

Guidelines for the management of paracetamol overdose

For Poisons Information Call
Australia 131 126
New Zealand 0800 764 766

General Information

- Paracetamol overdose is a significant cause of hospital admission, but severe liver injury is rare and even when it does occur the prognosis is usually good.¹
 - Death from paracetamol poisoning is rare and does not occur in patients treated with N-acetylcysteine (NAC) within 8 hours of acute ingestion.^{2,3}
- Signs consistent with paracetamol poisoning include repeated vomiting, abdominal tenderness in the right upper quadrant or mental status changes.⁴
 - Hypoglycaemia on presentation is very rare, but is important to consider in late presentations if liver failure has occurred.
- Any patient should be considered to be at risk of severe liver injury if they have ingested paracetamol above the thresholds below (See Table 1).⁴
 - Regardless of the potential ingested dose, all patients with deliberate self poisoning should have a serum paracetamol level measured to further refine the risk of hepatic injury and thus the need for NAC.
 - Adult and paediatric patients without deliberate self-poisoning who are not considered at risk according to the thresholds in Table 1 below do not require serum paracetamol levels, LFTs or follow-up.

TABLE 1. Thresholds: Potentially Hepatotoxic Paracetamol Overdoses

	Adults and children over 6 years of age	Children (aged 0-6 years)
Acute Single Ingestion	At least 10g or 200mg/kg (whichever is lower) over a period of less than 8 hours.	200mg/kg or more over a period of less than 8 hours. Death has not been reported in this setting
Repeated Supratherapeutic Ingestion (RSTI)	At least 10g or 200mg/kg (whichever is lower) over a single 24-hour period. At least 6g or 150mg/kg (whichever is lower) per 24-hour period for the preceding 48 hours. More than 4g/day or 100mg/kg (whichever is less) in patients with pre-disposing risk factors (see below).	200mg/kg or more over a single 24-hour period. 150mg/kg or more per 24-hour period for the preceding 48 hours. 100mg/kg or more per 24-hour period for the preceding 72 hours.

- Following acute overdose, the most important factor that determines prognosis is the delay beyond 8 hours before the initiation of NAC.^{2,4}
- Theoretical patient factors that might increase the risk of liver injury include:⁵
 - Chronic alcohol abuse
 - Patients taking microsomal-inducing drugs such as barbiturates, carbamazepine, rifampicin and isoniazid (not phenytoin)
 - Patients likely to have glutathione depletion (eg recent prolonged fasting, acute illness with prolonged vomiting or dehydration, anorexia nervosa, bulimia, malnutrition for other reasons such as malignancy, HIV-AIDS)
 - Patients with other factors causing liver injury (eg viral hepatitis, alcoholic hepatitis)
- NAC is an effective antidote that prevents mortality if administered within 8 hours of an acute overdose. It has also been shown to improve prognosis if administered at any time (beyond 8 hours) following overdose.
 - NAC is usually well tolerated. Severe reactions are uncommon and may be due to accidental overdose or predisposing factors such as asthma. Anaphylactoid reactions occur during the initial infusions in 4-23%, manifested by rash, bronchospasm, and rarely, hypotension.^{3,6} If there is a reaction, the infusion should be stopped until the reaction has resolved, then reinstated at a reduced rate and slowly titrated back up.

Administration of NAC

- When required, NAC is infused in a 3 stage intravenous infusion giving a total dose of 300 mg/kg of over 20 hours.⁷
 - First Infusion:** The initial dose (150mg/ml) is diluted in 200mL of 5% glucose and infused over 15 to 60 minutes under close medical supervision due to the incidence of anaphylactoid reactions.
 - Second Infusion:** The second dose (50mg/ml) is diluted in 500mL of 5% glucose and infused over the next 4 hours.
 - Third Infusion:** The third dose (100mg/ml) is diluted in 1000mL of 5% glucose is infused over the next 16 hours.
- Prescription errors can occur when calculating the dose of NAC using the recommended mg/kg dose. Using the "NAC intravenous infusion guide" allows the dose in mL to be calculated and charted in one step, reducing the potential for calculation and transcription errors.⁷

NAC Intravenous Infusion Dosage Guide

- NAC is supplied in 10mL ampoules.
- Table 2 allows easy calculation of the volume (and thus correct dose) of 200mg/mL NAC required for each infusion. Patient lean body weight is estimated to the nearest 10kg.
- In children, or adults more than 90kg, the volume of NAC required is calculated using the formula in the bottom row of Table 2. For adults >110kg, calculate volume based on 110kg.
- A previous adverse reaction to NAC prompts caution during the initial infusion, but is not a contraindication to its use.

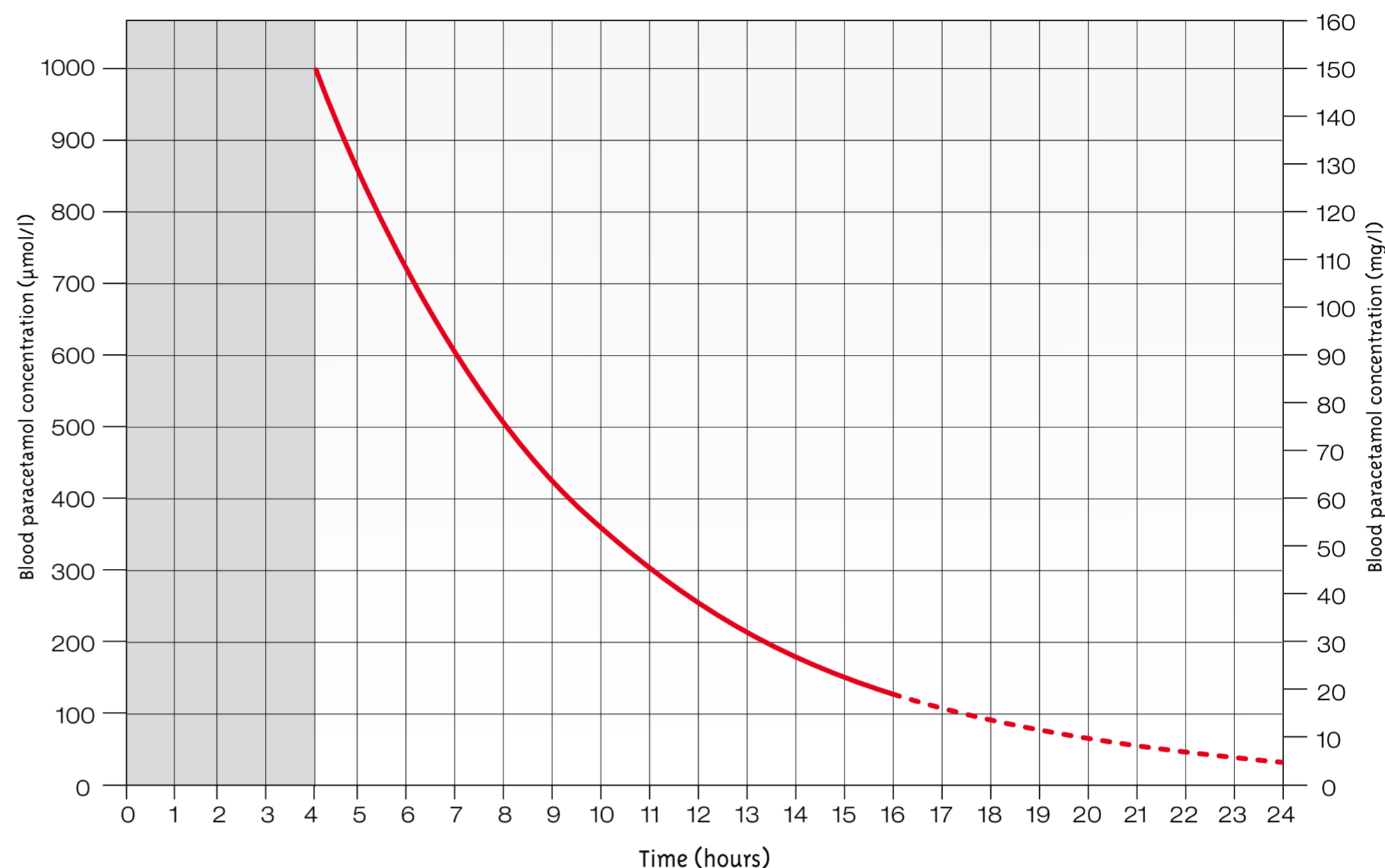
TABLE 2. NAC Intravenous Infusion Dosage Guide.

PATIENT'S LEAN BODY WEIGHT (kg)	INITIAL Volume (mL) of NAC to be added to 200 mL of 5% glucose	SECOND Volume (mL) of NAC to be added to 500 mL of 5% glucose	THIRD Volume (mL) of NAC to be added to 1000 mL of 5% glucose	Total Volume (mL) of NAC given over 20 hours
50	37.5	12.5	25	75
60	45.0	15.0	30	90
70	52.5	17.5	35	105
80	60.0	20.0	40	120
90	67.5	22.5	45	135
X	0.75X	0.25X	0.50X	1.5X

- In children the volume of 5% glucose into which NAC is diluted should be an appropriate volume for the patient's weight. For example:
 - Children <20 kg body weight: 150 mg/kg in 3 mL/kg of 5% dextrose over 15 minutes followed by 50 mg/kg in 7 mL/kg of 5% dextrose over 4 hours followed by 50 mg/kg in 7 mL/kg of 5% dextrose over 8 hours followed by 50 mg/kg in 7 mL/kg of 5% dextrose over 8 hours
 - Children >20 kg body weight: 150 mg/kg in 100 mL of 5% dextrose over 15 minutes followed by 50 mg/kg in 250 mL of 5% dextrose over 4 hours followed by 50 mg/kg in 250 mL of 5% dextrose over 8 hours followed by 50 mg/kg in 250 mL of 5% dextrose over 8 hours

Paracetamol Treatment Nomogram⁸

- Treat ALL patients with serum paracetamol levels above the nomogram treatment line.
- A single nomogram treatment line is recommended. This line has been lowered by 25% from standard lines to take into account:
 - Potential for minor error estimating the time of ingestion
 - Increased safety for all patients with potential risk factors
- Ensure that correct units are used (ie $\mu\text{mol/L}$ or mg/L)



Adapted from Rumack and Mathew (Smilkstein et al. Ann Emerg Med 1991; 20: 1058-63)

Management of Acute Single Ingestions

Decontamination

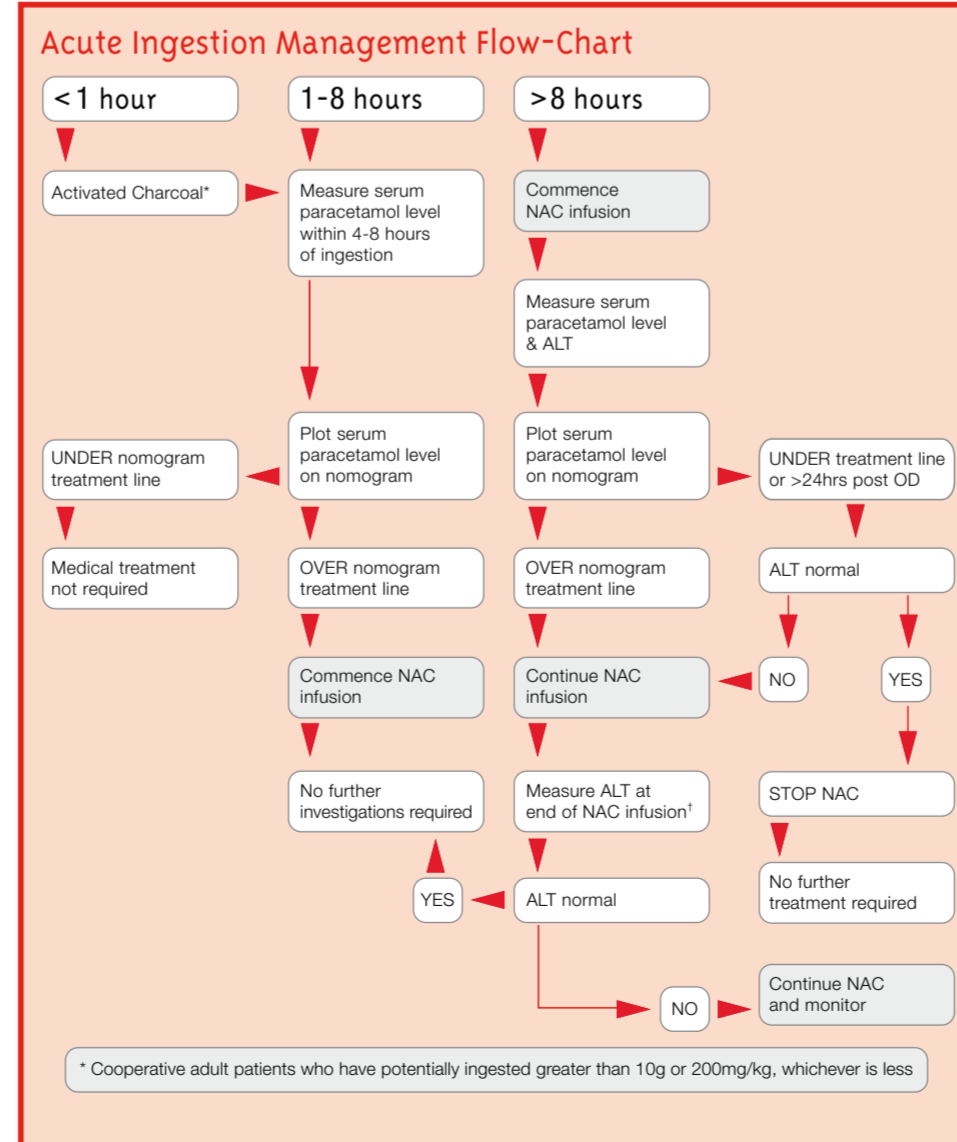
- No decontamination of any kind is indicated in paediatric patients.
- Decontamination using activated charcoal is indicated in adult patients if ALL of the following criteria are met:
 - Presentation within 1 hour
 - Cooperative patient
 - Ingestion of greater than 10g or 200mg/kg (whichever is less)
- Sorbitol is not indicated.

Specific Paediatric Considerations

- Decontamination is not indicated.
- Deliberate self poisoning should be considered in patients older than 6 years.
- Accidental exposures in children 6 years or less are based on the paracetamol dose ingested:
 - If the estimated dose ingested is less than 200mg/kg referral to hospital, decontamination, serum paracetamol level and follow-up are not required.
 - If the dose ingested is estimated to be more than 200mg/kg, manage as per the **Acute Ingestion Management Flow-Chart**

Management Flow-Chart

- Treatment recommendations are based on the time elapsed from the paracetamol ingestion. Refer to the **Acute Ingestion Management Flow-Chart**.
- If in doubt contact PIC.



What To Do When The Nomogram Does Not Apply

Unknown Time Of Paracetamol Ingestion

- If there is a detectable paracetamol level with an unknown time of ingestion, commence NAC and treat the patient as per the end of the > 8 hours scenario (i.e. at † on the **Acute Ingestion Management Flow-Chart**).

Staggered Overdose

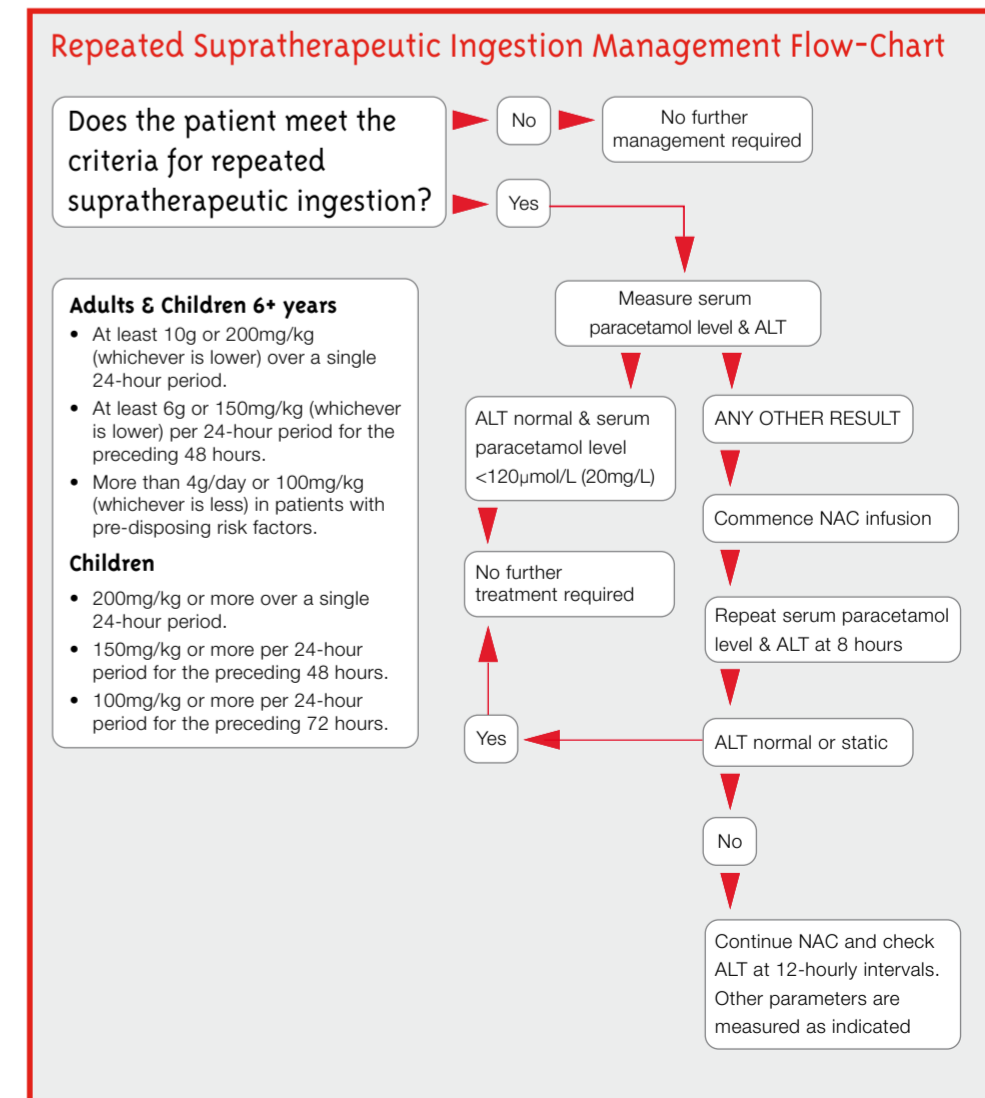
- A staggered overdose comprises several ingestions over a period of less than 24 hours.
- If the patient has taken an overdose of paracetamol at two time intervals within the last 8 hours, interpret the level as if all paracetamol was taken at the earliest overdose and treat the patient as per the 1-8 hours scenario in the **Acute Ingestion Management Flow-Chart**.
- If it has been MORE than 8 hours since the first dose, treat the patient as per the > 8 hours scenario in the **Acute Ingestion Management Flow-Chart**.

Sustained-Release Paracetamol Preparations

- If more than 10g or 200mg/kg (whichever is less) has been ingested commence NAC.
- Measure serum paracetamol level at 4 or more hours post-ingestion, then again 4 hours later if the first level is below the nomogram line.
- If both levels are below the nomogram line NAC may be discontinued.
- If either level is above the nomogram line NAC should be continued and management followed according to the **Acute Ingestion management Flow Chart**.

Repeated Supratherapeutic Ingestion in Adults and Children

- If the patient has ingested sufficient doses to suggest risk of developing hepatic injury (see Table 1), manage as per the **Repeated Supratherapeutic Ingestion Management Flow-Chart**, below.



Reference List

- Sheen CL, et al. QJM 2002; 95(9):609-619.
- Smilkstein MJ, et al. N Engl J Med 1988; 319:1557-1562.
- Buckley NA, et al. J Toxicol Clin Toxicol 1999; 37:759-767.
- Dart RC, et al. Clin Toxicol 2006; 44(1):1-18.
- Raid D & Hazel W. Emerg Med 2003; 15:486-496.
- Buckley N & Eddleston M. Clin Evid 2005; 1736-1744.
- Little M, et al. Med J Aust 2005; 193(10):535-536.
- Smilkstein MJ, et al. Ann Emerg Med 1991; 20:1058-1063.

These guidelines are not meant to be prescriptive. Each case should be considered individually. Health care professionals should use their clinical judgement to determine the most appropriate course of action. If in any doubt the Poisons Information Centre should be contacted. Prepared in consultation with Frank FS Daly[‡], John S Fountain[§], Lindsay Murray^{**}, Andis Graudins^{††} and Nicholas A Buckley^{‡‡}.

- [‡] Frank FS Daly, Clinical Toxicologist and Emergency Physician Royal Perth Hospital, Perth WA 6009
[§] John S Fountain, National Poisons Centre University of Otago, Dunedin, New Zealand
^{**} Lindsay Murray, Clinical Toxicologist and Emergency Physician Sir Charles Gairdner Hospital, Perth WA 6009
^{††} Andis Graudins, Medical Director, NSW Poisons Information Centre The Childrens Hospital at Westmead, Westmead, 2145, Clinical Toxicologist and Emergency Physician, Prince of Wales Hospital, Randwick, NSW, 2031
^{‡‡} Nicholas A Buckley, A/Prof in Clinical Pharmacology & Toxicology The Australian National University Medical School, Canberra ACT 0200

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GlaxoSmithKline Consumer Healthcare
82 Hughes Avenue, Ermington NSW 2115
Tel: (02) 9684 0888 Fax: (02) 9684 4312

