sup>). It is relatively easily saturated at higher paracetamol doses (>2 g).

Other studies have demonstrated that formation of the metabolites of the toxic pathway increase to a greater extent at high paracetamol doses than glucuronide or sulphate metabolites. This suggests that the capacity of direct conjugation pathways becomes progressively limited with increasing paracetamol dose.

### *Paediatric metabolism*

In children, particularly in very young children, sulphation is the major route of paracetamol metabolism as glucuronidation is not well developed. The age at which adult metabolism is reached appears unclear with some studies suggesting the pattern of urinary metabolites matches that of the adult at 12 years<sup>14</sup> while other studies suggest adult patterns may be reached much earlier.<sup>15</sup>

Expression of the critical CYP2E1 enzyme for the formation of the toxic paracetamol by-product NAPQI is low in very young children but by the age of 1 year is approximately 80% of the adult value.<sup>16</sup> The expression and activity of CYP enzymes, especially CYP3A4 and CYP2E1, are affected by a number of factors including age, development, pharmacogenetic factors, hormones, and drugs.<sup>17</sup>

### *Paediatric pharmacokinetics*

Drug clearance in children is influenced by many factors including size, bodyweight, organ weight and function and maturation.<sup>18,19</sup> There is a non-linear relationship between weight and drug elimination.<sup>20,19</sup> A sigmoidal  $E_{max}$  model (Hill equation) describes gradual maturation of clearance in early life leading to a mature adult clearance achieved at a later age.

For paracetamol, several studies,<sup>21,22,15</sup> predict a lower clearance in children than that reported in adults, with 88% of the mature value reached within one year of age.<sup>18</sup> Although another study<sup>14</sup> reported that the kinetics of excretion appeared similar across the age groups most of the data was derived from children >3 years of age when clearance would be expected to have reached adult rates. In line with this, in the same study, a lower overall paracetamol elimination rate was seen in neonates compared with children (3–12 years) and adults, although this did not reach significance. It is possible therefore that the reduced ability to conjugate paracetamol with glucuronic acid could result in drug accumulation in children if the sulphation pathway was inhibited.

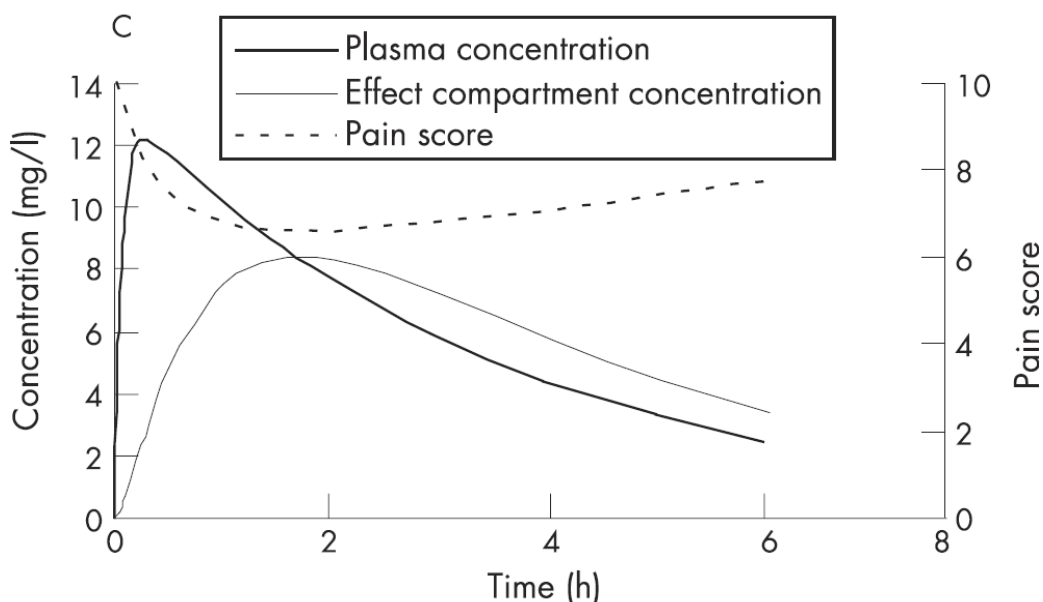
Rate of metabolism may also influence the toxicity thresholds. It has been predicted that 37.5% of the adult population may be 'slow metabolisers of paracetamol', with a paracetamol half-life of 4 hours or more.<sup>23</sup> Similarly in approximately 8%-14% of children aged 1–5yrs, paracetamol is estimated to have a half-life  $\geq 4$  hours. These individuals would be potentially at greater risk of developing higher paracetamol levels on repeated dosing due to their slower metabolism. Paracetamol levels can therefore vary widely between individual children.

Plasma paracetamol concentrations between 0.06–0.13 mmol/L have been reported to have an effective antipyretic effect.<sup>24</sup> However, interpretation of analgesic and antipyretic responses directly from paracetamol plasma concentrations is difficult



since it is likely that the responses are not directly related to the paracetamol concentration in the blood, but rather to the effect compartment concentration.<sup>25</sup> (figure 1). Furthermore there is a time delay between the maximum plasma concentration and effect compartment of approximately 1 hour, and then between maximum plasma concentration and maximum temperature reduction.<sup>21,25</sup>

**Figure 1.** Temporal relationships for plasma concentration, effect compartment concentration and analgesic effect in a child after administration of 12.5 mg/kg liquid paracetamol.



Absorption half-time used was 4.5 minutes. Parameter estimates taken from Anderson *et al.*<sup>26</sup>, graph from Gibb *et al.*<sup>25</sup>

## 2.3 Efficacy of paracetamol

### 2.3.1 Antipyresis

**Antipyresis efficacy summary:** Paracetamol is an effective antipyretic in children and adults at doses between 10-20 mg/kg. Some antipyretic activity may be present below 10 mg/kg but it is likely to be small. There are no data differentiating between the efficacy at 15 mg/kg and 20 mg/kg, and there is currently insufficient evidence to support a dose of 20 mg/kg. Therefore the most effective dose range for paracetamol antipyresis efficacy appears to be 10–15 mg/kg.

The maximum effects of paracetamol are generally seen 1.5–3 hours after administration

The amount of temperature reduction achievable with paracetamol depends on the initial temperature – the higher the temperature before paracetamol administration, the greater the amount of reduction seen with treatment.

**All data assessed:**

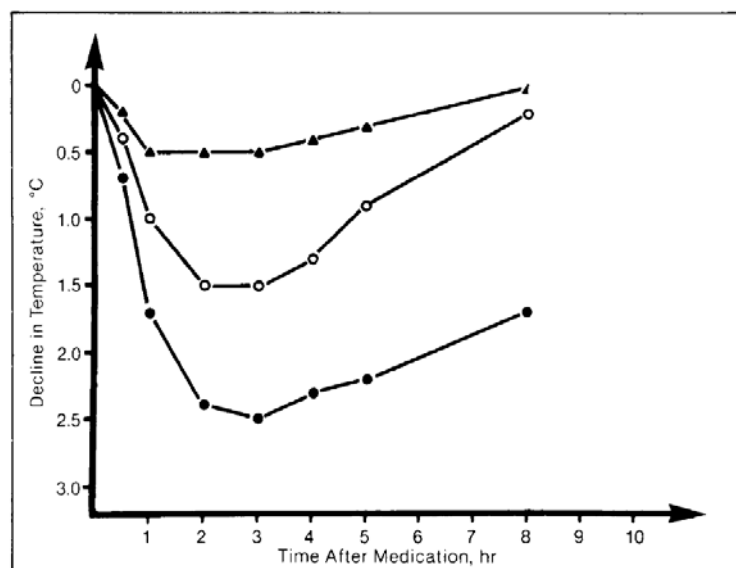
A range of studies have suggested that the effective antipyretic dose for paracetamol lies between 10-15 mg/kg, with a plasma serum concentration between 5–10 µg/mL.<sup>27,28,7,9,8,29,30,31,27,32,33,34,35,6,36,37</sup> Very few studies assess doses less than 10 mg/kg.<sup>38,39,40,41,6,34</sup>

The maximum temperature reduction achieved in studies with paracetamol ranged from 1°C to approximately 2.5°C. A study by Anderson *et al*<sup>21</sup> estimated a maximum temperature reduction of 3°C in children, but commented that that amount of temperature reduction may be conditional upon the initial temperature (ie, that the higher the initial temperature, the greater the amount of temperature reduction achieved with paracetamol). A later study by the same author predicted a linear response between temperature reduction and effect compartment concentrations between 5–15 µg/mL, reaching a maximum temperature reduction of 4.2°C at 20 µl/mL. Importantly, the effect plateaus thereafter.<sup>42</sup>

In line with Anderson *et al* 1998<sup>21</sup>, Wilson *et al*<sup>8</sup> confirmed that the initial temperature affected the antipyretic response of treatment. Normalised responses to antipyretic therapy (ibuprofen or paracetamol) was significantly lower in children who had a higher initial temperature.<sup>8</sup>

Very few studies have explored whether there is a dose response effect of oral paracetamol. One study, by Windorfer and Vogel<sup>40</sup>, investigated the effect of 5, 10 and 20 mg/kg paracetamol on fever in 26 children aged 1–8 years. Their initial temperatures were all greater than 39.5°C. At the lowest dose of paracetamol (5 mg/kg) no statistically significant fall in temperature was apparent (figure 2). Both 10 mg/kg and 20 mg/kg paracetamol resulted in a statistically significant fall in temperature with a clear dose-response effect. The antipyretic effect was also more prolonged at 20 mg/kg, with a substantial effect still apparent 8 hours after administration.

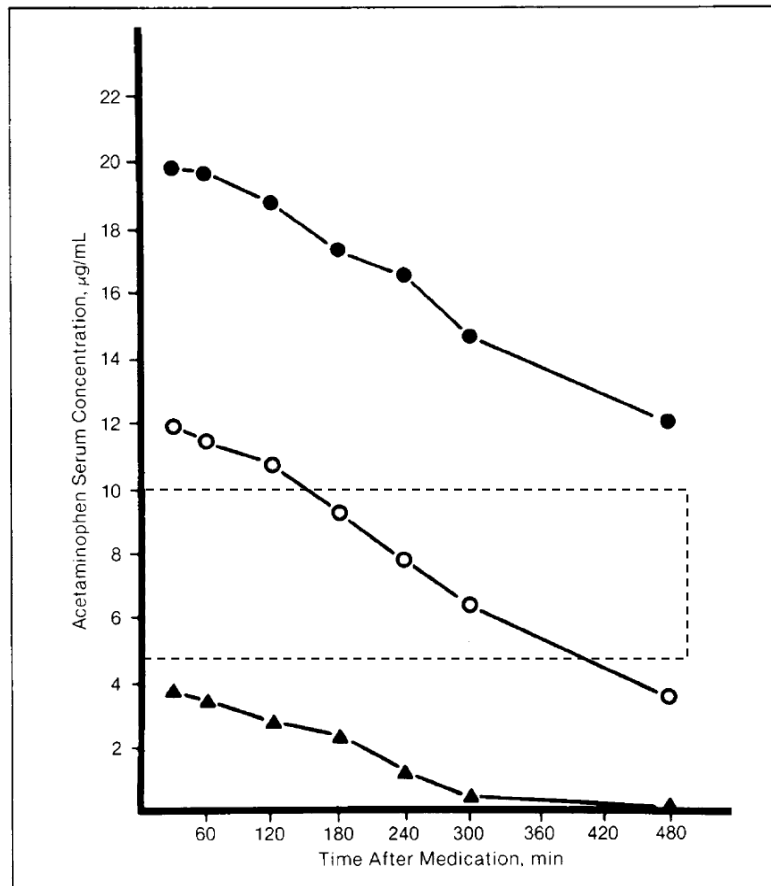
**Figure 2.** Temperature response in children to three different doses of paracetamol.



Filled triangles, 5 mg/kg; open circle, 10mg/kg; closed circle, 20 mg/kg.<sup>40</sup>

Plasma paracetamol concentrations were proportional to the dose administered, and the highest concentration achieved was 20  $\mu\text{g}/\text{mL}$  after a dose of 20  $\text{mg}/\text{kg}$  (figure 3). Serum concentrations of paracetamol following a 5  $\text{mg}/\text{kg}$  dose did not reach the level required for efficacy, in line with the lack of antipyresis activity at this dose. At 10  $\text{mg}/\text{kg}$ , the maximum temperature reduction was apparent after 2–3 hours at a serum concentration of approximately 9–11  $\mu\text{g}/\text{mL}$ .

**Figure 3.** Serum paracetamol concentrations in children after three different doses.



Filled triangles, 5  $\text{mg}/\text{kg}$ ; open circle, 10 $\text{mg}/\text{kg}$ ; closed circle, 20  $\text{mg}/\text{kg}$ .<sup>40</sup> Dotted area represents plasma concentration reported to be required for efficacy.

Thereafter, temperature began to rise again at a point when serum concentrations were still within the 5-10  $\mu\text{g}/\text{mL}$  range. With 20  $\text{mg}/\text{kg}$ , the maximum temperature reduction at 3 hours ( $-2.5^{\circ}\text{C}$ ) correlated with a plasma concentration of just under 18  $\mu\text{g}/\text{mL}$  and the antipyretic effect plateaued when plasma concentration was between 12-14  $\mu\text{g}/\text{mL}$ . These data suggest that plasma concentrations of 5-10  $\mu\text{g}/\text{mL}$  may deliver suboptimal efficacy.

With paracetamol given at doses between 10 –15  $\text{mg}/\text{kg}$ , temperature reduction is generally greater with larger doses, which supports a dose-related effect (table 2).

**Table 2.** Studies investigating the antipyretic effect of paracetamol in children at doses between 10–20 mg/kg.

Study	Paracetamol dose (mg/kg)	Max temp reduction (°C)	Study design
Walson <i>et al</i> , 1989 <sup>27</sup>	10	2.4	Double-blind, trial dummy design, placebo controlled, (compared to ibuprofen)
Vauzell-Kervroedan <i>et al</i> , 1997 <sup>35</sup>	10	1.5±0.61	Double blind, multicentre, randomised (compared to ibuprofen)
Autret <i>et al</i> , 1994 <sup>7</sup>	10	1.24	Double blind, randomised, parallel group (compared to ibuprofen).
Kelley <i>et al</i> , 1992 <sup>31</sup>	Approx. 10-12	2.2	Randomised, open label (no placebo, compared to ibuprofen), parallel.
Friedman <i>et al</i> , 1990 <sup>43</sup>	10-15	1.7	Randomised paracetamol versus sponging or sponging plus paracetamol.
Childs and Little, 1998 <sup>9</sup>	12	1.8	No placebo or comparative intervention.
Simila <i>et al</i> , 1976 <sup>28</sup>	12.5	1.4	No details. Compared with other interventions (ibuprofen, indomethacin, aspirin, aminophenazone)
Wilson <i>et al</i> , 1991 <sup>8</sup>	12.5	1.58	Single dose, placebo-controlled, randomisation on basis of age and initial temp, double blind (ibuprofen group).
Wong <i>et al</i> , 1996 <sup>37</sup>	12.5	1.55	Multicentre, single oral dose prospective, randomised, modified double blind parallel group study
Walson <i>et al</i> , 1989 <sup>27</sup>	15	~2.2	Double blind, double dummy, block randomised, multidose, parallel group study design.
McIntyre <i>et al</i> , 1996 <sup>37</sup>	15	1.6	Double blind, parallel, multidose study.
Windorfer and Vogel, 1976 <sup>40</sup>	5, 10 and 20	0.4, 1.6 and 2.0 respectively	No placebo.

In most studies, the maximum effects of paracetamol are generally seen between 1.5 – 3 hours after administration<sup>30,34,41,38,35,31,28,27,9,7,6</sup>. However a longer duration of effect occurs with higher paracetamol concentrations such that with doses of 20 mg/kg temperature reductions of >2°C were still present after 6 hours.

### 2.3.2 Analgesia

**Analgesia efficacy summary:** From the studies reviewed paracetamol is predicted to provide analgesia in children and adults at doses which achieve a plasma concentration of 10-20 µg/ml. This is approximately equivalent to the antipyretic dose of 10–15 mg/kg.

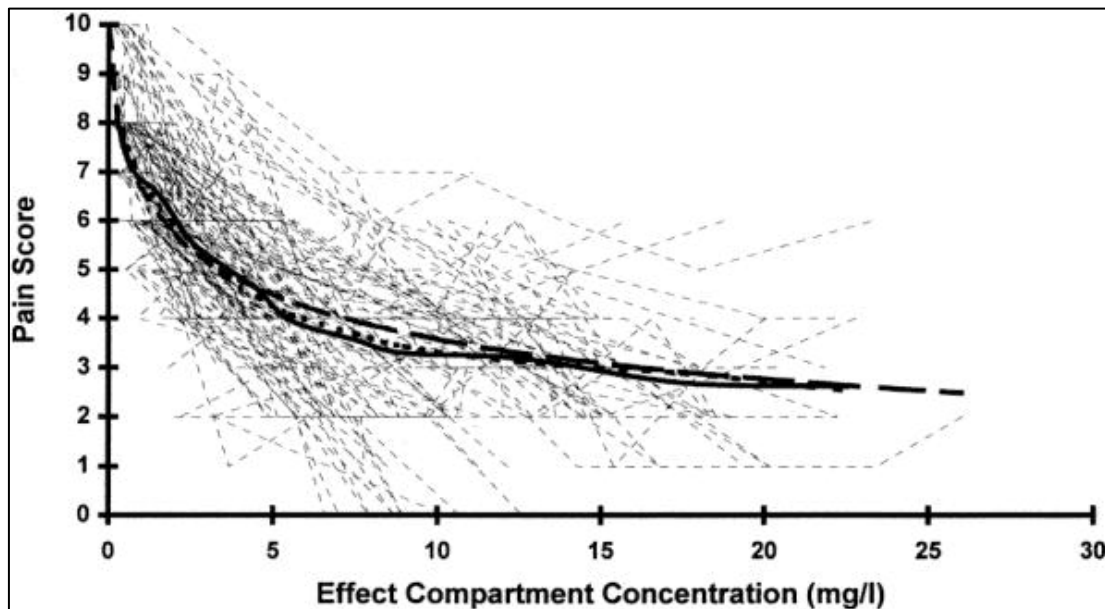
Doubling the concentration would seem to provide very little, if any additional analgesic effect. Therefore studies would suggest that under circumstances where paracetamol is not providing sufficient analgesia, increasing the dose further would not provide additional benefit.

The maximum analgesic effect of paracetamol is reached around 2 hours after administration.

#### **All data assessed:**

Some studies have attempted to examine the dose-response effects of paracetamol against pain. Anderson<sup>42,44</sup> modelled pooled data from children administered paracetamol either orally as a liquid (40 mg/kg or 100 mg/kg) or rectally as a suppository (125 or 250 mg) and suggested the dose-response curve was steep at low concentrations and shallower in its central portion (figure 4).

**Figure 4.** The relation between predicted effect compartment concentrations and observed pain scores for of 120 children (2-15 years) undergoing outpatient tonsillectomy and administered paracetamol either orally (40 mg/kg or 100 mg/kg) or rectally (125 mg or 250 mg).



Post operative pain was assessed using a visual analog scale. A score of 10 represents the worst pain imaginable to the individual child. The solid line is the mean observed profile and the dashed line is the mean predicted population profile. The mean post hoc profile, based on values of the parameters for the specific individual, is shown as a dotted line.<sup>44</sup>

The maximum analgesic effect was achieved at 10 mg/L, and these data demonstrate that little benefit would be derived from doubling the effect compartment concentration from 10 to 20 mg/L. Following administration of oral paracetamol, high plasma concentrations were achieved within 1 hour, after which time a linear decrease was observed. Paracetamol levels rose much more slowly with the suppositories but remained more stable for longer.

Only a few other studies have assessed the analgesic efficacy of paracetamol in children. Moore *et al*<sup>45</sup> evaluated the relative efficacies of four liquid analgesics in children aged 5-12 years following tooth extractions. In this study however, paracetamol was administered on the basis of age rather than weight, with 5-8 year olds receiving 240 mg and 8-12 year olds receiving 360 mg, which are not sufficient doses for most of the individuals in these groups.

2 hours were required to achieve a significant reduction in pain intensity for paracetamol compared with placebo. This may relate to paracetamol's relatively slow onset of action.

Another placebo-controlled study compared paracetamol (20 mg/kg) to diclofenac (a type of non-steroidal anti-inflammatory drug) (25 mg/kg rectally after anaesthetic induction) for pain relief following tooth extraction.<sup>4</sup> Diclofenac and paracetamol reduced pain scores significantly more than placebo.

In a different pain model, Bertin *et al*<sup>46</sup> investigated the efficacy of 10 mg/kg paracetamol against the pain associated with tonsillitis and pharyngitis in children after 2 days of administration. Paracetamol was only significantly better than placebo versus pain while swallowing. In contrast to this study, children, parents and paediatricians in another clinical study rated both ibuprofen (10 mg/kg) and paracetamol (15 mg/kg) as significantly different from placebo in terms of both pain intensity and change in pain against sore throat pain in children (aged 2-12 years) over a 6-hour period<sup>47</sup>.

## 2.4 Paracetamol toxicity

**Toxicity summary:** NAPQI – a toxic metabolite of paracetamol – is normally itself detoxified by glutathione contained in the liver. If the concentration of NAPQI is greater than the intracellular concentration of glutathione (eg, after a paracetamol overdose), there may not be sufficient glutathione to detoxify all NAPQI present. Any free NAPQI will bind to hepatocytes leading to necrosis and severe liver damage. A high dose of paracetamol can itself reduce glutathione levels, compounding the problem.

The threshold for paracetamol toxicity in children is unclear but is likely to be 150 mg/kg – 200 mg/kg. There is, however, substantial individual variability. In addition, the level of toxicity following repeated doses or chronic administration is even less clear. Pharmacokinetic studies suggest that maximum paracetamol plasma concentrations are likely to occur much earlier in younger children (< 5 years) than in older children.

Risk factors for paracetamol toxicity may include protein malnutrition or starvation (particularly in combination with repeated paracetamol dosing), and pre-existing liver disease. There is little evidence to confirm or refute these risk factors for hepatotoxicity. However there is sufficient doubt to strongly advocate the

administration of the lowest possible effective dose of paracetamol for children (10 mg/kg), especially when febrile children with poor intake of food may be administered paracetamol over a period of several days.

**All data assessed:**

**2.4.1. Mechanism**

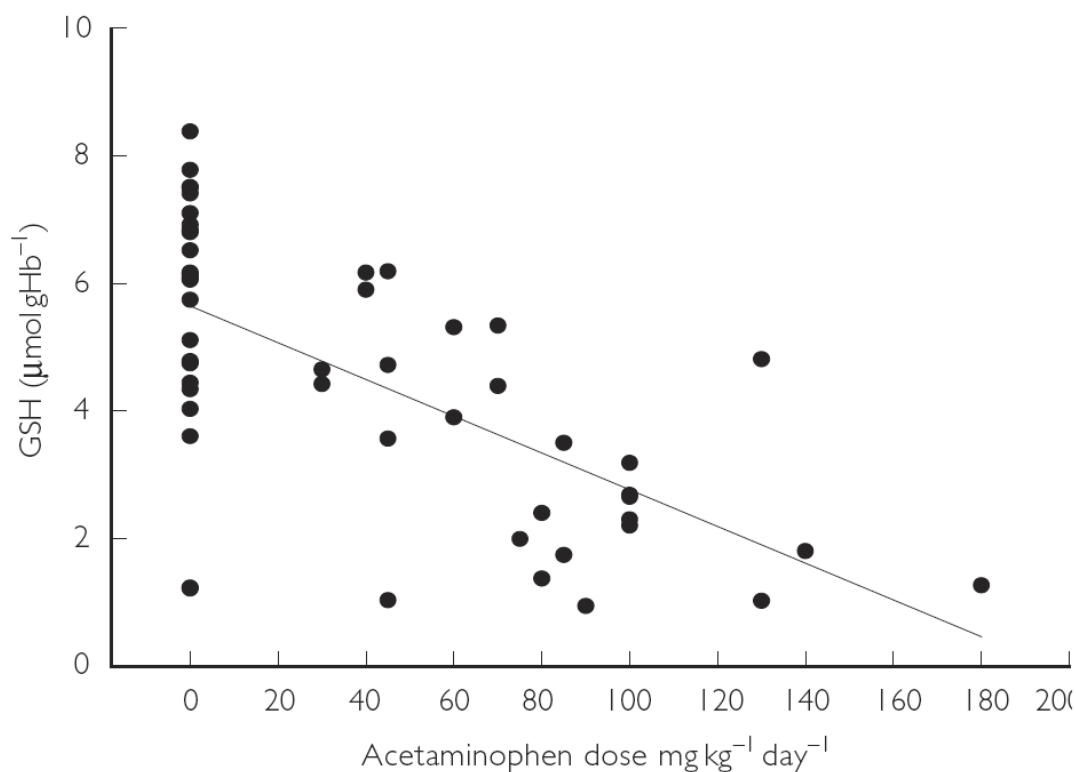
As discussed in section 2.2, a small percentage of paracetamol is metabolically oxidised by enzymes to form the highly reactive compound N-acetyl-p-benzoquinoneimine (NAPQI). In the presence of sufficient quantities of glutathione, NAPQI is immediately detoxified by conjugation with glutathione and subsequently excreted as cysteine and mercapturate conjugates. When the concentration of NAPQI exceeds that of intracellular glutathione, NAPQI covalently binds to hepatocytes leading to necrosis.

Mitchell *et al*<sup>48</sup> demonstrated that depletion of hepatic glutathione in mice by 75% with diethyl maleate potentiates paracetamol-induced hepatic necrosis. Administration of paracetamol alone caused a similar depletion of hepatic glutathione with maximal depletion of 75% present following 375 mg/kg of paracetamol as a single acute dose. Approximately 50% depletion occurred at 170 mg/kg. Although diethyl maleate rapidly depleted glutathione, no necrosis occurred in the absence of paracetamol. Further studies also revealed that covalent binding of paracetamol to hepatic proteins only occurred with doses of paracetamol that resulted in a 70% or greater depletion of hepatic glutathione. It should be noted however that rats appear to be more resistant to paracetamol-induced toxicity than humans, and the hepatotoxic dose may vary considerably among species.<sup>49</sup>

Another study by Kozer *et al*<sup>50</sup> investigated glutathione and antioxidant status changes in erythrocytes in febrile children presenting to a paediatric emergency department, who had received repeated suprathreshold levels of paracetamol. 51 children (age range 2 months-10 years) were included in the study and divided into three groups: group 1 (n=24, mean age  $\pm$  standard deviation [SD] 6 $\pm$ 3 years) included afebrile children who did not receive paracetamol but were examined for non-infectious causes; group 2, febrile children (temperature  $>35^{\circ}\text{C}$ ; n=13; 3.5 $\pm$ 2.6 years) who received paracetamol at repeated doses of 50 $\pm$ 15 (30-75) mg/kg/day for 4.1 $\pm$ 1.8 (3-10) days and group 3, febrile children (temperature  $>35^{\circ}\text{C}$ ; n=14; 2.2 $\pm$ 1.8 years) who received paracetamol at repeated doses of 107 $\pm$ 28 (80-180) mg/kg/day for 3.9 $\pm$ 1.7 (3-9) days.

There were no significant differences in the duration of fever or time from the last paracetamol dose or admission rates between the groups. Although there were no cases of severe hepatotoxicity, median aspartate transaminase (AST) levels were mildly but significantly elevated in group 3 compared with Groups 1 or 2. Erythrocyte glutathione (GSH) content was significantly lower in group 3 compared with groups 1 and 2 and the decrease was significantly related to the dose of paracetamol (Figure 5).

**Figure 5.** Glutathione content in erythrocytes of febrile children treated with paracetamol and controls in relation to dose ( $R=0.65$ ).<sup>50</sup>



This study supports the concept that repeated treatments with paracetamol at high paediatric doses may decrease hepatic glutathione to levels that are too low to process the toxic paracetamol by-product NAPQI.

#### 2.4.2. Toxicity resulting from a single acute dose

The threshold for paracetamol toxicity in children is unclear. Levels of 150 mg/kg have long been cited to be the threshold for toxicity.<sup>51</sup> However, there is little or no paediatric data to support this threshold for a single acute dose and it is likely that this figure has been extrapolated from adult data. In the adult, doses of 10-15 g are reported as a threshold for toxicity; a dose of 10 g in a 70 kg adult amounts to a dose of 143 mg/kg. Several studies suggest however that children, particularly young children, are more resistant to paracetamol toxicity and the threshold in children for toxicity resulting from a single acute ingestion may be closer to 200 mg/kg.<sup>51,23</sup>

In support of this were the results of Mohler *et al*<sup>62</sup> who carried out a prospective observational study of calls to a regional poison centre in California, US, over a 25-month period. A total of 1039 patients were included (519 girls and 520 boys, median age 2.3 years [all <6 years]) with acute maximum exposure to paracetamol of 20-200 mg/kg. Of these, 236 had exposures of 100-200 mg/kg and 68 had exposures



of 150-200 mg/kg. 72 hours after the initial contact, 1019 of these patients were well, without signs or symptoms of hepatotoxicity. 20 patients were either lost to follow up or had incomplete data.

Another study by Mahadevan *et al*<sup>63</sup> reviewed 10 years of experience from a single paediatric liver unit and similarly concluded that neither the paracetamol dose or serum level can predict the severity of hepatotoxicity with paracetamol. Children in this study were divided into two groups: group 1 included children who developed significant hepatotoxicity after a single dose of paracetamol but made a complete recovery with conservative management while group 2 children developed fulminant liver failure and required an orthotopic liver transplant.

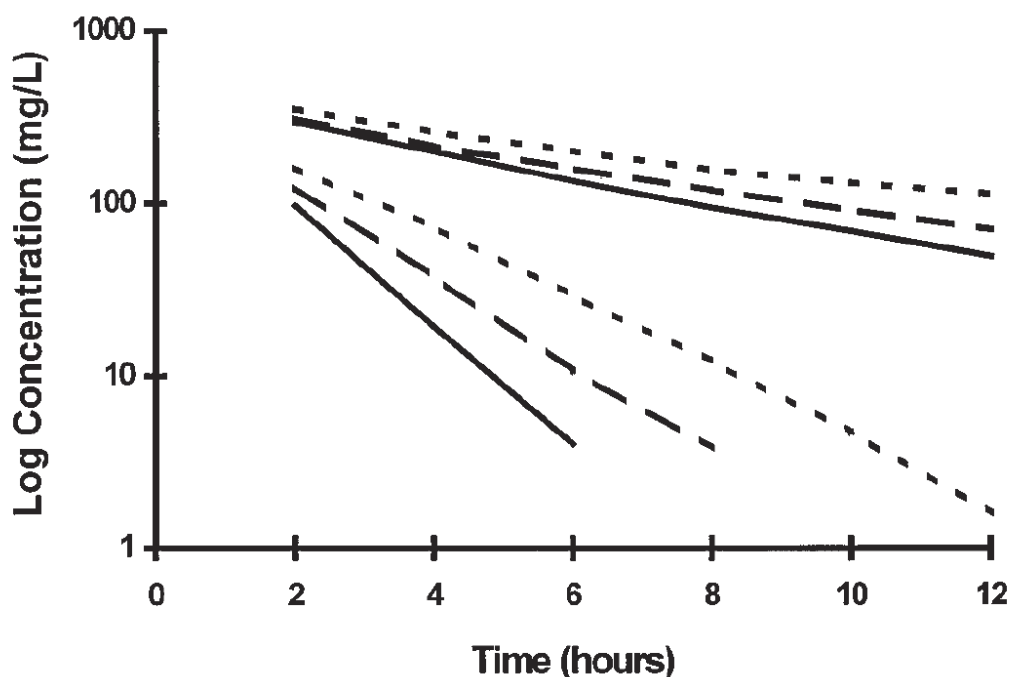
Despite these different outcomes there was no difference in the median paracetamol dose ingested (group 1: 348 (91-582) versus group 2: 285 (222-645) mg/kg), and the severity of liver disease. Furthermore there was no difference in the median serum paracetamol levels between the groups. All patients had raised hepatic transaminase levels but again the levels did not differ between groups. Critically however, the time to presentation at the liver unit was significantly longer in group 2 (44 hours (range 4-72)) than in group 1 (24 hours (range 4-72)).

James *et al*<sup>64</sup> similarly reported no significant differences in mean paracetamol dose taken by children and adolescents with different degrees of hepatotoxicity. Peak levels were not reached until 72 hours following ingestion.

Anderson *et al*<sup>23</sup> simulated paracetamol concentrations for 1000 children (1-5 years) with variable pharmacokinetic parameters. In this publication, the authors state that because clearance of drugs decreases as weight increases<sup>23</sup>, larger doses are required in younger children to achieve similar concentrations than older children or adults. As a consequence of this, predicted serum concentrations are lower than the per-kilogram dose.

As such, to achieve a peak plasma concentration of 200 mg/L would require a dose of 300 mg/kg in a 1-year old (8-12kg), 280 mg/kg in a 5-year old (16-22 kg) and 230 mg/kg in an adult (55-85 kg). Simulated time-concentration profiles (95% CI) for children and adults after 300mg/kg paracetamol are shown in figure 6. In terms of clinical management, maximum plasma paracetamol concentrations are likely to occur earlier in young children (<5years) than older individuals.

**Figure 6.** Confidence intervals (CI, 5% to 95%) of simulated concentration-time profiles for children and adults given 300mg/kg paracetamol



Solid line = 1 year; dashed line = 5 years; dotted line = adults). Rumack-Matthew action line is same as 95% CI concentration-time profile for 1-year-old child.

It can be noted from figure 6 that despite the careful modelling, predicted serum paracetamol concentrations arising from a 300 mg/kg dose still span a large range from 32-280 mg/L (95% CI) 4 hours after ingestion. Thus, even after allowing for age-related differences in clearance, substantial variability in paracetamol concentrations in children resulting from a single dose still exists. A study by Bond<sup>55</sup> also suggests that a single acute dose of 200 mg/kg is relatively safe in healthy children and should be used as a referral threshold for preschool children following acute unintentional ingestion of paracetamol. However neither of these studies considered children older than 5 years and how these recommendations relate to this age group is unclear. Furthermore the impact of co-existing risk factors on this threshold is not considered.

#### 2.4.3. Toxicity resulted from repeated doses

Children may be relatively protected against hepatotoxicity arising from a single acute dose of paracetamol; however, the situation following repeated doses or chronic administration is less clear. Nahata *et al*<sup>3</sup> have demonstrated that substantial increases in paracetamol serum concentrations occurs following repeated therapeutic doses over 1-3 days. This may explain the apparently higher incidence of toxicity reported after multiple dosing.

Rivera-Penera *et al*<sup>66</sup> also reported 10 cases of hepatotoxicity following multiple dosing in children age <10 years. In this study, the dose of ingested paracetamol was calculated on the basis of recalled frequency, type of measuring device, and concentration of the preparation. In three of these children, paracetamol doses

ranged from 160-760 mg/kg/day. Another three of these children had received the following doses respectively: six doses of 25 mg/kg over 2 days; six doses of 28 mg/kg over 2 days; three doses of 25 mg/kg over 5 days.

More recently in 2006, Kozer *et al*<sup>57</sup> reviewed the literature on chronic supratherapeutic paracetamol exposure and concluded that liver injury secondary to paracetamol should be considered when a child has received more than 75 mg/kg/day for at least 2 days or if risk factors for paracetamol toxicity have been identified (see section 2.4.4).

#### 2.4.4. Risk factors for paracetamol toxicity

In adults a number of risk factors have been associated with a greater incidence of paracetamol-induced hepatotoxicity including: starvation; CYP450-inducing agents, eg, phenobarbital; alcoholism; underlying hepatic injury; concomitant disease; and genetic factors.<sup>58,59,13,60,17</sup> However in children, there is very little literature investigating the extent to which factors such as starvation or pre-existing hepatic injury may increase the risk of hepatotoxicity.

There appears to be no studies evaluating the effect of fasting on hepatic glutathione status in children. Despite this, many studies implicate starvation as a factor in hepatotoxicity, particularly in cases where doses have been within therapeutic levels.<sup>61,62</sup> Mehta *et al*<sup>63,64,65</sup> report that the mean half-life of paracetamol was significantly longer in infants and children with protein-energy malnutrition (protein intake <20 g/day for 1 week) than in children with normal levels of protein intake (half-life: 8.14 hours versus 4.33 hours). There was also a decrease in half-life in malnourished children after nutritional rehabilitation. Therefore, the presence of protein malnutrition may result in paracetamol accumulation with repeated dosing, and increase the risk of hepatotoxicity.

There is also limited data in adults regarding the effects of starvation on the risk of paracetamol toxicity. Shi *et al*<sup>66</sup> reported that protein malnutrition in adults undergoing surgery decreased hepatic GSH levels ( $\mu\text{mol gHb}^{-1}$  mean $\pm$ SD) from  $3.42\pm 0.91$  to  $2.57\pm 0.63$  ( $p=0.029$ ), a reduction of 25%. Similarly, Martensson<sup>67</sup> reported that a 7-day period of total energy deprivation in healthy human subjects reduced both leukocyte and plasma-free glutathione concentrations by 41% and 37.5% respectively ( $p<0.05$  compared with pre-starvation levels). A decrease in leukocyte glutathione levels was seen within 1 day of starvation (23.7% reduction); the decrease became significant at day 4 (34.3% reduction).

Shaoul *et al*<sup>68</sup> reported that neither vomiting nor decreased food intake affected the observed paracetamol level or AST levels in febrile children. This was also the case if the degree of appetite was further divided into 'decreased' or 'not at all'. However in this study, mean duration of treatment was  $2.8\pm 1.8$  days, with approximately one third of the patients receiving a single dose. It is possible that this study may have sampled levels too early or used the wrong surrogate for hepatotoxicity.

Prescott<sup>13</sup> also reviewed a range of studies examining the influence of different diets on paracetamol metabolism in man, the majority of which revealed no significant effect.

Pre-existing liver disease has also been suggested to affect paracetamol metabolism. Al-Obaidy *et al*<sup>69</sup> reported that the clearance of paracetamol following acute single doses in 13 children (age 7 months-12 years) with chronic liver disease

was similar to those values reported for healthy children. However this study also found that adults with non-alcoholic liver disease (those with steatosis, fibrosis, inflammatory cell infiltrates, cell necrosis or a combination of these) had significantly lower hepatic glutathione levels ( $2.77 \pm 0.1 \mu\text{mol/g}$  liver) compared with adults without liver disease ( $4.14 \pm 0.1 \mu\text{mol/g}$  liver).

Another study found that hepatocellular injury was associated with presentation >24 hours after ingestion (odds ratio [OR], 33.5%; 95% CI, 408.8–275), older children age 10-17 yrs (OR 36.9%; 95% CI, 4.9–275.4), intentional overdose (OR, 37.2; 95% CI, 5.0-278.2), dose >150 mg/kg (OR, 17.9; 95% CI, 2.3-139.2) and white ethnic origin (OR, 2.8%; 95% CI, 1.1-7.2)<sup>70</sup>. Due to its retrospective nature however, possible risk factors such as pre-existing disease or reduced food intake were not considered.

#### *2.4.5. Case reports of hepatotoxicity associated with oral paracetamol in children*

Up to 31<sup>st</sup> July 2009 when this assessment was completed, there were 26 [Yellow Card](#) reports<sup>2</sup> associated with oral paracetamol and hepatotoxicity in children aged <18 years of age. Cases from published literature were not included in this assessment. Investigation of these reports found that 13 were intentional overdose/suicide cases age 12-17 years. Two fatal cases appeared unrelated to the ingestion of paracetamol. There were four cases of accidental overdose, three cases of young children consuming substantial amounts of a bottle of paracetamol and one case of a child being prescribed the wrong dose. The remaining 7 cases were of therapeutic overdose.

## **2.5 Paediatric posology**

As discussed previously in this report, it is generally accepted that the therapeutic dose of paracetamol in children, as well as in adults, is 10-15 mg/kg.<sup>33,71,27,28,7,8,27,31,9,29</sup> Very few studies have examined concentrations less than this.<sup>5,38,45,41,40</sup>

The current posology for paediatric paracetamol delivers wide variability with doses ranging from 7.7-34.3 mg/kg/dose (excluding infants under the age of 2 months). The review of efficacy supports a therapeutic range for paracetamol of 10-15 mg/kg and although the toxic threshold is unclear, there are no data to support the delivery of doses as high as 30 mg/kg. Doses less than 10 mg/kg are only seen in a few age bands in the heaviest children. This wide variability in mg/kg dose is partly due to the wide age bands and the allowance to double the dose at every age band. As a result, depending on the weight of the child, children could receive doses substantially more than the adult posology.

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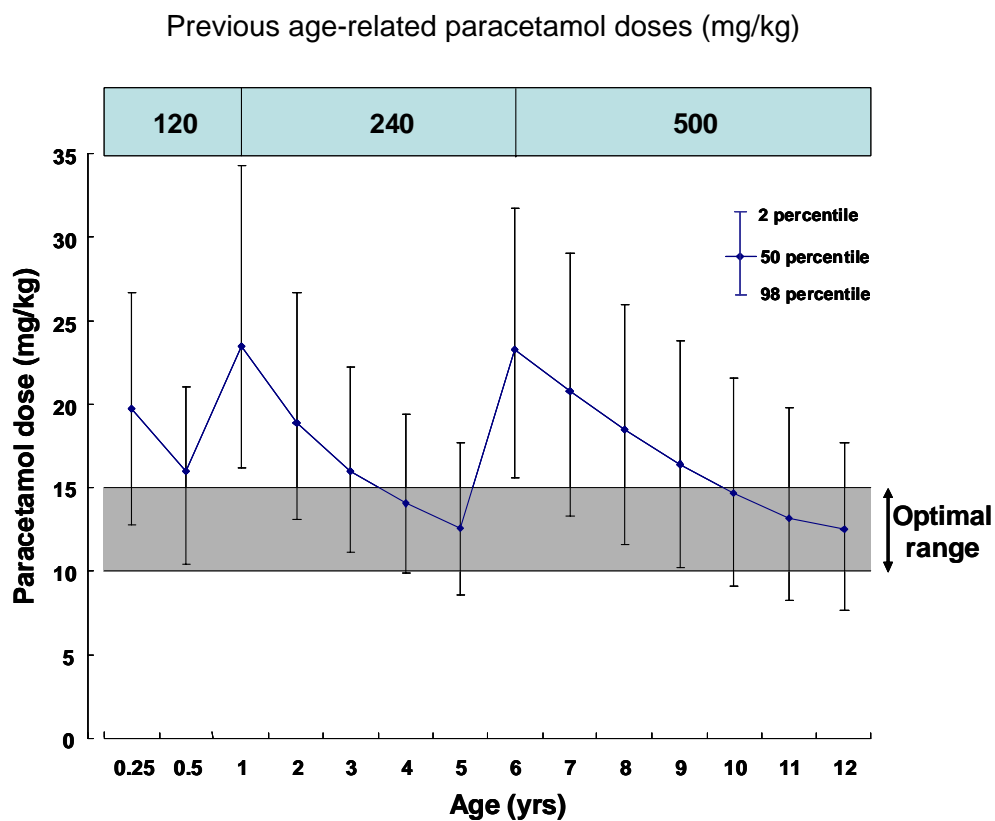
<sup>2</sup> The [Yellow Card Scheme](#), which is run by the MHRA and the CHM, is used to report suspected side effects to any medicine or vaccine in the UK. Both health professionals and the public should use the Scheme to report.

### 3. DISCUSSION

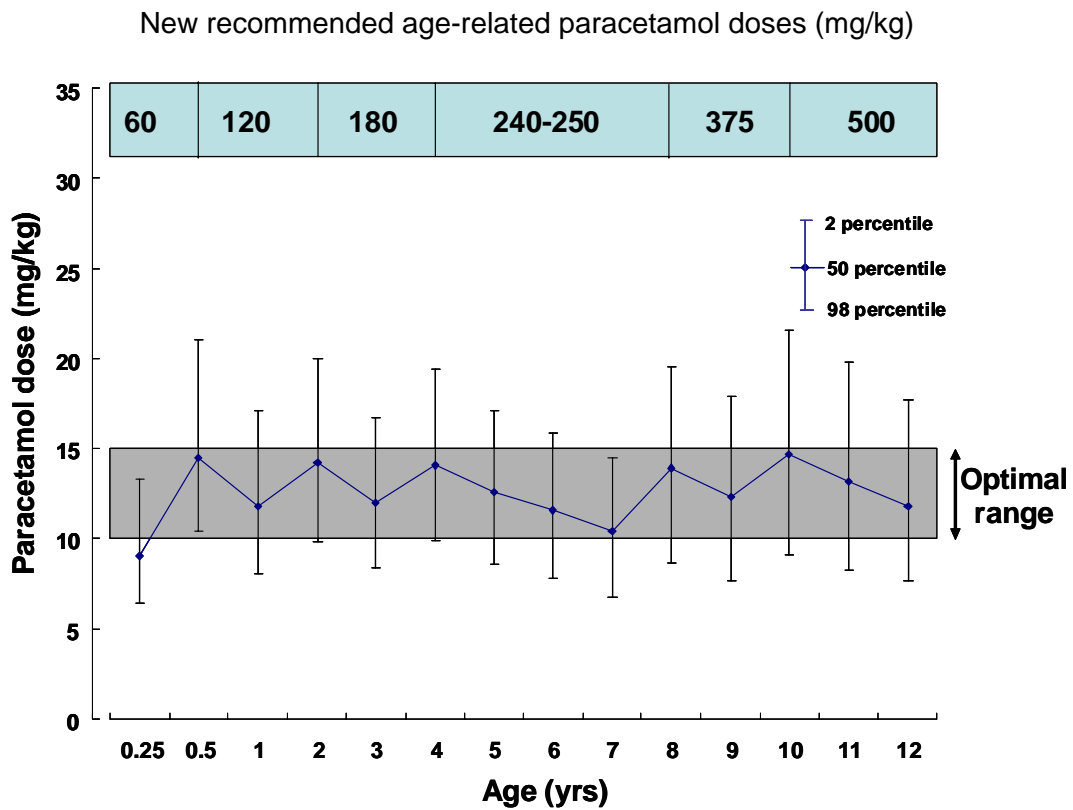
The effective dose range for antipyresis and analgesia with paracetamol in children is 10–15 mg/kg. However, it is clear that with the previous UK posology for paediatric paracetamol some children may not have received the optimal dose for their weight or their age.

The UK posology for paediatric liquid paracetamol has been revised (the revisions are outlined in the conclusions section [chapter 4]). The new posology retains the current dosage increments of 2.5 mL and 5.0 mL but provides narrower age ranges and specific doses, therefore maintaining the paracetamol dose within the 10–15 mg/kg range for the majority of children. This is illustrated in figures 7 and 8.

**Figure 7.** Comparison of previous age-related doses of paracetamol to the optimal dosage range of 10 – 15 mg/kg for children at the 2<sup>nd</sup>, 50<sup>th</sup> and 98<sup>th</sup> weight percentiles



**Figure 8.** Comparison of new recommended age-related doses of paracetamol to the optimal dosage range of 10 – 15 mg/kg for children at the 2<sup>nd</sup>, 50<sup>th</sup> and 98<sup>th</sup> weight percentiles.



Importantly, to ensure accurate delivery of the correct amount of paracetamol it is recommended in the product information that only the special spoon or syringe provided with the product should be used to measure it out.

#### 4. CONCLUSIONS AND NEW RECOMMENDATIONS.

On the basis of the review, the recommended doses of paracetamol for children in the UK have been changed in order to ensure that children get the most effective dose of paracetamol that is suitable for their age. The new dosing instructions and advice are presented in the tables below, and will become available in product information shortly. Parents and carers for children should follow the dosing instructions provided on the product packaging and in the leaflet in the box.

#### NEW DOSING INSTRUCTIONS FOR CHILDREN'S LIQUID PARACETAMOL PRODUCTS:

##### Infant paracetamol suspension (120 mg/5 mL)

Child's age	Condition(s) for treatment:	How much to give?	How often (in 24 hours)?
2 – 3 months	1. Post-vaccination fever 2. Other causes of pain and fever if your baby weighs over 4 kg and was born after 37 weeks	2.5 mL	Usually once. However, if necessary, after 4–6 hours a second 2.5 mL dose may be given
<ul style="list-style-type: none"> <li>Do not give to babies less than 2 months of age</li> <li>Do not give more than two doses</li> <li>Leave at least 4 hours between doses</li> <li>If further doses are needed, talk to your doctor or pharmacist</li> </ul>			

Child's age	Condition(s) for treatment	How much to give?	How often in 24 hours?
3 – 6 months	Pain and/or fever	2.5 mL	4 times
6 – 24 months		5 mL	4 times
2 – 4 years		7.5 mL	4 times
4 – 6 years		10 mL	4 times
<ul style="list-style-type: none"> <li>Do not give more than four doses in any 24-hour period</li> <li>Leave at least 4 hours between doses</li> <li>Do not give this medicine to your child for more than 3 days without speaking to your doctor or pharmacist</li> </ul>			

**Paracetamol six plus suspension (250 mg/5 mL):**

Child's age	Condition(s) for treatment	How much	How often (in 24 hours)?
6–8 years	Pain and/or fever	5 mL	4 times
8–10 years		7.5 mL	4 times
10–12 years		10 mL	4 times
<ul style="list-style-type: none"><li>• Do not give more than four doses in any 24-hour period</li><li>• Leave at least 4 hours between doses</li><li>• Do not give this medicine to your child for more than 3 days without speaking to your doctor or pharmacist</li><li>• Do not give to children under the age of 6 years</li></ul>			

- Paracetamol six plus suspension dose for children age 12 – 16 years: 10–15 mL up to 4 times a day
- Liquid paracetamol dose for adults and children aged over 16 years: 10–20 mL up to 4 times per day.

**Advice**

- The product information for all children's liquid paracetamol products is being updated with the new dosing instructions outlined above. Always follow the dosing instructions provided on the product packaging and in the leaflet in the box.
- A special spoon or syringe will be supplied with the liquid paracetamol product to ensure it is measured accurately. Do not use any other spoon or device to measure the product.
- If you have any questions regarding the new dosing instructions for children's paracetamol, please ask a pharmacist or healthcare professional

The above information has also been communicated in an article in the [July 2011 issue of Drug Safety Update](#), the monthly MHRA publication for health professionals containing the latest information and advice on medicines and vaccines safety.



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## 6. GLOSSARY

### **Absorption**

The movement of a substance across a cell membrane into a tissue or organ

### **Afebrile**

Without fever

### **Allometric**

Studying the growth of part of an organism, in relation to the growth of the whole organism

### **Alanine aminotransferase/alanine transaminase**

An enzyme found mainly in the liver, which is released into the blood when the liver is injured. A test which measures the amount of ALT in the blood is used to determine if a patient has liver damage

(See also **ALT**)

### **ALT**

(See **Alanine aminotransferase/alanine transaminase**)

### **Anaesthetic**

Medicines that are used for pain relief and temporary loss of consciousness during surgery

### **Analgesic**

Pain-reliever

### **Antipyretic**

A substance that reduces fever or suppresses it

### **Antipyrine**

A medicine used to relieve earache

### **Aspartate aminotransferase/ aspartate transaminase**

An enzyme found in high amounts in heart and liver muscle, which is released into the blood when either organ is damaged. Diseases that affect the liver increase the levels of AST in the blood.

### **AST**

(See **Aspartate aminotransferase**)

### **Azathioprine**

A medicine given to transplant patients to prevent organ rejection

### **Bilateral myringotomy**

A surgery involving one or more tubes inserted into the ears, which helps to minimise repeated ear infections

### **Cerebrospinal fluid**

A clear fluid surrounding the brain and spinal cord that provides nourishment and protection



**Clearance**

The rate at which a chemical or substance is removed from the body, eg, in urine

**Clinical study/trial**

A research study that tests the effectiveness and safety of medicines in humans

**Concomitant**

Two or more medicines given in the same period

**Conjugation**

Where two substances join together, forming a new substance

**Contraindicated**

Any factor or medical condition that makes it unwise to give a particular medicine to a patient

**Diclofenac**

A medicine belonging to the non-steroidal anti-inflammatory drug (**NSAID**) class which has **antipyretic** and **analgesic** actions

**Dose-response effect**

Where the size of effect of a substance in the body depends on the dose given

**Double-blind study**

A **clinical trial** in which the identity of the test medicine is hidden from both the volunteers and the study investigators (to remove any possible bias from the results)

**Effect compartment**

The actual site in the body (tissue, organ, etc) where the drug has an effect

**Efficacy**

The effectiveness of a drug measured under laboratory conditions or in clinical trials

**Elixir**

A sweetened solution that is used as a vehicle for a medicine, such as paracetamol

**Endotoxaemia**

The presence of bacterial toxins in the body which can cause adverse effects, such as uncontrolled internal bleeding, and damage to the kidneys

**Enzyme**

A protein produced by cells in the body that helps specific biological reactions to occur

**Erythrocyte**

A red blood cell

**Excretion**

The process by which a medicine is eliminated from the body

**Febrile**

Having a fever

**Fibrosis**

Thickening and scarring of connective tissue, usually as a result of injury

**Fulminant liver failure**

Rapid liver failure as a result of severe liver damage

**Gastrointestinal**

Related to the stomach and intestines

**Genetic factors**

Inherited traits

**Glucuronic acid**

A substance that combines in the body with certain drugs such as paracetamol during its **metabolism**

**Glucoronidation**

The process by which paracetamol is **metabolised** by **glucuronic acid** in the body

**Glutathione**

A protein contained in the body which helps to metabolise and process many substances, such as paracetamol

**Half-life**

The time required for the concentration or amount of drug in the body to be reduced by half

**Hepatic**

Related to the liver

**Hepatocytes**

Liver cells

**Hepatotoxicity**

Where a substance has toxic effects on the liver

**Heterogeneity**

Dissimilarity (between groups)

**Ibuprofen**

Type of pain-relief medicine

**Inflammatory cell infiltrates**

Substances released from cells in an inflamed area

**Leukocyte**

A white blood cell

**Metabolism**

The chemical processes or changes that occur in the body in order to maintain life. This involves either breaking down substances or making new ones

**Metabolite**

A substance produced by **metabolism**

**Methanol**

A type of alcohol used as a solvent

**N-acetyl-p-benzo-quinone imine (NAPQI)**

A toxic substance produced during the **metabolism** of **paracetamol**

**Necrosis**

The death of tissue or organs in a body, caused by disease, injury or interference with the blood supply to the affected part

**Non-steroidal anti-inflammatory drug (NSAID)**

A class of drug used to relieve pain, particularly pain associated with inflammation

**Observational study**

A type of **clinical study** where the investigators observe the patients' response to a treatment and measure their outcomes, but do not actively manage the study.

**Orthotopic transplant**

The transplant of tissue or an organ from a donor to a recipient

**Oxidase enzymes**

A group of enzymes that enable **oxidation** to occur

**Oxidation**

A chemical reaction involving the combination of a substance with oxygen, which is important for many bodily processes

**Paediatric**

Occurring in, or relating to, children

**Paediatrician**

A doctor specialising in the care of babies and children

**Paracetamol**

A widely used medicine for pain relief and reducing fever

**Pharmacokinetics**

The process by which a drug is absorbed, distributed, metabolised and eliminated by the body

**Pharyngitis**

Inflammation of a part of the throat called the pharynx

**Phenobarbital**

A medicine used as a sedative and a treatment for seizures or fits (also known as **phenobarbitone**)

**Placebo**

Inactive dummy treatment (eg, a sugar pill) given in a **clinical trial** to a particular patient group so their responses can be compared with the group receiving the test medicine

**Plasma**

The fluid part of blood that contains the blood cells

**Posology**

The science of the dosage of medicines

**Randomised study/trial**

A **clinical trial** in which the study participants are randomly assigned to receive a test medicine, or a **placebo** or comparator medicine

**Retrospective study**

A study in which the history of a group of individuals with a particular disease or condition is examined for a particular outcome, usually using their medical records for information

**Serum**

The clear component of blood

**Steatosis**

Accumulation of fat in the tissue of an organ

**Sulphation**

A biological reaction that uses an enzyme to combine a substance or compound with sulphur or a sulphate

**Suspension**

A mixture of solid particles visibly dispersed in a liquid

**Temporal**

Related to time (eg, the timing of when a drug is taken)

**Tonsillectomy**

A surgical operation involving the removal of the tonsils (specialised areas in the throat which fight infection)

**Urinary tract infection**

An infection that occurs anywhere in the bodily organs and tubes involved in the formation and excretion of urine

**Ventricular catheter**

A thin flexible tube surgically implanted into the heart that enables a doctor to monitor heart function and collect blood samples