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Recommendations from the Clinical Toxicology Recommendations Collaborative on the administration of activated charcoal in acute oral overdose

Lotte C. G. Hoegberg[a,b], Sophie Gosselin[c,d,e], Nicholas A. Buckley[f], David M. Wood[g,h], Greene Shepherd[i], James Hanley[j], Nicola Bates[k], Maude St-Onge[c,l], E. Martin Caravati[m], Silas W. Smith[n,o], Shahin Shadnia[p], Gudborg Gudjonsdottir[q], Thanjira Jiranantakan[r,s,t], Jami Johnson[u], Kent R. Olson[v], Régis Bédry[w], Florian Eyer[x], Man Li Tse[y], Wui Ling Chan[z], Andrew Stolbach[aa], Eddy Lang[bb] and Robert S. Hoffman[n]

[a]Department of Clinical Pharmacology, The Danish Poisons Information Centre, Copenhagen University Hospital Bispebjerg, Copenhagen, Denmark; [b]Danish Emergency Management Agency, Division of Chemical Operations, Copenhagen, Denmark; [c]Centre antipoison du Québec, Québec, Canada; [d]Department of Family Medicine and Emergency Medicine, Université de Sherbrooke, Sherbrooke, Québec, Canada; [e]Emergency Medicine Department, Centre Intégré de Santé et de Services sociaux de la Montérégie-Centre, Greenfield Park, Canada; [f]Pharmacology, Faculty of Medicine and Health, University of Sydney, Australia; [g]Clinical Toxicology, Guy's and St Thomas' NHS Foundation Trust and King's Health Partners, London, UK; [h]Faculty of Life Sciences and Medicine, King's College London, London, United Kingdom; [i]UNC Eshelman School of Pharmacy, Chapel Hill, NC, USA; [j]Division of Pediatric Emergency Medicine, Ochsner Clinic Hospital, New Orleans, LA, USA; [k]Veterinary Poisons Information Service, London, United Kingdom; [l]Department of Family and Emergency Medicine, Department of Anesthesiology and Critical Care, Faculty of Medicine, Université Laval, CHU de Québec, Canada; [m]Department of Emergency Medicine, University of Utah School of Medicine, Salt Lake City, UT, USA; [n]Division of Medical Toxicology, Ronald O. Perelman Department of Emergency Medicine, NYU Grossman School of Medicine, New York, NY, USA; [o]NYULH Institute for Innovations in Medical Education, New York, NY, USA; [p]Toxicology Research Center, Excellent Center of Clinical Toxicology, Department of Clinical Toxicology, Loghman Hakim Hospital, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran; [q]Faculty of Pharmaceutical Sciences, University of Iceland, Reykjavik, Icleland; [r]Centre for Alcohol and Other Drugs, NSW Ministry of Health, St Leonards, Australia; [s]Edith Collins Centre, Central Clinical School, Faculty of Medicine and Health, The University of Sydney, Australia; [t]NSW Poisons Information Centre, Sydney Children's Hospitals Network, Westmead, Australia; [u]Medical Affairs, SERB Pharmaceuticals, Department of Pharmacy: Clinical & Administrative Sciences, University of Oklahoma College of Pharmacy, Oklahoma City, OK, USA; [v]California Poison Control System, University of California, San Francisco, CA, USA; [w]UHSI, Hôpital Pellegrin, Bordeaux, France; [x]Division of Clinical Toxicology and Poison Control Centre Munich, Department of Internal Medicine II, TUM School of Medicine, Technical University of Munich, Germany; [y]Hong Kong Poison Information Centre, Hospital Authority, Hong Kong; [z]Emergency Department, Khoo Teck Puat Hospital, Singapore; [aa]School of Medicine, Department of Emergency Medicine, Johns Hopkins University, Baltimore, MD, USA; [bb]Department of Emergency Medicine at the Cumming School of Medicine, University of Calgary, Calgary, Canada

ABSTRACT

Introduction: The Clinical Toxicology Recommendations Collaborative was established by three international clinical toxicology societies and tasked to produce recommendations on the management of poisonings. The Activated Charcoal in Clinical Toxicology Workgroup (the Workgroup) was formed to provide recommendations on the administration of activated charcoal for gastrointestinal decontamination and enhanced elimination in poisoning.

Methods: Based on a systematic review of the literature, 43 poisons or poison categories were selected for appraisal. Voting statements were drafted using a predetermined format. Strength of consensus was measured using the Disagreement Index as defined by the RAND/University of California at Los Angeles Appropriateness Method. A two-round modified Delphi method was used to reach expert consensus.

Results: The Workgroup concluded that there is no role for activated charcoal in poisoning from arsenic, caesium, copper, ethanol, methanol, ethylene glycol, iron, lead, lithium, and metformin. Activated charcoal is appropriate after ingestion of antidysrhythmics (types I and III not discussed specifically), beta-adrenergic antagonists, bupropion, calcium-channel blockers, carbamazepine, cardiac glycosides, chloroquine, cocaine, colchicine, cyanide, dapsone, diphenhydramine, disopyramide, factor Xa inhibitors, ibuprofen, isoniazid, lamotrigine, methotrexate, moclobemide, opioids, organophosphorus insecticides, paracetamol (acetaminophen), paraquat, phenobarbital, phenytoin, quinidine and quinine, salicylates, selective serotonin reuptake inhibitors, sulfonylureas, thallium, theophylline, tricyclic antidepressants, valproic acid, venlafaxine, and warfarin. An additional dose

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CONTACT Sophie Gosselin sgosselinmd@gmail.com Centre antipoison du Québec, Québec, Canada; Université de Sherbrooke Department of Family Medicine and Emergency Medicine, Sherbrooke, Québec, Canada; Emergency Medicine Department, Centre Intégré de Santé et de Services sociaux de la Montérégie-Centre, Greenfield Park, Canada.

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of activated charcoal to complete gastrointestinal decontamination is appropriate after ingestion of carbamazepine, paracetamol, paraquat, phenobarbital, salicylates, thallium, theophylline, valproic acid and verapamil. The maximum time post-ingestion for which activated charcoal administration is recommended differs for each poison and different formulations. According to an individualized risk assessment, activated charcoal is appropriate up to 6 h post-ingestion for many poisons. If ongoing absorption is suspected, which may occur, for example, with pharmacobezoar formation, certain modified-release preparations, or when drug burden exceeds the limits of solubility, then activated charcoal can be administered beyond 6 h post-ingestion for gastrointestinal decontamination. Multiple-dose activated charcoal for enhanced elimination is appropriate in poisoning with carbamazepine, cardiac glycosides, colchicine, dapsone, phenobarbital, phenytoin, thallium and theophylline.

Use of endotracheal intubation to facilitate the administration of activated charcoal in patients who are conscious: Before deciding to perform endotracheal intubation to assist with the administration of activated charcoal, every clinician needs to weigh the potential complications and adverse effects of this procedure against the toxicity expected to be prevented by the administration of activated charcoal. This is a challenging decision, and a local poison centre and/or a bedside toxicology consultation can assist with this decision. Endotracheal intubation is not a benign procedure and is associated with a high rate of various adverse events, such as new haemodynamic instability, severe hypoxaemia, and cardiac arrest, which seem more common in children. In three studies that evaluated the risks of endotracheal intubation in over 2,200 poisoned patients, the rates of hypotension were between 1.5% and 11.8%, desaturation between 3.4% and 7.1%, and cardiac arrest in 0.4%. The risk of aspiration following administration of activated charcoal after endotracheal intubation is reported to be low (1-4%). Therefore, the decision to endotracheally intubate a patient to administer activated charcoal needs to carefully assess the patient's other comorbidities and the expected toxicity of the ingestion, which needs to be clinically significant to outweigh the risk of endotracheal intubation. Endotracheal intubation may also be considered if another treatment, such as haemodialysis or extracorporeal circulation, might be required or for transportation to another institution for ongoing clinical care. In these situations, for which endotracheal intubation has been performed for another indication, the risk-benefit will change in favour of activated charcoal administration. The following good practice statements were adopted to address the use of endotracheal intubation to facilitate the administration of activated charcoal.

1. Endotracheal intubation should not be performed solely for the purpose of administration of activated charcoal in patients not anticipated to develop clinically significant complications of poisoning.
2. In patients in whom endotracheal intubation is clinically indicated (e.g., compromised or unprotected airway, respiratory failure, significantly diminished level of consciousness, refractory seizures, hemodynamic instability), insertion of a nasogastric or orogastric tube is reasonable to facilitate gastrointestinal decontamination with activated charcoal.
3. In patients with a clinically significant risk of developing life-threatening toxicity, endotracheal intubation is reasonable to safely facilitate gastrointestinal decontamination, especially if other treatment options are nonexistent or unavailable.

Use of nasogastric or orogastric tube insertion without endotracheal intubation to facilitate the administration of activated charcoal: The following good practice statement was adopted: Nasogastric or orogastric tube insertion without endotracheal intubation should not be performed solely for the purpose of administration of AC.

Discussion: The decision to use activated charcoal is complex and depends primarily on the nature of the poison(s), the time since ingestion, the severity of the symptoms present at the time of decision or expected based on the dose ingested or patient comorbidities, and the availability of antidotes or other treatments. Although the existing level of evidence is primarily of low or very low quality, clinical decisions are still necessary.

Conclusions: The Workgroup recommends the administration of a single-dose of activated charcoal beyond the traditional 1 h post-ingestion time point in selected poisons and introduces the concept of an additional dose of activated charcoal to prevent further absorption of poisons that may remain in the gastrointestinal tract for prolonged periods of time. Multiple-dose activated charcoal is also recommended to enhance elimination in selected clinical scenarios.

Introduction

More than 25 years have passed since the American Academy of Clinical Toxicology and the European Association of Poison Centres and Clinical Toxicologists first published joint Position Statements in 1997 and 1999 on the administration of single-dose and multiple-dose activated charcoal (AC) in the management of poisoning [1,2]. According to the United States (US) Institute of Medicine Committee on Standards for Developing Trustworthy Clinical Practice Guidelines [3], a formal

process is needed to periodically assess, revise or reaffirm guidelines or recommendations. The single-dose AC Position Statement was updated and published as a revised Position Paper in 2005 [4]. The multiple-dose AC position statement has not been reviewed or updated since its publication. Following the publication of these Position Statements/Papers, new research, new medications, new pharmaceutical preparations, and more data on delayed gastric emptying and pharmacobezoars have been published, much of which challenges previous assumptions regarding the optimal time frame for administration of AC [5]. The Workgroup was commissioned to update the previous AC recommendations using the framework of its evidence- and consensus-based methodology [6]. This article describes the recommendations of the Workgroup on the administration of AC in poisoning.

Methodology

The Clinical Toxicology Recommendations Collaborative Workgroup was established in 2017 as a joint effort by the American Academy of Clinical Toxicology, the European Association of Poison Centres and Clinical Toxicologists, and the Asia Pacific Association of Medical Toxicology. An overview of the general methodology of the Clinical Toxicology Recommendations Collaborative Workgroup was published previously [6]. The Activated Charcoal in Clinical Toxicology Workgroup, a subgroup of the Clinical Toxicology Recommendations Collaborative Workgroup (hereafter referred to as the Workgroup), was tasked to evaluate the literature and provide recommendations on the administration of activated charcoal in poisoning. For this project, the Workgroup sought additional participation from the American College of Medical Toxicology, America's Poison Centers®, and the Canadian Association for Poison Centres and Clinical Toxicology. In its final composition, the Workgroup included 22 members from the following disciplines: medical and clinical toxicology, internal medicine, anesthesiology, emergency medicine, critical care, patient safety, and basic and clinical pharmacology, who were supported by medical librarians, methodologists, and a data manager (Table 1). A subgroup of the Workgroup produced a systematic review of the published literature on the administration of AC in poisoning [5]. The systematic review was registered under Prospero (PROSPERO International prospective register of systematic reviews) on 26 June 2017.

A generic format of voting statements was developed and revised during several in-person and virtual meetings to ensure clarity of language and generalizability to all poisons (Supplement 1). Voting statements focused on dose and time thresholds for the administration of single-dose AC and multiple-dose AC in poisoning, with the explicit understanding that, for the purpose of voting, single-dose AC was indicated to prevent absorption and multiple-dose AC was indicated to enhance elimination. As noted in the systematic review [5], cases reported that more than one dose of activated charcoal was given for decontamination purposes. Thus, the Workgroup decided to create a specific definition for this practice in recognition that an additional dose of activated charcoal might be indicated to prevent absorption following ingestions of modified-release pharmaceuticals or for any dose of a poison that exceeds the binding capacity of a single-dose AC and to avoid confusion with enhanced elimination.

A two-round modified Delphi method was used to reach a consensus on clinical recommendations. Members of the voting panel cast their votes on a nine-point Likert scale (Supplement 2) for each proposed statement for each poison, category of poisons, or situation included. The RAND/UCLA Appropriateness Method was used to quantify disagreement between the votes cast by the panel [6–8]. The voting results

Table 1. Activated charcoal workgroup members listed by their nominating societies.

Chair	Sophie Gosselin (AACT, CAPCCT)			
Co-chairs	Robert S. Hoffman (AACT)		Lotte C.G. Hoegberg (EAPCCT)	
Expert panel	AACT	APAMT	EAPCCT	Others
	E. Martin Caravati	Nick Buckley	Nicola Bates	Andrew Stolbach (ACMT)
	Jami Johnson	Wui-Ling Chan	Régis Bédry	Silas W. Smith (ACMT)
	James Hanley	Man Li Tse	Florian Eyer	Maude St-Onge (CAPCCT)
	Kent Olson	Thanjira Jiranantakan	Gudborg Gudjonsdottir	
	Greene Shepherd	Shahin Shadnia	David Wood	
Non-voting members	Eddy Lang (methodologist)			
	Monique Cormier (research assistant and data manager)			
	Martin Morris (medical librarian)			

AACT = American College of Clinical Toxicology; ACMT = American College of Medical Toxicology; APAMT = Asia Pacific Association of Medical Toxicology; CAPCCT = Canadian Association for Poison Centers and Clinical Toxicology; EAPCCT = European Association of Poison Centres and Clinical Toxicologists.

and disagreement index were combined to define the strength of recommendations as outlined in the Clinical Toxicology Recommendations Collaborative Workgroup methodology [6].

For the purposes of these recommendations, the Workgroup decided that neutral votes, reflecting a balance between the risks and benefits, and votes for which no consensus could be achieved, would be merged into a category called "individual risk assessment needed". The Workgroup discussions on this category reflected that a clinician faced with a potential poison ingestion would need guidance on the best course of action, even in the absence of published data. Thus, the need for an individualized risk analysis that considers the type and amount of poison ingested, possible co-ingestants, the time elapsed since the ingestion, the expected toxicity, as well as patient comorbidities and contraindications to the administration of AC, all of which are included in the evidence to decision framework (Appendix 1). Updated Tables were also constructed and provided to the members, as well as all full-text articles for each of the scientific literature (Appendices 2 to 8).

All recommendations are followed by the strength of recommendations and the grading of the level of evidence (A to D), in accordance with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (Table 2) [9,10]. During the voting on the poison-related questions, the Workgroup was encouraged to provide free-text comments on other clinically relevant questions for which no specific evidence was uncovered in the systematic review that met the criteria for good practice statements [11]. These free-text comments were reviewed by four members (SS, SWS, DW, SG) of the Workgroup, categorized, and aggregated into broad themes to construct good practice statements [12] that were subsequently approved unanimously by all workgroup members. All votes were deployed by a secure account on the platform SimpleSurvey (OutSideSoft Solutions Inc., Canada). Results were reviewed for clinical consistency, and all final recommendations were approved unanimously, regardless of original votes. A list of sponsoring and participating societies is provided in Table 3.

Table 2. Level of evidence to inform on the strength of recommendations.

Level of evidence (GRADE system)
Grade A: High level of evidence (The true effect lies close to our estimate of the effect).
Grade B: Moderate level of evidence (The true effect is likely to be close to our estimate of the effect, but there is a possibility that it is substantially different).
Grade C: Low level of evidence (The true effect may be substantially different from our estimate of the effect).
Grade D: Very low level of evidence (Our estimate of the effect is just a guess, and it is very likely that the true effect is substantially different from our estimate of the effect).
Strength of recommendation (consensus-based)
Level 1: Strong recommendation, hereafter "recommend" (The course of action is considered appropriate by the large majority of experts with no major dissension. The panel is confident that the desirable effects of adherence to the recommendation outweigh the undesirable effects.)
Level 2: Weak conditional recommendation, hereafter "suggest" (The course of action is considered appropriate by the majority of experts but some degree of dissension exists among the panel. The desirable effects of adherence to the recommendation probably outweigh the undesirable effects.)
Neutral position: The course of action is neither preferred nor rejected by the majority of experts; either due to a balance in the desirable and undesirable effects of adherence to the recommendation or due to major uncertainties to its evaluation.)
No recommendation: The group of experts reached no agreement

From: Wilks MF, Hoyte C, Cumpston KL, et al. The Clinical Toxicology Recommendations Collaborative: purpose, organization, and methodology. Clin Toxicol. 2024;62:76–81.

Results

A first vote occurred in August 2019, and the results were discussed in a meeting in the same month. After minor adjustments to clarify the wording of some voting statements, a second vote took place in January 2021. The Workgroup formally discussed the results of these votes and used the evidence to reach a decision on the final recommendations by consensus. The search described in the systematic review was repeated on 22 April 2024 and 10 June 2025, and a single article was identified [13] that required a repeat discussion and voting on metformin. The results are presented in two major sections:

i. General considerations that apply to all recommendations; and
ii. Poison-specific recommendations.

General considerations - good practice statements

Good practice statements are defined as follows: "Good practice statements typically represent situations in which a large body of indirect evidence, made up of linked evidence including several indirect comparisons, strongly supports the net benefit of the recommended action" [11].

Table 3. Sponsoring and participating societies.

Society name	
American Academy of Clinical Toxicology	Sponsoring
Asia Pacific Association of Medical Toxicology	Sponsoring
European Association of Poison Centres and Clinical Toxicologists	Sponsoring
American College of Medical Toxicology	Participating
Canadian Association for Poison Centers and Clinical Toxicology	Participating

Use of endotracheal intubation to facilitate the administration of activated charcoal in patients who are conscious

Before deciding to perform endotracheal intubation to assist with the administration of AC, every clinician needs to weigh the potential complications and adverse effects of this procedure against the toxicity expected to be prevented by the administration of AC. This is a challenging decision, and a local poison centre and/or a bedside toxicology consultation can assist with this decision. Endotracheal intubation is not a benign procedure and is associated with a high rate of various adverse events, such as new haemodynamic instability, severe hypoxaemia, and cardiac arrest [14–16], which seem more common in children [14,17–19]. In three studies [20–22] that evaluated the risks of endotracheal intubation in over 2,200 poisoned patients, the rates of hypotension were between 1.5% and 11.8% [20–22], desaturation between 3.4% and 7.1% [20–22], and cardiac arrest only occurred in 0.4% [20–22]. The risk of aspiration following administration of AC after endotracheal intubation is reported to be low (1-4%) [23]. Therefore, the decision to endotracheally intubate a patient to administer AC needs to carefully assess the patient's other comorbidities, the expected toxicity of the ingestion, which needs to be clinically significant to outweigh the risk of endotracheal intubation [24,25]. Endotracheal intubation may also be considered if another treatment, such as hemodialysis or extracorporeal circulation, might be required or for transportation to another institution for ongoing clinical care. In these situations, for which endotracheal intubation has been performed for another indication, the risk-benefit will change in favour of AC administration. Patients at risk of toxic seizures need to have preventive measures in place, such as sedation and electroencephalogram monitoring [26]. A detailed explanation of these considerations falls outside the scope of this work as they pertain to standard practices in emergency medicine and critical care [27].

The following good practice statements were adopted to address the use of endotracheal intubation to facilitate the administration of AC.

- Endotracheal intubation should not be performed solely for the purpose of administration of AC in patients not anticipated to develop clinically significant complications of poisoning.
- In patients in whom endotracheal intubation is clinically indicated (e.g., compromised or unprotected airway, respiratory failure, significantly diminished level of consciousness, refractory seizures, haemodynamic instability), insertion of a nasogastric or orogastric tube is reasonable to facilitate gastrointestinal decontamination with AC.
- In patients with a clinically significant risk of developing life-threatening toxicity after a large ingestion, endotracheal intubation to safely facilitate gastrointestinal decontamination is reasonable, especially if other treatment options are nonexistent or unavailable.

Use of nasogastric or orogastric tube insertion without endotracheal intubation to facilitate the administration of activated charcoal

The following good practice statement concerns the use of nasogastric or orogastric tube insertion without endotracheal intubation to facilitate the administration of AC.

- Nasogastric or orogastric tube insertion without endotracheal intubation should not be performed solely for the purpose of administration of AC.

The dose of activated charcoal and the interval for activated charcoal dosing with additional-dose activated charcoal, and multiple-dose activated charcoal

The following good practice statements address the dose of AC and the interval for AC dosing with additional-dose AC and multiple-dose AC based on the data analyzed from the prior systematic review [5].

- The dose of AC for single-dose AC and additional-dose AC is 50 g in adults or 1 g/kg (up to the adult dose) in children.
- The dose of AC for additional-dose AC can be administered to complete decontamination at any point in time following single-dose AC when there is evidence or suspicion of ongoing absorption.
- The multiple-dose AC regimen begins with the same AC dose as for single-dose AC and repeats with that dose every 4 h or a half-dose every 2 h.

We could not find specific evidence regarding the interval for AC dosing for multiple-dose AC. However, most AC formulations are formulated as 50 g in 250 mL. Drawing on experience with pediatric patients and gastroenteritis, we concluded that if multiple-dose AC is administered orally, the tolerability of two doses of 250 mL taken apart in time would be better tolerated than a larger dose of 500 mL.

Contraindications

Because of a lack of poison-specific data regarding contraindications for the administration of AC, the Workgroup voted on and agreed to the following statements describing when the administration of AC is not desirable:

- We make a strong recommendation against the administration of AC in patients with absent airway protective reflexes who are not endotracheally intubated (1D).
- We make a strong recommendation against the administration of AC in patients when their airway protective reflexes are at risk or expected to become absent (1D).
- We make a strong recommendation against the administration of AC in patients who are at risk of gastrointestinal perforation (1D).
- We make a weak recommendation against the administration of AC when administration may increase the risk of aspiration (2D).
- We make a weak recommendation against the administration of AC in patients with absent peristalsis (2D).
- We make a weak recommendation against the administration of AC in patients who are likely to require upper gastrointestinal endoscopy (2D).
- The administration of AC in patients with decreased peristalsis requires an individualized risk assessment.
- The administration of AC in patients for whom there is an effective oral antidote requires an individualized risk assessment.

Special populations

In most publications included in the systematic review, the poison-specific evidence for children, pregnant patients, and the elderly was sparse and of very low quality. The Workgroup identified this as an area for future research and reached consensus on the following statements regarding each special population. The treatment of morbidly obese patients and those who have had bariatric surgery was also identified as an area in need of future research and, therefore, requires an individualized risk assessment. Similarly, patients of all ages on maintenance medications that would otherwise be adsorbed by AC, and which cannot be delivered by an alternative route (e.g., intravenous, intramuscular, sublingual), require an individualized risk assessment as to whether AC administration is appropriate.

- Children: The indications for, and the contraindications against, the administration of single-dose AC, additional-dose AC, and multiple-dose AC in adults are generally applicable to children (2D).
- Pregnant patients: The indications for, and the contraindications against, the administration of single-dose AC, additional-dose AC, and multiple-dose AC in adults are applicable to pregnant patients (2D).
- The elderly: The indications for, and the contraindications against, the administration of single-dose AC, additional-dose AC, and multiple-dose AC in adults are applicable to the elderly (2D).

Evidence to decision rationale

Children. The treatment of children presents an added challenge regarding the decision to administer AC, as it encompasses a wide range of ages and potential age-related variations in toxicokinetics and toxicodynamics that include differences in gastric pH and gastric emptying [28,29]. In young children, the ingestion is often minimal as a result of exploratory tasting [30] or the undesirable taste of the potentially toxic substance. Although most ingestions involve cosmetics and household products, which present a low risk of severe outcome [31–33], some medications, even when ingested in small quantities, are potentially lethal [34–36]. As caretakers are typically unable to accurately quantify the amount ingested, situations involving high-risk poisons [37], particularly in the absence of available antidotes [38], often warrant consideration of AC administration. In older children and adolescents, self-harm is frequently the cause of poisoning, resulting in a potential combination of a large poison dose and or ingestion of multiple poisons [39–42]. In these patients, when appropriate antidotes are not available, stronger consideration for the administration of AC would be warranted. The patient with special healthcare needs (e.g., epilepsy, developmental delay, cardiac disorders impacting haemodynamic stability) requiring maintenance medication that could also be adsorbed by AC or those with an inability to cooperate to drink AC presents additional challenges and calls for an individualized risk assessment.

Pregnant patients. The presence of a fetus evokes additional questions when a clinician is faced with a pregnant patient with an overdose. Although poisoning represents approximately 2% of pregnancy-associated deaths [43], the rates of poisoning mortality

in pregnancy are increasing [44,45]. Most self-poisonings occur during the first trimester, perhaps due to unwanted pregnancies [46], such that the best way to ensure fetal survival is to focus on maternal outcomes. Clinicians, however, must weigh the risk of the ingestion to the fetus versus the possible risk of a treatment to the fetus and the risk of not treating the mother. Given the ethical considerations in this group of subjects, none of the volunteer human studies in the systematic review [5] involved pregnant subjects.

Furthermore, few, if any, publications specifically address overdose in pregnancy and its associated physiological changes [47–49]. While the Workgroup recognized the vulnerability of the maternal-fetal pair, it is very unlikely that AC poses a direct risk to the fetus, as it is both inert and not systemically absorbed. Because of the paucity of data, we decided that, pending further research, recommending the same criteria for AC administration in pregnant patients as in any other adult patient was appropriate. Additionally, safety concerns over the risks of emesis and aspiration of AC may vary throughout pregnancy. This was identified as an area for future study as the extent of transplacental distribution, which varies with individual poisons, may become a significant factor in future recommendations [50–52].

The elderly. With an ageing population, three events are increasingly likely: a decline in organ function, increasingly complex pharmacotherapy, and cognitive impairment. These factors predispose the elderly to severe toxicity from drug interactions and unintentional overdose [53,54]. Although many hospitalizations for adverse drug events, including overdose in the elderly, are due to errors in prescribing, administration, or monitoring, underreported rates of depression, social isolation, and intentional self-harm by overdose are also well described. Attempted suicide in the elderly carries an increased lethality due to the higher burden of medical illness and access to large quantities of prescription and non-prescription medications [55–58]. Many of the same concerns expressed above with regard to children, such as the accuracy of history and willingness to take AC, apply to the elderly. Not a single human volunteer study in the systematic review [5] included elderly subjects. Furthermore, few if any publications [59,60] specifically address the management of overdose in the elderly. Faced with a paucity of data, and while the vulnerability of many elderly patients was recognized, the Workgroup recommends that AC administration in elderly patients should use the same criteria as in any other patient. This was identified as an additional area for future study.

Poison-specific recommendations

This section includes the AC recommendations to the 43 poisons or poison categories selected for appraisal based on the systematic review of the literature on the administration of AC for gastrointestinal decontamination following acute oral overdose or toxic substance ingestion [5]. The summary of poison-specific recommendations for single-dose AC, additional-dose AC and multiple-dose AC is presented in Table 4.

Single-dose activated charcoal recommendations

The dose threshold for AC administration for each poison, when known, is listed, as well as the different formulations of poisons when applicable. The latest time to administer AC, if recommended, in reference to the time of ingestion (time zero), is highlighted in colour. Dark green represents a strong recommendation; lighter green represents a weak recommendation. Orange represents a weak recommendation against; red represents a strong recommendation against. Grey represents a need for an individualized risk assessment with the assistance of a clinical/medical toxicologist or a poison centre. The GRADE of evidence is listed at the end of each column.

The Tables containing the summary of findings of these poisons for single-dose AC, additional-dose AC, and multiple-dose AC are available in the Appendices. The evidence-to-decision rationale (detailed explanation) for each poison or category of poisons is also available in the Appendices.

Additional-dose activated charcoal

When a single-dose of AC may not provide sufficient gastrointestinal decontamination, an additional dose of AC is reasonable in certain clinical scenarios. The dose threshold at which additional-dose AC is recommended is listed in the appropriate column for each poison (Table 4).

Multiple-dose activated charcoal

The last column for each poison lists the recommendation for or against the administration of multiple-dose AC for enhanced elimination, as well as the poison suspected ingested dose threshold.

Discussion

Gastrointestinal decontamination with AC has always been an area of controversy. Following the first iterations of the joint American Academy of Clinical Toxicology and European Association of Poison Centres and Clinical Toxicologists position papers [1,2,4], which stated that there was no evidence that AC

Table 4. Summary of recommendations on the use of activated charcoal in poisoning for the 43 selected poisons or poison groups.

Strong recommendation for	Weak recommendation for	Individualized risk assessment required (no data OR balance between risks and benefits)	Weak recommendation against	Strong recommendation against

Poison	Formulation	Prevention of absorption (decontamination)											Enhanced elimination	
		Single-dose activated charcoal, time post ingestion (h)								Evidence GRADE	Additional-dose activated charcoal	Evidence GRADE	Multiple-dose activated charcoal	Evidence GRADE
		0.5	1	2	3	4	5	6	>6					
Antidysrhythmics (class I and III except for disopyramide, digoxin, phenytoin and quinidine)	IR MR	5 TD								D		D		D
Benzodiazepines					any dose					D	any dose	D	any dose	D
Beta adrenergic antagonists (atenolol)	IR MR	6 mg/kg								D		D		D
(nadolol)	IR MR	5 mg/kg								D		D		D
(propranolol)	IR MR	5 mg/kg								D		D		D
(sotalol)	IR MR	6 mg/kg								D		D		D
Bupropion	IR MR	20 mg/kg								D		D		D
Calcium channel blockers (amlodipine)	IR	5 TD								D		D		D
(diltiazem)	IR MR	3 TD								D		D		D
(verapamil)	IR MR	3 TD								D	5 TD	D		D
Carbamazepine	IR MR	25 mg/kg								C	>50 mg/kg >40 mg/kg	D	>40 mg/kg	C
Cardiac glycosides (digoxin)		75 µg/kg								C		D	100 µg/kg	C
(oleander)		4 seeds								C		D	≥6 seeds	B
Chloroquine		35 mg/kg								D		D		D
Cocaine		5 mg/kg								D		D		D
Colchicine		0.4 mg/kg								D		D	0.7 mg/kg	D
Cyanide		2 mg/kg								D	≤4 mg/kg	D		D
Dapsone		6 mg/kg								D		D	10 mg/kg	D
Diphenhydramine	IR MR	15 mg/kg								D		D		D
Disopyramide	IR MR	1 g	1 g							D		D		D
Ethanol										C		D		D
Factor Xa Inhibitors (apixaban)		40 mg								C		D		D
(rivaroxaban)		80 mg												
Ibuprofen		250 mg/kg								D		D		D
Iron										C		D		D
Isoniazid		40 mg/kg								D		D		D
Lamotrigine	IR MR	30 mg/kg								D		D		D
Lithium	IR MR									D		D		D
Metals (lead, arsenic, copper, cesium, mercury)										D		D		D
Metformin	IR MR									D		D		D
Methotrexate		10 mg/kg								D		D		D
Moclobemide	IR MR	50 mg/kg								D		D		D
Opioids	IR MR	5 TD								D		D		D
Organophosphate insecticides		any dose								D		D		D
Paracetamol	IR MR	200 mg/kg								B	350 mg/kg 300 mg/kg	D		B
Paraquat		5 mg/kg								D	40 mg/kg	D		D
Phenobarbital		20 mg/kg								C	50 mg/kg	D	50 mg/kg	C
Phenytoin	IR MR	40 mg/kg								D		D		D
Quinidine	IR MR	750 mg								D		D		D
Quinine	IR MR	20 mg/kg								D		D		D
Salicylates	IR MR	200 mg/kg								C	500 mg/kg 350 mg/kg	D		C
Selective serotonin reuptake inhibitors	IR MR	15 TD								C	<20 TD	D		D
Sulfonylureas		5 TD								D	<9 TD	D		D
Thallium		10 mg/kg								D	50 mg/kg	D	10 mg/kg	D
Theophylline and aminophylline	IR MR	20 mg/kg								C	40 mg/kg 50 mg/kg	D	50 mg/kg 50 mg/kg	C
Toxic alcohols (methanol, ethylene glycol)										D		D		D
Tricyclic antidepressants		10 mg/kg								D		D		D
Valproic acid	IR MR	200 mg/kg								D	400 mg/kg 400 mg/kg	D		D
Venlafaxine	IR MR	25 mg/kg								D		D		D
Warfarin		0.7 mg/kg								D	any dose	D	any dose	D

Legend: IR, immediate release; MR, modified release; MDD, maximal daily doses; TD; maximal therapeutic doses; Doses listed are the lowest intervention dose. For additional-dose activated charcoal and mulptle-dose activated charcoal see text for additional recommentations

administration beyond 1 h improved outcomes, reports of potential benefit of AC beyond 1 h emerged [61–68].

Aggregate reports and publications, such as the National Poison Data System®, are limited to US data, do not give details of the amount ingested for a particular exposure and fail to report outcomes of interest such as morbidity, length of endotracheal intubation, aspiration and intensive care or hospital stays. Nonetheless, such reports are useful to identify trends and suggest in-depth studies. As with all medical therapies, the risks and benefits of administration of AC must be appropriately evaluated by the treating clinician in the context of existing evidence.

Activated charcoal is not indicated in the routine management of many patients who ingest poisons for several reasons. The poison may not be ingested in a quantity expected to cause toxicity. The poison may not be adsorbed to AC. Thus, many patients are unlikely to benefit from AC, including those who ingest low-risk poisons or minimal amounts of higher-risk poisons. In addition, many patients present after a delay, when most of the ingested poison is expected to have been absorbed, such that administration of AC is unlikely to have a role in decontamination. Finally, despite the presence of an indication for AC, there may be a contraindication to its administration. In studies of single-dose AC, large numbers of patients had similar low rates of adverse outcomes and complications, and the administration of AC did not provide a significant clinical benefit [69–73]. For multiple-dose AC, there is one study that demonstrates a survival advantage in yellow oleander poisoning [74].

For carefully selected groups of patients with known ingestions at relatively known times and with no contraindications to AC, the potential benefits of AC are likely to be maximized (see Table 4 for poisons, doses and delay post-ingestion), while steps are taken to minimize potential risks of AC administration (for example, vomiting and aspiration). For individuals with an ingestion of an unknown or undisclosed poison and/or an unclear time since ingestion, clinicians are advised to use their best clinical judgment on whether the administration of AC is likely to be beneficial, supported by the "General approach to activated charcoal administration in poisoning" algorithm developed by the Workgroup (Figure 1). When the clinician is unsure, further advice on whether the administration of AC is appropriate can be obtained from a clinical/medical toxicologist or a poison centre. The administration of multiple-dose AC to enhance the elimination of a poison in the post-absorptive phase is further limited to drugs with toxicokinetics that involve sufficient enterohepatic or enteroenteric circulation. In the evidence to decision rationale (Appendix 1), the Workgroup balanced the published evidence with their knowledge of the real-world practice of toxicology, emergency, and critical care medicine, including the risk of untreated overdose, costs of prolonged emergency or critical unit stays, resource constraints such as geographical and rural settings and the efficacy, costs and availability of antidotes or other treatments.

The risks of AC administration were included in the evidence-to-decision framework. The systematic review [5] identified pulmonary aspiration of gastric contents containing AC as an infrequent but serious complication often associated with either inadequate airway protection or the placement of a nasogastric tube. It is worth noting, however, that the overall published incidence of aspiration pneumonia after poisoning is low, and in one study [75] risk factors such as seizure (odds ratio [OR] 8.05), Glasgow Coma Scale less than 15 (OR 5.47), and spontaneous emesis (OR 4.07) were clinically significant risk factors but administration of AC was not (OR 1.03; 95% CI: 0.63–1.7). The systematic review also identified 10 deaths from pulmonary aspiration following administration of activated charcoal. The true incidence of adverse events following AC administration is unknown, as published data are scarce, selection bias towards publication of serious events and the denominator of all patients receiving AC will remain largely unknown. Confounding factors, such as adverse events from the ingestion itself, require clinicians to perform an individualized risk assessment of expected benefits versus the risk of adverse events in all patients. That being said, experimental evidence [76] suggests that pulmonary administration of AC increases lung permeability.

Additionally, several reports [77–79] demonstrate rapid deterioration and demise, especially when AC was directly instilled into the airway. It is also worth noting that the texture of AC is generally considered to be somewhat unpleasant [80,81], and while many attempts have been made to improve patient acceptance (for example [82–85]), dedicated staff resources may be required to obtain, mix, and coach patients to swallow the AC.

Specific acknowledgement of the risks associated with AC administration can be found in the general good practice statements, contraindications section, and Figure 1, which collectively preclude the administration of AC when there is a concern for an unprotected airway. When considering the time of administration, the Workgroup relied on multiple human volunteer and clinical studies that demonstrated the ability of AC to significantly reduce absorption several hours post-ingestion [5,68].

Similarly, the common prescription of modified-release pharmaceutical preparations, the occurrence of massive

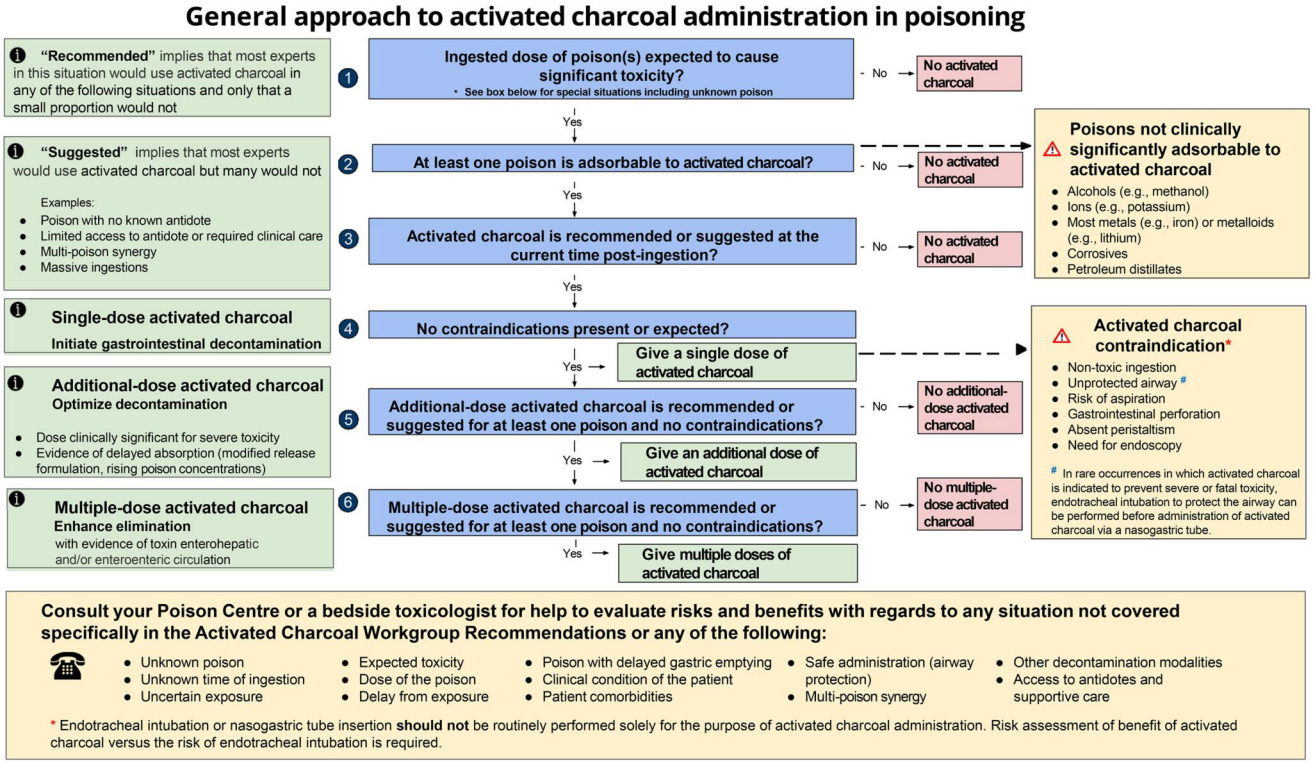

Figure 1. General approach to activated charcoal administration in poisoning.

overdoses or poisonings, and pharmacobezoars, add to the data demonstrating prolonged dissolution time leading to prolonged absorption time or delayed gastric emptying in actual overdosed or poisoned patients [86–89]. Gastric emptying half-time has been studied in drug overdose patients who served as their own controls during the follow-up period [86]. A significantly prolonged gastric emptying time was shown in overdose patients following the ingestion of tricyclic antidepressants, paracetamol, opioid-paracetamol co-formulations, and carbamazepine. Gastroparesis was expected and confirmed in overdoses with antimuscarinic or opioid drugs. Many patients had unexpected severe gastroparesis. The observed prolongation in gastric emptying time was 2.2–3.3 times longer after an overdose compared to the same individuals following recovery. For poisons not known to inhibit gastric motility, a hypothesis was that the prolonged emptying time may have been a direct effect of the large volume ingested, causing hypomotility, as there was no evidence that AC influenced the gastric emptying time in these study patients [86]. The residual content of the ingested poison was evaluated in 167 patients admitted to the emergency department following an oral overdose of a solid pharmaceutical preparation [88]. The patients were classified into three groups based on the appearance of the gastric contents as determined by upper gastrointestinal endoscopy, regardless of the specific type of drug ingested. The three phases were tablet/food phase, soluble/fluid phase, and reticular/empty phase. The study concluded that the gastric content in 44% of the patients was tablet/food or soluble/fluid phase from 1 h up to 4 h post-ingestion. Between 4 h and 12 h post-ingestion, 14% of patients had tablet/food or soluble/fluid phase gastric contents [88]. It is assumed that the tablet/food phase and the soluble/fluid phase contain remnants from the pharmaceutical preparation ingested, including the toxic compound. While these studies do not address toxicokinetics or outcome, they make it clear that ingested poisons may be present and available for adsorption to AC long after the previously recommended 1 h limitation.

The administration of an additional-dose of AC was introduced by this Workgroup as a new AC dosing concept with the main purpose of assisting in the reduction of absorption of a poison that is likely to be present in the gastrointestinal tract for a prolonged time based on either the dose, preparation, or the toxicodynamics despite the administration of a first AC dose [86–89]. The Workgroup members who observed this practice in their own clinical experience and reviewed it in publications believe this procedure of giving more than one dose of AC needed its own definition to better distinguish it from multiple-dose AC, which has a different therapeutic goal and endpoint (decontamination versus enhanced elimination).

With all these deliberations taken into consideration, the main change from the previous position

statements is the extension of the time for AC administration beyond the 1 h limit for selected poisons and the option for additional-dose AC if needed, as well as guidance on the safe administration of activated charcoal with regard to airway protection and risk of aspiration. The Workgroup consensus is based on evidence from the systematic review and new evidence on altered gastric emptying in oral poisoning, as well as clinical judgment to provide advice to clinicians on reasonable actions to take in the absence of strong evidence. Whilst these recommendations are intended to help clinicians in formulating management plans, they are not prescriptive because of the multiplicity of overdose scenarios, co-ingestants and patients' individual comorbidities which warrant an individual risk assessment of expected benefits and potential risks or adverse effects. We acknowledge that in some cases, the level of evidence for activated charcoal is weak. However, in spite of the lack of high-quality evidence, consensus recommendations can provide guidance for clinical decision-making. As for any recommendations or guidelines, the clinician should always use their professional discretion whether to follow our advice or not based on patient-specific factors.

Limitations

As with all evidence-based recommendations, the strength of the effort is limited by the quality of the evidence. While the Workgroup recognizes that almost all of the recommendations are based on low-quality evidence, we systematically collected and analyzed that evidence, including data from benchwork science, investigations in animals, human volunteers, patients who took overdoses or were poisoned, population pharmacokinetics and probabilistic analyses. Caution was applied by systematically downgrading the level of evidence from volunteer studies with subtoxic doses or from studies in which the administration of AC was immediately after ingestion, a scenario not often encountered in clinical practice.

Additionally, as the strength of recommendations was determined by consensus, it is possible that a different panel of experts would reach different conclusions. While we appreciate that other clinicians may disagree with our recommendations, it must be acknowledged that the members of the Workgroup were specifically selected for this task by the respective Boards of the American Academy of Clinical Toxicology, European Association of Poisons Centres and Clinical Toxicologists, Asia Pacific Association of Medical Toxicology, American College of Medical Toxicology, America's Poison Centers®, and the Canadian Association for Poison Centres and Clinical Toxicology to provide an international perspective on the administration of AC in poisoning. Included in the Workgroup were members with expertise in research with activated charcoal, broad-based toxicology experience, previous experience with systematic reviews, evidence-based recommendations, position statements, as well as journal and textbook editing.

The method of consensus was mathematically based, reproducible and designed not to force consensus when it did not exist, while also providing a basis for open and frank discussions that allowed dissenting opinions to be voiced and considered. The process was overseen by a GRADE-trained methodologist (EL). Our recommendations cannot be based on every possible scenario with every possible poison, including mixed ingestions or cases in which the ingestion is totally unknown. Instead, we provide a framework to help clinicians manage these clinical circumstances and provide structure to deal with common contraindications. We recognize that while the dose thresholds we provide are based on the best available literature, for many patients reported doses are unavailable or unreliable. We encourage clinicians to obtain all available patient history, use their clinical judgement, and seek expert consultation with a poison centre or clinical/medical toxicologist when they need assistance.

Gastrointestinal decontamination with AC is uncommonly performed in addition to other modalities such as orogastric lavage and whole bowel irrigation. It was beyond the mandate of this work to assess the relative risks and benefits of these other modalities when used in combination with or instead of AC. This comparative assessment is needed, and hopefully, this work will serve as a stimulus for the next steps, as recommendations need to evolve as new knowledge is being published.

Areas for future research

Current knowledge gaps lead to the following suggested research opportunities.

1. Identify a new cohort of potentially ill patients with confirmed single-substance ingestions for whom a clinical study of the utility of AC in a poison of interest (such as bupropion) could be performed.
2. Develop a strategy to systematically identify the role of AC in the management of patients who overdose on new pharmaceuticals, novel formulations of existing pharmaceuticals, or emerging drugs of abuse.

3. Optimize toxicokinetic and toxicodynamic modelling to predict the utility of AC from data collected in overdose patients.
4. Develop methods to study special populations such as the elderly, pediatric, or pregnant patients, and those who have had bariatric surgery.
5. Design and implement studies to specifically address the utility of additional-dose AC in clinically relevant scenarios, as there is no direct evidence to support the efficacy of additional-dose AC or the optimal dosing of AC.
6. Study the toxicokinetics of absorption in models of delayed gastric emptying or modified-release preparations, along with the ability of delayed AC to modify those parameters.
7. As poisoned patients usually receive a multitude of concomitant treatment modalities, serial quantitative drug concentrations (ideally before and after AC administration) should be performed as an ideal outcome measure in any study planning to evaluate the efficacy of AC in poisoning and to identify which clinical effects are truly attributable to AC.

Conclusions

The Clinical Toxicology Recommendations Collaborative Workgroup recommends the administration of a single-dose of AC beyond the traditional 1 h post-ingestion timeframe in selected poisons. We also introduce the concept of additional-dose AC to prevent absorption of poisons that may remain in the gastrointestinal tract for prolonged periods of time. Multiple-dose AC is also recommended to enhance elimination in selected clinical scenarios.

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ORCID

Lotte C. G. Hoegberg http://orcid.org/0000-0003-0252-2470
Sophie Gosselin http://orcid.org/0000-0002-0694-5588
Nicholas A. Buckley http://orcid.org/0000-0002-6326-4711
E. Martin Caravati http://orcid.org/0000-0002-8918-0903
Florian Eyer http://orcid.org/0000-0002-4753-2747
Robert S. Hoffman http://orcid.org/0000-0002-0091-9573

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Appendix 1. Evidence to decision framework for each poison

Antidysrhythmics (excluding calcium-channel blockers, beta-adrenergic antagonists, digoxin, disopyramide, phenytoin, and quinidine)

Evidence to decision rationale

The term "antidysrhythmic" is broad. Calcium-channel blockers, beta-adrenergic antagonists, digoxin, disopyramide, phenytoin, and quinidine are specifically discussed elsewhere in these recommendations. The *in vitro* evidence for the remaining poisons in this group is

very limited. Mexiletine is well adsorbed to activated charcoal (AC) with a maximum adsorption capacity as high as 328 mg/g AC [90]. Adsorption is also demonstrated for lidocaine and procaine [91]. Human volunteers were provided oral amiodarone, followed immediately by either water or AC, with a third group taking AC with a 1.5 h delay post-ingestion. Immediate AC reduced the area under the plasma concentration-time curve by 98% ($P<0.001$), whereas delayed AC reduced the area under the plasma concentration-time curve by 50% ($P<0.05$) [92]. Volunteer study subjects ingested mexiletine, followed by AC at either 5 or 60 min. When AC was given at 5 min post-ingestion, the area under the plasma concentration-time curve for mexiletine was reduced by 96% ($P<0.05$), but there was no significant effect demonstrated with the 60 min delay to AC administration [93]. Although there is limited evidence for the class I and class III antidysrhythmics not discussed elsewhere, the Workgroup recommended single-dose AC in larger ingestions of these drugs given the potential life-threatening, cardiovascular, and other toxicity that can occur, the prolonged hospital stay required (often in critical care beds and related costs), may be obviated by judicious use, low rate of adverse events and low cost of AC for decontamination.

- For both immediate- and modified-release antidysrhythmics at a dose threshold of five therapeutic doses or more, we recommend single-dose AC for up to 1 h post-ingestion (1, D).
- For immediate-release antidysrhythmics at a dose threshold of five therapeutic doses or more, we suggest single-dose AC for up to 2 h post-ingestion (1, D).
- For modified-release antidysrhythmics at a dose threshold of five therapeutic doses or more, we recommend single-dose AC for up to 6 h post-ingestion (1, D).
- For all other time points and doses, an individualized risk assessment is required for single-dose AC administration.
- For doses, an individualized risk assessment is required for both additional-dose AC and multiple-dose AC administration.

Benzodiazepines

Evidence to decision rationale

Benzodiazepines are generally considered to have a relatively low toxicity when ingested as a single poison in overdose. The early onset of sedation also makes oral administration of AC often unsafe, unless airway protection is performed. In patients with exceedingly large overdoses, individual risk assessment is warranted. If these larger doses are associated with a more significant reduction in level of consciousness such that endotracheal intubation for airway protection is required, then administration of single-dose AC following nasogastric tube insertion would be appropriate based on our best practice recommendations. Although *in vitro* data on the adsorption to AC are not available for most specific substances in this category, some data exist. Lorazepam is rapidly adsorbed to AC *in vitro* [94]. Diazepam is exceedingly well adsorbed to high surface area AC with a maximum adsorptive capacity of 890 mg/g AC [95]. When AC was given immediately following diazepam in rats, the absorption was reduced by 98% ($P<0.01$) [96]. When healthy volunteers were given AC 30 min after ingestion of diazepam, the area under the plasma concentration-time curve was reduced by 27% compared to water ($P<0.05$) [97]. In a similar study by the same authors [98], the area under the plasma concentration-time curve for temazepam was reduced by 95% compared to water ($P<0.01$) when AC was given 5 min after the ingestion. However, when the time to AC extended to 30 min post-ingestion, the area under the plasma concentration-time curve for temazepam was only reduced by 45% compared to water ($P<0.05$) [99]. In one case report in which multiple-dose AC (40 g every 6 h for 6 doses) was given to a patient with an iatrogenic intravenous diazepam overdose, the elimination half-life was reduced from 195 h to 18 h [100]. As the toxicity expected from pure benzodiazepine overdoses is limited to sedation and related loss of airway protection, the balance of risks and benefits does not favour administration of AC in most benzodiazepine overdoses.

- For ingestions of benzodiazepines, an individualized risk assessment is required for single-dose AC administration if patients present within 30 min.
- For ingestions of benzodiazepines, we suggest against single-dose AC for ingestions that occurred between 30 min and 2 h (2, D).
- For ingestions of benzodiazepines, we recommend against single-dose AC for ingestions beyond 2 h (1, D).
- For ingestions of benzodiazepines, we recommend against additional-dose AC (1, D).
- For ingestions of benzodiazepines, we recommend against multiple-dose AC (1, D).

Beta-adrenergic antagonists

Evidence to decision rationale

Beta-adrenergic antagonists have a high toxicity potential when ingested as a single poison in overdose. However, in symptomatic patients, untreated hemodynamic instability can affect the level of consciousness and make the administration of AC unsafe. In addition, more lipid-soluble beta-adrenergic antagonists (e.g., propranolol) have greater central nervous system toxicity, which can further reduce the level of consciousness despite normal hemodynamics. Data for the vast majority of beta-adrenergic antagonists are lacking. The Workgroup decided to consider published information on specific beta-adrenergic antagonists and allow clinicians to make analogies to other members of the substance class based on an individualized risk assessment. In a controlled study of healthy volunteers, the administration of AC 15 min after ingestion of atenolol or propranolol showed a decreased effect of beta-adrenergic antagonists post-exercise [101]. In a pharmacokinetic study performed with sotalol, the administration of single-dose AC 5 min after ingestion significantly decreased the area under the plasma concentration-time curve and maximal plasma or serum concentration, but multiple-dose AC had no additional benefit [102]. Another pharmacokinetic study that evaluated multiple-dose AC in volunteers who ingested nadolol showed a significantly decreased area under the plasma concentration-time curve and maximal plasma or serum concentration [103]. However, those results were outliers compared to other beta-adrenergic antagonist studies. Therefore, due to the severe toxicity requiring critical care resources, the costs, and risks of other treatments such as vasopressors, intubation, high-dose insulin-glucose, or even extracorporeal membrane oxygenation (ECMO), the relative inefficacy of glucagon for significant overdoses even at large doses requiring labor intensive nursing efforts, the Workgroup concluded in favor of single-dose AC, but against multiple-dose AC. Despite the absence of evidence, it may be reasonable to extend these recommendations to other beta-adrenergic antagonists.

- For immediate-release beta-adrenergic antagonist ingestions at the following dose thresholds (atenolol 6 mg/kg, nadolol 5 mg/kg, propranolol 5 mg/kg, sotalol 6 mg/kg), we recommend single-dose AC for up to 1 h post-ingestion (1, D).
- For modified-release beta-adrenergic antagonist ingestions at the following dose thresholds (atenolol 6 mg/kg, nadolol 5 mg/kg, propranolol 5 mg/kg), we recommend single-dose AC for up to 2 h post-ingestion (1, D).
- For modified-release sotalol ingestions at a dose threshold of 6 mg/kg, we recommend single-dose AC for up to 1 h post-ingestion (1, D).

- For immediate-release beta adrenergic antagonist ingestions at the following dose thresholds (atenolol 6 mg/kg, nadolol 5 mg/kg, propranolol 5 mg/kg, sotalol 6 mg/kg), we suggest single-dose AC for up to 2 h post-ingestion (2, D).
- For modified-release beta-adrenergic antagonist ingestions at the following dose thresholds (atenolol 6 mg/kg, nadolol 5 mg/kg, propranolol 5 mg/kg, sotalol 6 mg/kg), we suggest single-dose AC for up to 3 h post-ingestion (2, D).
- For immediate-release beta-adrenergic antagonist ingestions at the following dose thresholds (atenolol 6 mg/kg, nadolol 5 mg/kg, propranolol 5 mg/kg, sotalol 6 mg/kg), we suggest against single-dose AC beyond 5 h post-ingestion (2, D).
- For modified-release beta-adrenergic antagonist ingestions at the following dose thresholds (atenolol 6 mg/kg, nadolol 5 mg/kg, propranolol 5 mg/kg), we suggest against single-dose AC beyond 6 h post-ingestion (2, D).
- For all other beta-adrenergic antagonist ingestions at other time points, an individualized risk assessment is required for single-dose AC administration.
- For all beta-adrenergic antagonist ingestions, an individualized risk assessment is required for additional-dose AC administration.
- For all ingestions of either immediate or modified release atenolol, nadolol, propranolol, or sotalol, we suggest against multiple-dose AC administration (2, D).
- For all other beta-adrenergic antagonist ingestions at other time points, an individualized risk assessment is required for multiple-dose AC administration.

Bupropion

Evidence to decision rationale

The Workgroup was unable to find any published clinical evidence for the role of AC in bupropion poisoning. Only preliminary data are available to suggest that bupropion is well adsorbed to AC [104]. Given that no specific data exists for bupropion overdose, that seizures are reported to occur in up to a third of patients with bupropion overdose [105], and that refractory to supportive care cardiovascular toxicity (including QRS complex and QT interval prolongation and cardiac dysrhythmias) often follows, the Workgroup was in favor of the administration of AC to patients presenting with potentially clinically significant overdoses.

- For immediate-release bupropion ingestions at a dose threshold of 20 mg/kg, we recommend single-dose AC for up to 1 h post-ingestion (1, D).
- For modified-release bupropion ingestions at a dose threshold of 20 mg/kg, we recommend single-dose AC for up to 2 h post-ingestion (1, D).
- For immediate release bupropion ingestions at a dose threshold of 20 mg/kg, we suggest single-dose AC for up to 2 h post-ingestion (2, D).
- For modified-release bupropion ingestions at a dose threshold of 20 mg/kg, we suggest single-dose AC for up to 3 h post-ingestion (2, D).
- For immediate release bupropion ingestions, we suggest against single-dose AC beyond 2 h post-ingestion (2, D).
- For all other bupropion ingestions at other time points, an individualized risk assessment is required for single-dose AC administration.
- For all bupropion ingestions, an individualized risk assessment is required for additional-dose AC administration.
- For all bupropion ingestions, an individualized risk assessment is required for multiple-dose AC administration.

Calcium-channel blockers

Evidence to decision rationale

Calcium-channel blockers have a high toxicity potential when ingested, even as a single poison in overdose. The toxic dose is variable and also subject to a patient's own cardiovascular physiological reserve, other comorbidities, and co-ingested poisons when applicable. However, in symptomatic patients, hemodynamic instability affects the level of consciousness and other toxic symptoms such as nausea, vomiting or ileus make the administration of AC unsafe unless the airway is protected. In a controlled study of healthy volunteers, the administration of AC immediately after ingestion of immediate-release verapamil showed a decreased area under the plasma concentration-time curve and maximal plasma or serum concentration ($P<0.0005$), but not when the AC was administered 2 h after ingestion [106]. The same manuscript included a second study with the ingestion of modified-release verapamil. The administration of AC immediately, 2 h and 4 h after ingestion showed a decrease in the area under the plasma concentration-time curve ($P=0.04$ and $P=0.001$, respectively) [106]. In healthy volunteers who ingested amlodipine, single-dose AC decreased the area under the plasma concentration-time curve when administered up to 2 h post-ingestion ($P=0.001$) [107]. A case series reported a potential benefit of administration of AC in patients with diltiazem overdose but no role for multiple-dose AC[108].

However, due to the absence of a specific, the need for prolonged critical care in patients with severe calcium channel blocker toxicity, challenges with other treatments such as vasopressors or high-dose insulin-glucose therapy, the Workgroup recommends AC for immediate and modified release formulations up to 2 h for amlodipine, diltiazem, and verapamil immediate release formulations, and 5 h for modified release formulations of the three calcium channel blockers. Beyond that timeframe, administration of AC may also be indicated (weak recommendation up to 5 h for modified release formulation) based on the current symptoms and expected toxicity if the calcium channel blocker dose ingested is significant. Attempts at decontamination with AC may also be warranted within 6 h post-ingestion if the clinical environment (remote setting, for example) precluded a safe transfer to a critical care bed, should the patient deteriorate, and such situations require an individualized risk assessment. The Workgroup concluded that, based on similar properties, it is reasonable to extend the recommendations to other calcium channel blockers.

- For immediate-release calcium channel blocker ingestions at the following dose thresholds (amlodipine five therapeutic doses, diltiazem three therapeutic doses, verapamil three therapeutic doses), we recommend single-dose AC for up to 2 h post-ingestion (1, D).
- For immediate-release calcium-channel blocker ingestions at the following dose thresholds (diltiazem three therapeutic doses, verapamil three therapeutic doses), we suggest single-dose AC for up to 3 h post-ingestion (2, D).
- For modified-release amlodipine ingestions at a dose threshold of five therapeutic doses, we recommend single-dose AC for up to 2 h post-ingestion (1, D).
- For modified-release calcium-channel blocker ingestions at the following dose thresholds (diltiazem, three therapeutic doses; verapamil, three therapeutic doses), we recommend single-dose AC for up to 3 h post-ingestion (1, D).
- For modified-release calcium-channel blocker ingestions at the following dose thresholds (diltiazem, three therapeutic doses; verapamil, three therapeutic doses), we suggest single-dose AC for up to 5 h post-ingestion (2, D).
- For both immediate and modified-release amlodipine ingestions, we suggest against single-dose AC beyond 6 h post-ingestion (2, D).

- For immediate release diltiazem and verapamil ingestions, we suggest against single-dose AC beyond 6 h post-ingestion (2, D).
- For all other doses, time periods, and all other calcium-channel blockers, an individualized risk assessment is required for single-dose AC administration.
- For all three calcium-channel blockers, an individualized risk assessment is required for additional-dose AC administration.
- For all three calcium-channel blockers, an individualized risk assessment is required for multiple-dose AC administration.

Carbamazepine

Evidence to decision rationale

Two human volunteer studies performed by the same researchers demonstrate the effect of single-dose AC on carbamazepine absorption. When single-dose AC was given at 5 min or 1 h post-ingestion, the area under the plasma concentration-time curve for carbamazepine was reduced by greater than 95% ($P<0.05$) or 41% ($P<0.05$), respectively, compared to control [109,110]. In a similar study, single-dose AC given 5 min after carbamazepine reduced the area under the plasma concentration-time curve by 90% ($P<0.01$) compared to control [109]. When multiple-dose AC was initiated 10 h after carbamazepine ingestion, the area under the plasma concentration-time curve was reduced by 27% ($P<0.05$) [109,110]. One small clinical trial that randomized carbamazepine poisoned patients to single-dose AC or multiple-dose AC demonstrated that patients who got multiple-dose AC had a shorter carbamazepine elimination half-live (12.6 h versus 27.9 h, $P<0.004$), a shorter duration of coma (20.3 h versus 29.3 h, $P=0.02$), a shorter duration of mechanical ventilation (24.1 h versus 36.4 h, $P=0.001$), and a shorter hospital length of stay (30.3 h versus 39.7 h, $P<0.001$) [111]. In uncontrolled data, other authors report that multiple-dose AC resulted in a reduction in elimination half-life of overdose patients compared to published values [112,113] or untreated patients [114]. In a volunteer study that compared the effects of single-dose AC, multiple-dose AC, and control on oxcarbazepine kinetics demonstrated that single-dose AC given 30 min after ingestion reduced the maximal plasma or serum concentration of oxcarbazepine and the 10,11-epoxide metabolite ($P<0.01$) but only reduced the area under the plasma concentration-time curve significantly for the metabolite ($P<0.01$) [115]. In contrast, multiple-dose AC beginning at 12 h post-ingestion had no effect on any parameter studied. The Workgroup concluded that the prolonged cyclical toxicity of carbamazepine, often requiring intubation and critical care, the lack of a specific antidote and the potential for single-dose AC and multiple-dose AC to reduce the toxicity justified the administration of AC in carbamazepine overdose.

- For immediate release carbamazepine ingestions at a dose threshold of 25 mg/kg, we recommend single-dose AC for up to 2 h post-ingestion (1, C).
- For immediate release carbamazepine ingestions at a dose threshold of 25 mg/kg, we suggest single-dose AC for up to 3 h post-ingestion (2, C).
- For modified-release carbamazepine ingestions at a dose threshold of 25 mg/kg, we recommend single-dose AC for up to 3 h post-ingestion (1, C).
- For modified-release carbamazepine ingestions at a dose threshold of 25 mg/kg, we suggest single-dose AC for up to 4 h post-ingestion (2, C).
- For all other doses and time periods, an individualized risk assessment is required for single-dose AC administration.
- For immediate release carbamazepine ingestions at a dose threshold of >50 mg/kg, we recommend additional-dose AC (1, D).
- For modified-release carbamazepine ingestions at a dose threshold of >40 mg/kg, we suggest additional-dose AC (2, D).
- For either immediate-release or modified-release carbamazepine ingestions at a dose threshold of >40 mg/kg, we suggest multiple-dose AC (2, C).

Cardiac glycosides

Evidence to decision rationale

Toxicity from digoxin is possible from either an ingestion of an overdose (acute toxicity), ingestion of a therapeutic dose with comorbidities or conditions such as acute kidney injury or P-glycoprotein inhibition, which result in greater plasma digoxin concentrations despite therapeutic intent (chronic toxicity), or a combination of both (acute-on-chronic toxicity). In acute overdose, the dose range for initial symptoms is reported as 2–3 mg (or around 20 µg/kg body weight), but ingestions less than 5 mg rarely cause life-threatening toxicity. A dose exceeding 10 mg is generally considered to cause cardiac arrest in healthy adults. In children, otherwise healthy, unintentional ingestions exceeding 0.1 mg/kg are likely to cause toxic effects. A dose of 2 mg is probably tolerable in a healthy child, but more than 4 mg may be fatal [116,117]. Digoxin is well adsorbed by AC *in vitro* [118]. Volunteer studies demonstrate reduced digoxin absorption following administration of AC [109,119,120]. Activated charcoal immediately after oral administration of digoxin inhibited total absorption by approximately 96-98% [109,120], and by approximately 40% when given 1 h after ingestion [120]. Similarly, multiple-dose AC decreased the elimination half-lives of digoxin [121,122] and digitoxin [123] in clinical cases. The administration of multiple-dose AC also increased digoxin clearance in healthy volunteers following intravenous administration [124,125] and in a case of intravenous overdose [126]. In low-dose digoxin overdose, the risks of AC administration outweigh any potential benefit and therefore presents unnecessary risk. However, in high-dose digoxin overdose, single-dose AC may obviate the use of digoxin-specific antibody fragment therapy, which is expensive in some countries and unavailable in others.

In vitro studies also demonstrate that AC adsorbs oleander leaf extract [127] and oleandrin and oleandrigenin from *Nerium oleander* (common oleander) [128]. Activated charcoal reduced the 24 h mean residence time and the apparent terminal elimination half-life of cardenolides in patients who ingested *Cascabela thevetia* (*Thevetia peruviana*, yellow oleander) seeds compared to controls. This effect was approximately equal in patients administered single-dose AC or multiple-dose AC [129].

Studies on the effect of multiple-dose AC on mortality in these patients have had variable outcomes. In one randomized study of 401 patients, death was reduced (percentage difference 5.5%; 95% CI 0.6–10.3; $P=0.025$) as were life-threatening cardiac dysrhythmias in those who had received multiple-dose AC compared to single-dose AC [74]. In a subsequent larger study comparing placebo, single-dose AC or multiple-dose AC in a range of poisonings (1,647 patients had ingested yellow oleander seeds), there was no difference in mortality in those who had ingested oleander seeds and were treated with multiple-dose AC compared to those treated with placebo [73]. Despite this conflicting evidence regarding AC, and clear evidence of efficacy of treatment with digoxin-specific antibody fragments treatment in patients with yellow oleander poisoning [130], there may be clinical reasons that support the administration of single-dose AC and/or multiple-dose AC in patients ingesting yellow oleander. It is often used, especially when digoxin-specific antibody fragments are unavailable and/or in settings with insufficient critical care capacity.

- For digoxin ingestions at a dose threshold of 75 µg/kg, we recommend single-dose AC for up to 1 h post-ingestion (1, C).
- For digoxin ingestions at a dose threshold of 75 µg/kg, we suggest single-dose AC for up to 2 h post-ingestion (2, C).
- For digoxin ingestions, we recommend against single-dose AC beyond 6 h post-ingestion (1, C).
- For all other digoxin doses and intervals, an individualized risk assessment is required for single-dose AC administration.
- For digoxin ingestions, we suggest against additional-dose AC (2, D).
- For digoxin ingestions at a dose threshold of 100 µg/kg, we suggest multiple-dose AC (2, C).
- For oleander ingestions at a dose threshold of four seeds, we recommend single-dose AC for up to 1 h post-ingestion (1, C).
- For oleander ingestions at a dose threshold of 4 seeds, we suggest single-dose AC for up to 2 h post-ingestion (2, C).
- For digoxin ingestions, we recommend against single-dose AC beyond 6 h post-ingestion (1, C).
- For all other oleander doses and intervals, an individualized risk assessment is required for single-dose AC administration.
- For oleander ingestions, an individualized risk assessment is required for administration.
- For oleander ingestions at a dose threshold of six seeds, we suggest multiple-dose AC administration (2, B).

Chloroquine

Evidence to decision rationale

Doses greater than 30 mg/kg are associated with adverse effects, and those greater than 70 mg/kg are associated with life-threatening effects and death [131]. *In vitro* data demonstrate that chloroquine is well adsorbed to AC [132]. When human volunteers ingested 500-1,000 mg chloroquine phosphate immediately followed by single-dose AC, absorption was decreased by as much as 69% ($P < 0.05$) [133,134]. The reduction in urinary excretion was 44.5% [133], and the area under the plasma concentration-time curve and maximal plasma or serum concentration were reduced by 99% [134]. Because of the rapid onset of cardiovascular collapse in patients with large chloroquine ingestions, the majority will either have or require endotracheal intubation prior to gastrointestinal decontamination. However, given the protracted severe course and lack of specific antidotes for this poisoning often produce dire outcomes, the Workgroup concluded that a single dose of AC could decrease the overall toxic burden, especially with its low costs and wide availability.

- For chloroquine ingestions at a dose threshold of 35 mg/kg, we recommend single-dose AC for up to 1 h post-ingestion (1, D).
- For chloroquine ingestions at a dose threshold of 35 mg/kg, we suggest single-dose AC for up to 2 h post-ingestion (2, D).
- For chloroquine ingestions, we suggest against single-dose AC beyond 6 h post-ingestion (2, D).
- For all other chloroquine doses and intervals, an individualized risk assessment is required for single-dose AC administration.
- For chloroquine ingestions, an individualized risk assessment is required for additional-dose AC administration.
- For chloroquine ingestions, an individualized risk assessment is required for multiple-dose AC administration.

Cocaine

Evidence to decision rationale

Prior to voting, the committee narrowed the focus of these recommendations to exclude consideration of body-packers and body-stuffers. Cocaine is well adsorbed to AC [135,136]. Although no published human data exists, a single mouse experiment demonstrated a reduction in seizures and death when AC was given one minute after the cocaine [137]. In human volunteers, cocaine concentrations peak at 45 to 100 min [138,139] following ingestion. From a clinical perspective, it is unlikely that many individuals will present with significant cocaine ingestion (as opposed to nasal or parenteral routes), outside of the setting of body-stuffing and body-packing of cocaine. The management and the use of gastrointestinal decontamination in body packers and stuffers is best performed with whole bowel irrigation and falls outside the scope of this work [140]. However, ingested cocaine can be fatal and adsorption to AC is demonstrated, the Workgroup concluded that there is a role for single-dose AC, but no role for additional-dose AC or multiple-dose AC.

- For cocaine ingestions at a dose threshold of 5 mg/kg, we recommend single-dose AC for up to 1 h post-ingestion (1, D).
- For cocaine ingestions at a dose threshold of 5 mg/kg, we suggest single-dose AC for up to 2 h post-ingestion (2, D).
- For cocaine ingestions, we suggest against single-dose AC at 5 h and beyond post-ingestion (2, D).
- For cocaine ingestions at other doses and time frames, an individualized risk assessment is required for single-dose AC administration.
- For cocaine ingestions, we suggest against additional-dose AC (2, D).
- For cocaine ingestions, we suggest against multiple-dose AC (2, D).

Colchicine

Evidence to decision rationale

The workgroup was unable to find any published clinical evidence for the role of AC in patients with colchicine overdose [5]. In experimental models, colchicine binds to AC in simulated gastric and intestinal colchicine conditions [141]. The high lethality, the lack of an antidote, and the potential to easily consume lethal doses supported a favourable risk-benefit assessment for the administration of AC in pharmaceutical colchicine poisoning. In addition to pharmaceutical colchicine, there are colchicine-containing plants (*Colchicum autumnale* and *Gloriosa superba*). There was no consensus by the Workgroup on the role of single-dose AC, additional-dose AC or multiple-dose AC following the ingestion of a colchicine-containing plant. This was due to the difficulties in estimating ingested colchicine amounts. The Workgroup concluded that when a colchicine-containing plant is ingested, an individualized risk assessment is warranted.

- For colchicine ingestions at a dose threshold of 0.4 mg/kg, we recommend single-dose AC for up to 3 h post-ingestion (1, D).
- For colchicine ingestions at a dose threshold of 0.4 mg/kg, we suggest single-dose AC for up to 4 h post-ingestion (2, D).
- For colchicine ingestions at other doses and time frames, an individualized risk assessment is required for single-dose AC administration.
- For colchicine ingestions, an individualized risk assessment is required for additional-dose AC administration.
- For colchicine ingestions at a dose threshold of 0.7 mg/kg, we suggest multiple-dose AC (2, D).

Cyanide

Evidence to decision rationale

The Workgroup was unable to find any published clinical evidence for the role of AC in patients with cyanide poisoning [5]. Cyanide salts are poorly adsorbed to AC with a maximum adsorption capacity of only 35 mg/g AC [142]. In a rat study, the immediate administration of a high surface area AC was able to delay and prevent mortality statistically significantly [143]. *In vitro* studies suggest that cyanide does bind to AC (maximal binding of 35 mg cyanide per gram of AC) [142], but with a lower affinity than most pharmaceuticals (range at pH 1.3, 51–262 mg/g of AC) [144]. Rats given 35–40 mg/kg of potassium cyanide followed immediately by 4 g/kg of AC had a marked reduction in mortality (8/26 rats) compared with controls given no AC (25/26 rats) [145]. Thus, it would be logical to give a larger dose of AC very early after cyanide ingestion (e.g., in a ratio of 100:1 AC:cyanide) [144]. Given that a few hundred milligrams of a cyanide salt is rapidly absorbed and would be lethal in an adult, and given that a large AC:drug ratio could be achieved with standard AC dosing, the Workgroup supported a role for single-dose AC very early post-ingestion (up to 30 min), acknowledging and conceding that clinicians would have difficulty in establishing an ingested dose. In addition, the workgroup recognized that because toxicity usually occurs rapidly following ingestion it is likely that individuals may already have severe acute toxicity (e.g., coma, convulsions, or cardiovascular toxicity) which would preclude single-dose AC use. Expeditious antidotal administration (e.g., hydroxocobalamin, or sodium nitrite plus sodium thiosulfate) should be prioritized over single-dose AC administration in symptomatic patients. Recommendations for AC administration do not apply to cyanide inhalation, as occurs commonly in fire victims.

- For cyanide ingestions at a dose threshold of 2 mg/kg, we recommend single-dose AC for up to 30 min post-ingestion (1, D).
- For cyanide ingestions at a dose threshold of 2 mg/kg, we suggest single-dose AC for up to 2 h post-ingestion (2, D).
- For cyanide ingestions, we suggest against single-dose AC administration beyond 6 h post-ingestion (2, D).
- For cyanide ingestions at all other doses and time intervals, an individualized risk assessment is required for single-dose AC administration.
- For cyanide ingestions at a dose threshold of <4 mg/kg, we suggest against additional-dose AC administration (2, D).
- For cyanide ingestions, we recommend against multiple-dose AC administration (1, D).

Dapsone

Evidence to decision rationale

The workgroup was unable to find any published *in vitro* studies demonstrating the adsorption of dapsone to AC, nor any animal trials, or human volunteer clinical single-dose AC data [5]. Ingestion of dapsone doses greater than 4 mg/kg is associated with adverse effects, and ingestions greater than 700 mg are reported to result in severe toxicity and death [146]. In volunteers, multiple-dose AC starting 10 h after dapsone ingestion and continuing for 2 days reduced the elimination half-life of dapsone by 43% (P <0.01) and that of the active metabolite by 51% (P <0.01) [147]. The reduction in elimination half-life during multiple-dose AC was confirmed in three overdose cases [148]. The Workgroup concluded that single-dose AC followed by multiple-dose AC in selected cases could decrease the overall toxic burden and related costs, as no specific antidote exists for this poisoning.

- For dapsone ingestions at a dose threshold of 6 mg/kg, we recommend single-dose AC for up to 2 h post-ingestion (1, D).
- For dapsone ingestions at a dose threshold of 6 mg/kg, we suggest single-dose AC for up to 3 h post-ingestion (2, D).
- For dapsone ingestions at all other doses and time intervals, an individualized risk assessment is required for single-dose AC administration.
- For dapsone ingestions, an individualized risk assessment is required for additional-dose AC administration.
- For dapsone ingestions at a dose threshold of 10 mg/kg, we recommend multiple-dose AC administration (1, D).

Diphenhydramine

Evidence to decision rationale

Doses greater than 7.5 mg/kg are associated with significant adverse effects, and doses greater than 10 mg/kg are associated with severe toxicity and mortality [149]. The *in vitro* maximum adsorption capacity of diphenhydramine to AC ranges between 70.8 mg/g AC [150] and 120 mg/g AC [151]. When human volunteers were given single-dose AC at 5 min after ingestion of 50 mg of diphenhydramine, there was a 94.8% reduction in the maximal plasma or serum concentration and a greater than 90% reduction in the area under the plasma concentration-time curve, both of which were statistically significant (P <0.05) [150]. In the same study, when AC was delayed 60 min post-ingestion, there was no statistical difference from control. When single-dose AC with sorbitol was given immediately to volunteers who ingested diphenhydramine in combination with paracetamol and codeine, the area under the plasma concentration-time curve for diphenhydramine was reduced by 72% (P <0.01) [151]. As the antidote physostigmine may present inherent challenges in both administration and availability, the Workgroup concluded that single-dose AC could decrease the overall toxicity burden and related costs of diphenhydramine poisoning.

- For immediate-release diphenhydramine ingestions at a dose threshold of 15 mg/kg, we recommend single-dose AC for up to 1 h post-ingestion (1, D).
- For immediate-release diphenhydramine ingestions at a dose threshold of 15 mg/kg, we suggest single-dose AC for up to 2 h post-ingestion (2, D).
- For modified-release diphenhydramine ingestions at a dose threshold of 15 mg/kg, we recommend single-dose AC for up to 3 h post-ingestion (1, D).
- For modified-release diphenhydramine ingestions at a dose threshold of 15 mg/kg, we suggest single-dose AC for up to 4 h post-ingestion (2, D).
- For immediate-release diphenhydramine ingestions, we recommend against single-dose AC administration beyond 6 h post-ingestion (2, D).
- For all other doses and time periods, an individualized risk assessment is required for single-dose AC administration.
- For either immediate- or modified-release diphenhydramine ingestions, an individualized risk assessment is required for additional-dose AC administration.
- For either immediate- or modified-release diphenhydramine ingestions, we suggest against multiple-dose AC administration (2, D)

Disopyramide

Evidence to decision rationale

The influence of pH on the adsorption of disopyramide was studied at AC:disopyramide ratios 5:1 and 12.5:1. Adsorption of weak acids and bases to AC is influenced by pH, as charge affects binding. Adsorption of disopyramide to AC was demonstrated at both pH values simulating conditions in the stomach (1.2) and small intestine (7.0), and a lower and unabsorbed disopyramide fraction correlated with a higher AC: disopyramide ratio. At pH 1.2, the unadsorbed fraction was 38% and 17% at the 5:1 and 12.5:1 AC: drug ratios, respectively. At pH 7.0, the unadsorbed fraction was 12% and 1.3% at the 5:1 and 12.5:1 AC:drug ratios, respectively [152]. When AC and disopyramide were mixed at a pH of 7.0 in a 1:1 AC:disopyramide ratio, 64% of the disopyramide was unadsorbed. This increased to over 99% at a 20:1 ratio. At pH 1.2 and a 20:1 ratio, only 90% was adsorbed [153]. Ingestion of AC 5 min after disopyramide reduced the area under the plasma concentration-time curve by 89% ($P<0.05$) in healthy volunteers [153]. When multiple-dose AC was given (at 4, 6, 8, and 12 h) post-ingestion of disopyramide in human volunteers, the area under the plasma concentration-time curve was reduced by 16% ($P<0.01$) [154]. The Workgroup concluded that single-dose AC could decrease the overall toxicity and related costs, as no specific antidote exists for this poisoning.

- For immediate-release disopyramide ingestions at a dose threshold of 1 g, we recommend single-dose AC for up to 1 h post-ingestion (1, D).
- For immediate-release disopyramide ingestions at a dose threshold of 1 g, we suggest single-dose AC for up to 2 h post-ingestion (2, D).
- For immediate-release disopyramide ingestions at a dose threshold of 1 g, we suggest against single-dose AC for 6 h and greater post-ingestion (2, D).
- For modified-release disopyramide ingestions at a dose threshold of 1 g, we recommend single-dose AC for up to 2 h post-ingestion (1, D).
- For modified-release disopyramide ingestions at a dose threshold of 1 g, we suggest single-dose AC for up to 3 h post-ingestion (2, D).
- For all other doses and time periods, an individualized risk assessment is required for single-dose AC administration.
- For either immediate- or modified-release disopyramide ingestions, an individualized risk assessment is required for additional-dose AC administration.
- For either immediate or modified release disopyramide ingestions, individualized risk assessment is required for multiple-dose AC administration.

Ethanol

Evidence to decision rationale

An ingested dose of 480 mg/kg approximately produces a blood ethanol concentration of 800 mg/L (17 mmol/L or 0.8 g/L). An ingestion of several g/kg is required to produce a lethal concentration in a naïve patient. Although ethanol is well adsorbed to AC on a mg/g basis (300 mg/g AC [142], 506 mg/g AC [155]), obtaining clinically relevant AC:ethanol binding ratios is not practical given the stoichiometry of the ingested dose. In one randomized crossover human volunteer study, single-dose AC failed to alter the peak ethanol concentration, the area under the plasma concentration-time curve, or the ethanol elimination rate [156]. Taking into account the fast systemic absorption of ethanol and that the toxicity expected from acute ethanol intoxication is limited to sedation and related loss of airway protection, the Workgroup concluded that the balance of risks and benefits does not favour administration of AC.

- For ingestions of ethanol, we recommend against single-dose AC (1, C).
- For ingestions of ethanol, we recommend against additional-dose AC (1, D).
- For ingestions of ethanol, we recommend against multiple-dose AC (1, D).

Factor Xa inhibitors

Evidence to decision rationale

There is no formal toxic dose established; however, many poison control centres use the concept of any dose outside the therapeutic range as potentially toxic. TOXBASE® suggests doses of apixaban greater than 0.5 mg/kg, edoxaban greater than 3 mg/kg, and rivaroxaban greater than 1 mg/kg warrant medical attention [116]. Both rivaroxaban and apixaban have significant enterohepatic circulation. When human volunteers were given a single dose of rivaroxaban followed by AC, the area under the plasma concentration-time curve for rivaroxaban was reduced by 43% when the delay to AC was 2 h, 31% when the delay was 5 h and 29% even when the delay was 8 h [157]. In a similar study with apixaban, AC reduced the area under the plasma concentration-time curve by 51% and 28% when the delay to administration was 2 h or 6 h, respectively [158]. For the other Factor Xa inhibitors currently available (betrixaban and edoxaban), data were insufficient for voting, but the Workgroup would recommend extrapolation of the recommendations for apixaban and rivaroxaban at this time. Given that overdoses of factor Xa inhibitors rarely produce significant toxicity in the absence of physical trauma, specific antidotes are extremely costly, and contraindications to AC, such as sedation and loss of airway protective reflexes, are not expected, the Workgroup concluded that the risk:benefit ratio was in favour of the administration of single-dose AC.

- For factor Xa inhibitor ingestions at the following dose thresholds (apixaban 40 mg, rivaroxaban 50 mg), we recommend single-dose AC for up to 1 h post-ingestion (1, C).
- For factor Xa inhibitor ingestions at the following dose thresholds (apixaban 40 mg, rivaroxaban 50 mg), we suggest single-dose AC for up to 4 h post-ingestion (1, C).
- For apixaban and rivaroxaban ingestions at other doses and time intervals, an individualized risk assessment is required for single-dose AC administration.
- For apixaban and rivaroxaban ingestions at other doses and time intervals, an individualized risk assessment is required for additional-dose AC administration.
- For apixaban and rivaroxaban ingestions, we recommend against multiple-dose AC administration (1, D).

Ibuprofen

Evidence to decision rationale

Although data are not available for many drugs in this class, it is likely that all nonsteroidal anti-inflammatory drugs (NSAIDs) are well adsorbed to AC based on *in vitro* or animal experiments [153,159–162]. The Workgroup decided to only make a recommendation on ibuprofen, given that this is the most common overdose in the class, and that data on dosing thresholds for other NSAIDs were either more limited or unavailable. A dose of ibuprofen less than 200 mg/kg rarely causes significant toxicity; severe effects may occur after ingestion of greater than 400 mg/kg. In a randomized crossover trial, human volunteers were given 400 mg of ibuprofen followed in 30 min by water

or 25 g of AC. Administration of AC reduced the area under the plasma concentration-time curve by 30% ($P<0.05$ compared to control) [97]. No data was found on modified-release ibuprofen, and the management is left to an individual risk assessment. Given that the expected toxicity of a significant ibuprofen ingestion leads to severe metabolic acidosis and acute kidney injury necessitating a protracted critical care admission, the Workgroup concluded that single-dose AC could decrease the overall toxic burden and related costs, as no specific antidote exists for this poisoning.

- For ibuprofen ingestions at a dose threshold of 250 mg/kg, we suggest single-dose AC administration for up to 2 h post-ingestion (2, D).
- For ibuprofen ingestions at a dose threshold of 250 mg/kg, we suggest against single-dose AC administration at 5 h and beyond post-ingestion (2, D).
- For ibuprofen ingestions, other doses and time intervals, an individualized risk assessment is required for single-dose AC administration.
- For ibuprofen ingestions, an individualized risk assessment is required for additional-dose AC administration.
- For ibuprofen ingestions, we suggest against multiple-dose AC administration (2, D).

Iron

Evidence to decision rationale

Doses greater than 20 mg/kg are associated with adverse effects, and doses greater than 40 mg/kg are associated with severe toxicity and mortality [163]. Adsorption of iron to AC is generally felt to be poor [155,164]. One controlled human volunteer study failed to show a reduction in the area under the plasma concentration-time curve, maximal plasma or serum concentration, or time to maximum concentration when ingestion of iron mixed with AC was compared to ingestion of iron alone [165]. The Workgroup concluded against the administration of AC in iron poisoning as it is not only ineffective but also may induce emesis, confounding the clinical assessment of the patient.

- For ingestions of iron, we recommend against single-dose AC (1, C).
- For ingestions of iron, we recommend against additional-dose AC (1, D).
- For ingestions of iron, we recommend against multiple-dose AC (1, D).

Isoniazid

Evidence to decision rationale

Ingestion of doses greater than 20 mg/kg results in adverse effects, and doses greater than 80 mg/kg are associated with severe toxicity and mortality [166]. Isoniazid is well adsorbed to AC *in vitro* [167]. The immediate administration of AC to rabbits given isoniazid numerically lowered the area under the plasma concentration-time curve compared to control (no statistical analysis presented) [168]. In rats, tissue concentrations were reduced by 80% when AC was immediately administered following Isoniazid at an AC:isoniazid ratio of 8:1, but only 35% when the AC:isoniazid ratio was 4:1 [169]. Similarly, in human volunteers the immediate administration of AC completely prevented the absorption of isoniazid [170]. In contrast, a greater than 16:1 AC:isoniazid ratio was unable to reduce the area under the plasma concentration-time curve in human volunteers when AC was delayed 1 h post-ingestion. Administration of intravenous pyridoxine as an antidote is compatible with AC use. When only oral pyridoxine is available, AC is not recommended, as AC may bind pyridoxine [171]. Given the severity of seizures expected with isoniazid overdose and that pyridoxine may be unavailable or in insufficient quantity in some settings, the Workgroup concluded that single-dose AC could decrease the overall toxic burden if given prior to the onset of toxicity (up to 1 h post-ingestion). In such situations the airway should be protected prior to administration of AC. When only oral pyridoxine is available, AC is not recommended as AC may bind pyridoxine which may be essential for seizure control.

- For isoniazid ingestions at a dose threshold of 40 mg/kg, we recommend single-dose AC administration for up to 1 h post-ingestion (1, D).
- For isoniazid ingestions at a dose threshold of 40 mg/kg, we suggest single-dose AC administration for up to 2 h post-ingestion (2, D).
- For isoniazid ingestions at a dose threshold of 40 mg/kg, we suggest against single-dose AC administration beyond 6 h post-ingestion (2, D).
- For isoniazid ingestions at other doses and time intervals, individualized risk assessment is required for single-dose AC administration.
- For isoniazid ingestions, an individualized risk assessment is required for additional-dose AC administration.
- For isoniazid ingestions, we recommend against multiple-dose AC administration (1, D).

Lamotrigine

Evidence to decision rationale

Ingestion of doses greater than 525 mg is associated with seizures and those greater than 4 g with moderate to severe symptoms, including cardiotoxicity [172]. The Workgroup did not find evidence of *in vitro* adsorption of lamotrigine to AC. Additionally, no controlled animal trials were found. Two human volunteer studies were identified. In the first, six volunteers were given lamotrigine (100 mg), followed by either no therapy or single-dose AC, 50 g at 30 min, or multiple-dose AC, 50 g at 30 min and then 20 g at 6, 12, 24, and 48 h post-ingestion. While there was no effect on the maximal plasma or serum concentration, the area under the plasma concentration-time curve was reduced by 43% with single-dose AC and by 55% with multiple-dose AC. Administration of multiple-dose AC reduced the elimination half-life by 58% (no statistical analysis presented) [173]. In an essentially identical volunteer study (the only difference is the addition of a 72 h multiple-dose AC dose), the same authors demonstrated a statistically significant reduction in the areas under the plasma concentration-time curve of 41% and 51% for single-dose AC and multiple-dose AC, respectively. The elimination half-life was only significantly reduced in the multiple-dose AC group (55% $P<0.001$) [115]. Given the severity of seizures expected with lamotrigine overdose and that no specific antidote exists, the Workgroup concluded that single-dose AC could decrease the overall toxic burden if given early post-ingestion at a time expected to be before the onset of toxicity.

- For ingestions of either immediate- or modified-release lamotrigine at a dose threshold of 30 mg/kg, we recommend single-dose AC administration for up to 1 h post-ingestion (1, D).
- For ingestions of immediate-release lamotrigine at a dose threshold of 30 mg/kg, we suggest single-dose AC administration for up to 2 h post-ingestion (2, D).

- For ingestions of modified-release lamotrigine at a dose threshold of 30 mg/kg, we suggest single-dose AC administration for up to 4 h post-ingestion (2, D).
- For ingestions of either immediate- or modified-release lamotrigine at other doses and time intervals, an individualized risk assessment is required for single-dose AC administration.
- For ingestions of either immediate- or modified-release lamotrigine, an individualized risk assessment is required for additional-dose AC administration.
- For ingestions of either immediate- or modified-release lamotrigine, an individualized risk assessment is required for multiple-dose AC administration.

Lithium

Evidence to decision rationale

Two *in vitro* studies demonstrate trivial adsorption of lithium to AC even at excessive AC:lithium ratios [174,175]. When mice were given oral lithium in a dose expected to produce a concentration of 2–3 mmol/L immediately followed by 6.7 g/kg of AC, there was no statistical difference in resultant lithium concentrations compared to control [176]. There are no human data to support the administration of single-dose AC, additional-dose AC, or multiple-dose AC in patients with lithium poisoning. Therefore, the Workgroup recommended against the administration of AC in patients with lithium poisoning, given that in the absence of a likely benefit, any risk would be unacceptable.

- For ingestions of either immediate- or modified-release lithium, we recommend against single-dose AC (1, D).
- For ingestions of either immediate- or modified-release lithium, we recommend against additional-dose AC (1, D).
- For ingestions of either immediate- or modified-release lithium, we recommend against multiple-dose AC (1, D).

Metals

Evidence to decision rationale

Evidence identified includes a narrow range of metals or metal salts, and mainly *in vitro* studies, showing minor or no adsorption to AC (copper [177], lead [177], caesium [178], and mercury [142,179,180]). No human studies on AC in metal poisoning were included. The Workgroup recommended against the administration of AC in metal poisonings (all formulations, excluding iron, lithium, and thallium, discussed in separate sections), given that in the absence of a likely benefit, any risk would be unacceptable.

- For ingestions of metals with the exceptions noted above, we recommend against single-dose AC (1, D).
- For ingestions of metals with the exceptions noted above, we recommend against additional-dose AC (1, D).
- For ingestions of metals with the exceptions noted above, we recommend against multiple-dose AC (1, D).

Metformin

Evidence to decision rationale

The toxic dose of metformin is not precisely defined, although some sources use a dose of 100 mg/kg in children up to an adult dose of 5 g as a threshold for concern [181]. In adults, reported ingestions greater than 36.7 g are associated with symptoms and those greater than 48 g are associated with death [182]. Consequential cases develop profound metabolic acidosis with an associated elevation of blood lactate concentration [183–185]. One *in vitro* study demonstrated that metformin is poorly adsorbed to AC with a maximum adsorption capacity of 10.6 mg/g at pH 1.2, and a maximum absorption capacity of 55.9 mg/g at pH 6.8, or approximately 2.8 g in the intestine per standard 50 g AC dose [13]. The Workgroup was unable to find any other supporting evidence for the role of AC in patients with metformin poisoning. The current data do not support AC, given the low adsorptive capacity and the large doses of metformin required to produce toxicity. Because this low reported adsorption to AC was not studied *in vivo*, and the potential severity of large gram ingestions, the Workgroup added some uncertainty to its recommendations for single-dose AC and additional-dose AC.

- For ingestions of either immediate- or modified-release metformin, we suggest against single-dose AC administration (2, D).
- For ingestions of either immediate- or modified-release metformin, we suggest against additional-dose AC administration (2, D).
- For ingestions of either immediate- or modified-release metformin, we recommend against multiple-dose AC administration (1, D).

Methotrexate

Evidence to decision rationale

Methotrexate overdose is increasingly reported as a result of outpatient use for a variety of rheumatological disorders. Most acute overdoses involve doses that are much less than 10 mg/kg and have no acute consequences (no statistical analysis was presented) [186,187], although there is concern for potential delayed genotoxicity in children [188]. There is a lack of data on much larger overdoses, although severe toxicity is likely limited by dose-related decreases in oral bioavailability [189]. Because of this dose-limited absorption, the Workgroup concluded with a weak recommendation for single-dose AC to decrease the overall toxic burden up to 2 h post-ingestion, but against additional-dose AC. An additional concern was that additional-dose AC could interfere with oral folinic acid therapy [186]. Although one pharmacokinetic study in patients receiving intravenous methotrexate demonstrated a significant reduction ($P<0.01$) in the area under the plasma concentration-time curve when multiple-dose AC was added to a standardized regimen of urine alkalinization and folinic acid [190], the Workgroup was specifically tasked with the treatment of patients following oral overdose. As such the decision to use multiple-dose AC was left to and to an individualized risk assessment and might be favored when folinic acid is used parenterally.

- For methotrexate ingestions with a dose threshold of 10 mg/kg, we suggest single-dose AC for up to 2 h post-ingestion (2, D).
- For methotrexate ingestions at other doses and time intervals, an individualized risk assessment is required for single-dose AC administration.
- For ingestions of methotrexate, we suggest against additional-dose AC (2, D).
- For methotrexate ingestions at other doses and time intervals, an individualized risk assessment is required for multiple-dose AC administration.

Moclobemide

Evidence to decision rationale

Moclobemide, a reversible inhibitor of monoamine oxidase, poses a significant risk in overdose, due to increases in serotonin, noradrenaline, and dopamine. The risk is greatest in patients who are maintained on another serotonergic drug or who have co-ingested other drugs that increase serotonin concentrations. In a randomized human volunteer crossover study, AC given 5 min after moclobemide reduced the area under the plasma concentration-time curve by greater than 99% ($P<0.01$) [98]. When the same authors repeated the study with a 30 min delay between ingestion and AC, the area under the plasma concentration-time curve was still significantly reduced, although only 55% ($P<0.05$) [99]. Based on the potential for severe toxicity from monoamine oxidase inhibitors (MAOIs) and the lack of a specific antidote, the Workgroup concluded that AC could decrease the overall toxic burden of moclobemide.

- For ingestions of either immediate or modified-release moclobemide with a dose threshold of 20 mg/kg, we suggest single-dose AC for up to 2 h post-ingestion (2, D).
- For ingestions of immediate-release moclobemide with a dose threshold of 50 mg/kg, an individualized risk assessment is required for single-dose AC administration between 2 h and 4 h post-ingestion.
- For ingestions of immediate-release moclobemide with a dose threshold of 50 mg/kg, we suggest against single-dose AC administration at >5 h post-ingestion.
- For ingestions of modified-release moclobemide with a dose threshold of 50 mg/kg, an individualized risk assessment is required for single-dose AC administration at other time intervals.
- For ingestions of either immediate or modified-release moclobemide, an individualized risk assessment is required for additional-dose AC (2, D).
- For ingestions of either immediate or modified-release, we suggest against multiple-dose AC administration.

Opioids

Evidence to decision rationale

Although there are surprisingly little data on *in vitro* adsorption of opioids to AC, existing data support good adsorption: the maximum adsorption capacity for morphine is 800 mg/g AC [142]; the maximum adsorption capacity for tilidine is 170.1 mg/g AC at pH 1.2 and 185.5 mg/g AC at pH 7.5 [191]; the maximum adsorption capacity for tramadol was only 50 mg/g AC, but complete adsorption was noted at a 16:1 AC:tramadol ratio [192]; the maximum adsorption capacity for diphenoxylate is 200 mg/g AC at pH 4 and 416 mg/g AC at pH 7 [193]. In a controlled study, rabbits given oral AC immediately after an intravenous dose of morphine had a statistically significant 42% reduction in the area under the plasma concentration-time curve ($P<0.001$) [194]. When rats were given AC 30 min after oral dextropropoxyphene, a statistically significant reduction in lethality was reported compared to rats given propoxyphene alone (30% versus 63%) ($P<0.01$) [195]. Mice given AC 30 min after diphenoxylate showed a statistically significant 4-fold reduction in the effect of diphenoxylate to slow gastric motility compared with control mice ($P=0.02$) [193]. In a randomized cross-over trial, when human volunteers received 130 mg of dextropropoxyphene followed in 5 min with 50 g of AC or control, the area under the plasma concentration-time curve was reduced by 92% ($P<0.001$) [196]. In this same model, multiple-dose AC beginning at 6 h post-ingestion only had a small effect on elimination half-life ($P<0.05$) [196]. In a similar study, the immediate administration of 4 g of AC after 130 mg of dextropropoxyphene reduced the area under the plasma concentration-time curve by 59% compared to control ($P<0.001$) [197]. In a randomized crossover study, human volunteers took 100 mg of pholcodine (an opioid antitussive) syrup with water and either 25 g of AC immediately, 25 g of AC at 2 h or multiple-dose AC starting at 5 h. Compared with control, immediate AC reduced the area under the plasma concentration-time curve by 91% ($P<0.0005$), but the area under the plasma concentration-time curve was only reduced by 26% when AC was delayed by 2 h. The administration of multiple-dose AC with a delay of 5 h to the first dose only reduced the area under the plasma concentration-time curve by 17% ($P=0.06$), but reduced the ($P=0.006$) [198]. Although naloxone is readily available and highly effective, prolonged use of naloxone in high dependency or critical care beds requires monitoring and can be costly. The overall benefit of the administration of AC versus naloxone (cost effectiveness) needs to be weighed on a case-by-case basis according to local resources, suspected ingested dose and opioid formulations. The Workgroup discussed that the early administration of AC could limit the duration or prevent severe toxicity, especially with ingestions of modified release products, as long as airway protection issues are addressed.

- For ingestions of immediate-release opioids with a dose threshold of five therapeutic doses, we suggest single-dose AC for up to 1 h post-ingestion (2, D).
- For ingestions of immediate-release opioids with a dose threshold of five therapeutic doses, an individualized risk assessment is required for single-dose AC administration between 1 h and 4 h post-ingestion.
- For ingestions of immediate-release opioids with a dose threshold of five therapeutic doses, we suggest against single-dose AC at ≥5 h post-ingestion (2, D).
- For ingestions of modified-release opioids with a dose threshold of five therapeutic doses, we suggest single-dose AC for up to 2 h post-ingestion (2, D).
- For ingestions of modified-release opioids with a dose threshold of five therapeutic doses, an individualized risk assessment is required for single-dose AC administration beyond 2 h post-ingestion.
- For ingestions of immediate-release opioids, we suggest against additional-dose AC administration (2, D).
- For ingestions of modified-release opioids, an individualized risk assessment is required for additional-dose AC administration beyond 2 h post-ingestion.
- For ingestions of either immediate or modified release opioids, we recommend against multiple-dose AC administration (1, D).

Organophosphorus insecticides

Evidence to decision rationale

Fenitrothion, tolelofos methyl, piperophos, and salithion are all well adsorbed to AC *in vitro* [199]. While the immediate administration of multiple-dose AC to rats produced a statistically significant reduction in the fenitrothion area under the plasma concentration-time curve (*P* not reported), this effect was lost when the first dose of multiple-dose AC was delayed 1.5 h after administration [199]. In a retrospective study of 198 patients with organophosphorus insecticide ingestion, the authors were unable to show either benefit or harm of AC [200]. In a randomized trial of single-dose AC versus multiple-dose AC versus no AC in poisoned patients in Sri Lanka, a subgroup analysis of the 4,629 patients with organophosphorus insecticide ingestion was unable to demonstrate a benefit of any AC regimen [73]. Owing to this lack of benefit, the data above, combined with rapid absorption of organophosphorus insecticides, and the frequent emesis and airway concerns associated with toxicity, the Workgroup made a weak rec-

ommendation against the administration of additional-dose AC, and a strong recommendation against the administration of multiple-dose AC, regardless of the dose ingested.

- For ingestions of organophosphorus insecticides, we suggest single-dose AC for up to 2 h post-ingestion (2, D).
- For ingestions of organophosphorus insecticides, an individualized risk assessment is required for single-dose AC administration between 2 h and 6 h post-ingestion (2, D).
- For ingestions of organophosphorus insecticides, we suggest against single-dose AC administration beyond 6 h post-ingestion (2, D).
- For ingestions of organophosphorus insecticides, we suggest against additional-dose AC administration (2, D).
- For ingestions of organophosphorus insecticides, we suggest against multiple-dose AC administration (2, D).

Paracetamol (acetaminophen)

Evidence to decision rationale

The toxic dose threshold for paracetamol is well established. Ingestions less than 10 g in adults or 200 mg/kg in children rarely produce plasma/serum concentrations that require antidotal treatment [201]. In contrast, doses much greater than 350–500 mg/kg may cause hepatotoxicity despite antidotal treatment [202]. Although the 200 mg/kg threshold has been widely accepted and used for many years [203], there is less certainty about higher risk thresholds, and this is reflected in the conservative threshold chosen for an additional-dose AC. The systematic review [5] highlighted two clinical studies as providing data to support the administration of AC beyond 1 h post-ingestion [201,202]. Benefit was most pronounced in the first 2 h, but smaller benefits exist beyond this, reflecting slower absorption in overdose, which in turn is determined by total dose and formulation [204]. This was supported by several volunteer studies demonstrating pharmacokinetic efficacy of AC at 2 h post-ingestion [205–209], and one at 3 h [208]. Additionally, one retrospective study demonstrated a statistically significantly reduced odds ratio of requiring *N*-acetylcysteine if AC was given up to 3 h post-ingestion [210]. A high maximum adsorption capacity of paracetamol to AC, ranging from 624 to 723 mg/g AC depending on the AC type, was demonstrated *in vitro* [211]. The Workgroup discussed that the antidote *N*-acetylcysteine is most often given intravenously. As the Rumack-Matthew nomogram requires a 4 h plasma paracetamol concentration to initiate acetylcysteine therapy [212], the role of AC in patients with early paracetamol ingestions potentially reduces the amount of paracetamol absorption sufficiently enough to obviate the subsequent need for acetylcysteine antidotal therapy. It is noteworthy that the current Australia and New Zealand guidelines further extend that time frame for modified-release paracetamol and following massive ingestions [202,213].

- For immediate-release paracetamol ingestions ≥200 mg/kg, we recommend single-dose AC for up to 2 h post-ingestion (1, B) and suggest single-dose AC for up to 3 h post-ingestion (2, B).
- For immediate-release paracetamol ingestions, we suggest against single-dose AC >6 h post-ingestion. (2, B)
- For modified-release paracetamol ingestions ≥200 mg/kg, we recommend single-dose AC for up to 5 h post-ingestion (1, B) and suggest single-dose AC for up to 6 h post-ingestion (2, B).
- For all other time points and doses, an individualized risk assessment is required for single-dose AC administration.
- For immediate-release paracetamol ingestions ≥350 mg/kg, we recommend additional-dose AC (1, D).
- For modified-release paracetamol ingestions ≥300 mg/kg, we recommend additional-dose AC (1, D).
- For both immediate- and modified-release paracetamol ingestions, we recommend against multiple-dose AC (1, B).

Paraquat

Evidence to decision rationale

Paraquat is a highly lethal poison that lacks any clearly effective antidote. It is well adsorbed to AC [214–216]. In one rat model, simultaneous administration of AC and paraquat reduced lethality compared to control (0/6 versus 6/6) ($P<0.05$), and this effect persisted even when the delay to AC administration was as long as 3 h [216]. While results vary in different animal models, there is an overall trend toward a protective effect of AC [214,217]. When AC was given to rabbits 2 h after paraquat, the area under the plasma concentration-time curve was reduced by 39% ($P<0.05$) [218]. In a similar animal model, the benefit of AC only achieved statistical significance when combined with magnesium citrate ($P<0.01$) [214]. There were no human data identified to quantify the clinical or pharmacokinetic effect of single-dose AC, additional-dose AC, or multiple-dose AC on paraquat absorption or elimination [5]. Paraquat doses greater than 5–10 mg/kg (i.e., about 10 mL of a 20% product) are highly lethal [219], and even smaller reported doses have been fatal. Peak concentrations generally occur within 4 h [220].

- For ingestions of paraquat with a dose threshold of 5 mg/kg, we recommend single-dose AC administration for up to 3 h post-ingestion (1, D).
- For ingestions of paraquat with a dose threshold of 5 mg/kg, we suggest single-dose AC administration for up to 4 h post-ingestion (1, D).
- For ingestions of paraquat at other doses and time intervals, an individual risk assessment is required for single-dose AC administration.
- For paraquat ingestions with a dose threshold of 40 mg/kg, we suggest additional-dose AC administration (2, D).
- For ingestions of paraquat, an individual risk assessment is required for multiple-dose AC administration.

Phenobarbital

Evidence to decision rationale

The toxic dose of phenobarbital varies between individuals largely based on tolerance, but naïve adult doses of 2–4 g reportedly cause moderate toxic effects, and doses greater than 5 g in total are expected to be associated with severe toxicity [221]. In children, oral doses in excess of 5 mg/kg are of concern. Phenobarbital is well adsorbed to AC *in vitro*, with variations in maximum adsorption capacity related to AC surface area. Published maximum adsorption capacities range from 200 to 400 mg/g AC for typical surface area AC and approach 1 g/g AC for higher surface area AC preparations [222–225]. A randomized crossover volunteer study confirmed this relationship [226]. When human volunteers were given single-dose AC 5 min after phenobarbital, there was a 97% reduction in the area under the plasma concentration-time curve compared to controls [110]. However, when single-dose AC was delayed to 1 h post-ingestion in the same volunteers, the reduction in AUC was

only 47%. There were no controlled studies evaluating single-dose AC dosing beyond 1 h post-ingestion. Several multiple-dose AC studies demonstrated a reduction in the elimination half-life by as much as 50% in one [227,228] and from 148 h without multiple-dose AC to 19 h with multiple-dose AC [229]. The most influential study randomized actual overdose patients to single-dose AC to multiple-dose AC [230]. The multiple-dose AC group had a shorter elimination half-life (36 h versus 93 h, $P<0.01$) that returned to baseline after multiple-dose AC ended. These data were sufficient for the Workgroup to recommend single-dose AC with the recognition that many of the sickest patients will require airway protection and nasogastric administration of the AC.

- For ingestions of phenobarbital with a dose threshold of 20 mg/kg, we recommend single-dose AC administration for up to 3 h post-ingestion (1, C).
- For ingestions of phenobarbital with a dose threshold of 20 mg/kg, an individual risk assessment is required for single-dose AC administration between 3 h and 6 h post-ingestion.
- For ingestions of phenobarbital with a dose threshold of 20 mg/kg, we suggest against single-dose AC administration beyond 6 h post- ingestion (2, C).
- For ingestions of phenobarbital with a dose threshold of 50 mg/kg, we suggest additional-dose AC administration (2, D).
- For ingestions of phenobarbital with a dose threshold of 50 mg/kg, we recommend multiple-dose AC administration (2, C).

Phenytoin

Evidence to decision rationale

Loading doses of phenytoin are 10–15 mg/kg, and doses on the order of 40–50 mg/kg cause lethargy and ataxia but are rarely life-threatening. *In vitro* adsorption of phenytoin to AC was demonstrated in an equilibrium dialysis model [231]. When human volunteers were given single-dose AC 5 min after oral phenytoin, the area under the plasma concentration-time curve was reduced by 99% ($P<0.01$) [120]. In actual overdose patients, single-dose AC did not reduce the duration of phenytoin toxicity in hospitalized patients [232].

Following intravenous administration of 10 mg/kg of phenytoin to rats, multiple-dose AC had little effect on enhancing elimination. However, multiple-dose AC given after an intravenous phenytoin dose of 50 mg/kg reduced the area under the plasma concentration-time curve by 25% ($P<0.01$) [233]. This effect may have resulted from the amount of free drug available for clearance by multiple-dose AC. When human volunteers were given multiple-dose AC after a 15 mg/kg intravenous dose of phenytoin, the elimination half-life was reduced from 44.5 h in controls to 22.3 h in those given multiple-dose AC ($P<0.001$) [234]. In a similar study, multiple-dose AC reduced the area under the plasma concentration-time curve in volunteers given intravenous phenytoin by 25% compared to controls ($P=0.008$) [235]. When actual overdose patients were given multiple-dose AC, the median time to return to reach a therapeutic phenytoin concentration was reduced from 41.1 h in the control group to 19.3 h in patients given multiple-dose AC ($P=0.049$) [236]. While phenytoin overdose is rarely lethal, the zero-order development of Michaelis-Menten kinetics prolongs elimination and often results in long hospitalizations that consume critical beds. Given the absence of alternative therapies, these data were sufficient for the Workgroup to conclude that single-dose AC and multiple-dose AC could decrease the overall toxic burden with the potential to shorten hospital or intensive care unit length of stay.

- For ingestions of immediate-release phenytoin with a dose threshold of 40 mg/kg, we recommend single-dose AC administration for up to 1 h post-ingestion (1, D).
- For ingestions of immediate-release phenytoin with a dose threshold of 40 mg/kg, we suggest single-dose AC administration for up to 2 h post-ingestion (2, D).
- For ingestions of immediate-release phenytoin with a dose threshold of 40 mg/kg, an individualized risk assessment is required for single-dose AC administration between 3 h and 5 h post-ingestion.
- For ingestions of immediate-release phenytoin with a dose threshold of 40 mg/kg, we suggest against single-dose AC administration beyond 5 h post-ingestion (2, D).
- For ingestions of modified-release phenytoin with a dose threshold of 40 mg/kg, we recommend single-dose AC administration for up to 3 h post-ingestion (1, D).
- For ingestions of modified-release phenytoin with a dose threshold of 40 mg/kg, we suggest single-dose AC administration for up to 4 h post-ingestion (1, D).
- For ingestions of modified-release phenytoin with a dose threshold of 40 mg/kg, an individualized risk assessment is required for single-dose AC administration beyond 4 h post-ingestion.
- For ingestions of either immediate or modified-release phenytoin, an individualized risk assessment is required for additional-dose AC administration.
- For ingestions of either immediate- or modified-release phenytoin, we suggest multiple-dose AC administration (2, D).

Quinine and quinidine

Evidence to decision rationale

The *in vitro* adsorption of quinine and quinidine to AC is supported by several studies [133,237]. In one *in vitro* study, a 5:1 AC:quinidine ratio adsorbed 84% of the drug [238]. When rabbits were given single-dose AC immediately after quinine or quinidine, the area under the plasma concentration-time curve for quinidine was reduced by 27% ($P<0.05$), which corresponded to a shorter elimination half-life and a larger elimination constant (k_e) [239]. None of the pharmacokinetic parameters for quinine reached statistical significance. When single-dose AC was given to human volunteers 5 min after ingesting quinidine, the bioavailability was reduced by 99% compared to control ($P<0.01$) [238]. Administration of multiple-dose AC beginning at 4 h post-ingestion of quinine reduced the elimination half-life by 45% ($P<0.001$) and reduced the area under the plasma concentration-time curve by 32% ($P<0.05$) [240]. Although these data are limited, when combined with significant toxicity following overdose and a lack of an effective antidote, the Workgroup concluded that single-dose AC could decrease the overall toxic burden of these drugs.

Quinidine

- For ingestions of immediate-release quinidine with a dose threshold of 750 mg, we recommend single-dose AC administration for up to 1 h post-ingestion (1, D).
- For ingestions of immediate-release quinidine with a dose threshold of 750 mg, we suggest single-dose AC administration for up to 2 h post-ingestion (2, D).

- For ingestions of immediate-release quinidine with a dose threshold of 750 mg, an individualized risk assessment is required for single-dose AC administration between 3 h and 5 h post-ingestion.
- For ingestions of immediate-release quinidine with a dose threshold of 750 mg, we suggest against single-dose AC administration ≥6 h post-ingestion (2, D).
- For ingestions of modified-release quinidine with a dose threshold of 750 mg, we recommend single-dose AC administration for up to 3 h post-ingestion (1, D).
- For ingestions of modified-release quinidine with a dose threshold of 750 mg, we suggest single-dose AC administration for up to 4 h post-ingestion (2, D).
- For ingestions of modified-release quinidine with a dose threshold of 750 mg, an individualized risk assessment is required for single-dose AC administration beyond 4 h post-ingestion.
- For ingestions of either immediate- or modified-release quinidine, an individualized risk assessment is required for additional-dose AC administration.
- For ingestions of either immediate- or modified-release quinidine, an individualized risk assessment is required for multiple-dose AC administration.

Quinine

- For ingestions of immediate-release quinine with a dose threshold of 20 mg/kg, we recommend single-dose AC administration for up to 1 h post-ingestion (1, D).
- For ingestions of immediate-release quinine with a dose threshold of 20 mg/kg, we suggest single-dose AC administration for up to 2 h post-ingestion (2, D).
- For ingestions of immediate-release quinine with a dose threshold of 20 mg/kg, an individualized risk assessment is required for single-dose AC administration between 3 h and 5 h post-ingestion.
- For ingestions of immediate-release quinine with a dose threshold of 20 mg/kg, we suggest against single-dose AC administration ≥6 h post-ingestion (2, D).
- For ingestions of modified-release quinine with a dose threshold of 20 mg/kg, we recommend single-dose AC administration up to 3 h post-ingestion (1, D).
- For ingestions of modified-release quinine with a dose threshold of 20 mg/kg, we suggest single-dose AC administration for up to 4 h post-ingestion (2, D).
- For ingestions of modified-release quinine with a dose threshold of 20 mg/kg, an individualized risk assessment is required for single-dose AC administration beyond 4 h post-ingestion.
- For ingestions of either immediate- or modified-release quinine, an individualized risk assessment is required for additional-dose AC administration.
- For ingestions of either immediate- or modified-release quinine, an individualized risk assessment is required for multiple-dose AC administration.

Salicylates

Evidence to decision rationale

Acute acetylsalicylic acid ingestions of greater than 150 mg/kg or 6.5 g of acetylsalicylic acid equivalents are likely to produce adverse effects, and doses greater than 500 mg/kg are potentially lethal [241]. Salicylate adsorption to AC is well established *in vitro*, with maximum adsorption capacities reported as large as 500 mg/g AC [5,81,142,152,155,237,238,242–256]. Animal studies of the administration of single-dose AC showed various results ranging from no statistical benefit [257] to absorption reductions of 50% or greater [248,258–261]. Several animal studies evaluated the administration of multiple-dose AC following intravenous salicylic acid administration. Three studies failed to show a reduction in the area under the plasma concentration-time curve [262–264]. In contrast, one study demonstrated a statistically significant 39% reduction in elimination half-life ($P<0.05$) and a statistically significant 40% reduction in the area under the plasma concentration-time curve ($P<0.05$) [265]. Numerous human volunteer studies demonstrate an effect of single-dose AC up to 1 h post-ingestion, with reported reductions in absorption from as little as 25% or less [83,266–269] to greater than 75% [120,238,270]. In one human volunteer study, both multiple-dose AC given at 1 h and 5 h post-ingestion and multiple-dose AC given at 1, 5, and 9 h post-ingestion significantly reduced the area under the plasma concentration-time curve more than single-dose AC given at 1 h h post-ingestion ($P<0.01$) [269]. In two volunteer studies that gave multiple-dose AC beginning at 4 h post-ingestion and continued at 6, 8, and 10 h, there was no significant difference in the area under the plasma concentration-time curve [271,272]. In a similar human volunteer study, multiple-dose AC reduced the area under the plasma concentration-time curve by only 8% ($P<0.05$) [273]. Finally, when human volunteers were given AC immediately following ingestion, followed by multiple-dose AC every 4 h for 24 h, a statistically significant reduction in the area under the plasma concentration-time curve was reported ($P=0.028$) [274]. Salicylate ingestion can be lethal, with haemodialysis as the only definitive therapy in life-threatening cases. Unfortunately, haemodialysis is neither universally nor immediately available, and other therapies are required. Salicylates are well absorbed to AC. In addition, the Workgroup assessed that as no specific antidote exists and urine alkalinization is limited by plateau effects in its ability to eliminate salicylate [275] and is dependent on several factors such as potassium concentration and kidney function. Thus, the Workgroup concluded that single-dose AC could decrease the overall toxic burden of salicylate ingestions (up to 2 h for immediate-release preparations and 3 h for modified-release preparations). Because lethal ingestions often exceed the adsorptive capacity of a standard dose of AC, the Workgroup concluded that salicylate ingestion was an ideal example of when additional-dose AC was indicated.

- For ingestions of immediate-release salicylates with a dose threshold of 200 mg/kg, we recommend single-dose AC administration for up to 2 h post-ingestion (1, C).
- For ingestions of immediate-release salicylates with a dose threshold of 200 mg/kg, we suggest single-dose AC administration for up to 4 h post-ingestion (2, C).
- For ingestions of immediate-release salicylates with a dose threshold of 200 mg/kg, an individualized risk assessment is required for single-dose AC administration between 5 h and 6 h post-ingestion.
- For ingestions of immediate-release salicylates with a dose threshold of 200 mg/kg, we suggest against single-dose AC administration beyond 6 h post-ingestion (2, C).
- For ingestions of modified-release salicylates with a dose threshold of 200 mg/kg, we recommend single-dose AC administration for up to 3 h post-ingestion (1, C).
- For ingestions of modified-release salicylates with a dose threshold of 200 mg/kg, we suggest single-dose AC administration for up to 5 h post-ingestion (2, C).

- For ingestions of modified-release salicylates with a dose threshold of 200 mg/kg, an individualized risk assessment is required for single-dose AC administration beyond 5 h post-ingestion.
- For ingestions of immediate-release salicylates with a dose threshold of 500 mg/kg, we suggest additional-dose AC administration (1, D).
- For ingestions of modified-release salicylates with a dose threshold of 350 mg/kg, we suggest additional-dose AC administration (1, D).
- For ingestions of either immediate- or modified-release salicylates, an individualized risk assessment is required for multiple-dose AC administration.

Selective serotonin reuptake inhibitors (excluding bupropion and venlafaxine)

Evidence to decision rationale

Doses greater than five times the lowest adult initial therapeutic dose of any selective serotonin reuptake inhibitor merit emergency department referral [276].

Fluoxetine. *In vitro* studies demonstrate that fluoxetine is adsorbed by AC [277–280]. In rats given AC 15 min after fluoxetine, the amount of drug eliminated decreased 87.4% compared to controls (*P* not reported) [281]. In human volunteers, when AC was administered immediately after fluoxetine, the area under the plasma concentration-time curve was reduced by more than 96% ($P < 0.0005$), and the maximal plasma or serum concentration was reduced by more than 98% ($P < 0.0005$). When the administration of AC was delayed 2 h or 4 h, the reduction in the area under the plasma concentration-time curve did not reach statistical significance. Neither the maximal plasma nor serum concentration nor the elimination half-life of fluoxetine was significantly reduced by late administration of AC [282].

Escitalopram. In overdose patients, single-dose AC reduced the fraction of escitalopram absorbed by 31% and reduced the individual predicted area under the plasma concentration-time curve adjusted for dose. Administration of single-dose AC reduced QT interval prolongation and reduced the risk of having an abnormal QT interval by approximately 35% for escitalopram doses above 200 mg [283].

Sertraline. In overdose patients, single-dose AC given up to 4 h after ingestion increased the clearance of sertraline by a factor of 1.9, decreased the area under the plasma concentration-time curve and decreased the maximal plasma or serum concentration [284].

Paroxetine. In a human volunteer study, single-dose AC reduced the area under the plasma concentration-time curve, the maximal plasma or serum concentration, time to maximum concentration, and elimination half-life of paroxetine when given within 1 h of ingestion [285].

Citalopram. In overdose patients, administration of AC increased citalopram clearance by 72% and decreased bioavailability by 22% [286]. In another study of patients with citalopram overdose, the estimated relative risk of having an abnormal QT interval, RR interval combination in those given single-dose AC compared to no single-dose AC was 0.28 (95% CI: 0.06-0.70) [67].

Thus, for the majority of selective serotonin reuptake inhibitors studied, the evidence for the administration of single-dose AC is based on changes in pharmacokinetic parameters. Outcome data exists for escitalopram in terms of a reduction in QT interval prolongation. Given the risks of toxicity, especially from escitalopram and citalopram and the absence of a specific antidote or other effective therapy, the Workgroup recommends the use of single-dose AC in larger ingestions of these drugs but recommends against additional-dose AC and multiple-dose AC because of the absence of clear rationale or data and the risks associated with subsequent administration of AC in patients with seizure risks.

- For ingestions of immediate-release selective serotonin reuptake inhibitors with a dose threshold of 15 therapeutic doses, we recommend single-dose AC administration for up to 30 min post-ingestion (1, C).
- For ingestions of immediate-release selective serotonin reuptake inhibitors with a dose threshold of 15 therapeutic doses, we suggest single-dose AC administration for up to 2 h post-ingestion (2, C).
- For ingestions of immediate-release selective serotonin reuptake inhibitors with a dose threshold of 15 therapeutic doses, an individualized risk assessment is required for single-dose AC administration between 3 h and 5 h post-ingestion.
- For ingestions of immediate-release selective serotonin reuptake inhibitors with a dose threshold of 15 therapeutic doses, we suggest against single-dose AC administration at 6 h post-ingestion (2, C).
- For ingestions of immediate-release selective serotonin reuptake inhibitors with a dose threshold of 15 therapeutic doses, we recommend against single-dose AC administration beyond 6 h post-ingestion (1, C).
- For ingestions of modified-release selective serotonin reuptake inhibitors with a dose threshold of 15 therapeutic doses, we recommend single-dose AC administration for up to 1 h post-ingestion (1, C).
- For ingestions of modified-release selective serotonin reuptake inhibitors with a dose threshold of 15 therapeutic doses, we suggest single-dose AC administration for up to 4 h post-ingestion (2, C).
- For ingestions of modified-release selective serotonin reuptake inhibitors with a dose threshold of 15 therapeutic doses, an individualized risk assessment is required single-dose AC administration beyond 4 h post-ingestion.
- For ingestions of immediate-release selective serotonin reuptake inhibitors with a dose threshold of ≤20 therapeutic doses, we suggest against additional-dose AC administration (2, D).
- For ingestions of modified-release selective serotonin reuptake inhibitors, an individualized risk assessment is required for additional-dose AC administration.
- For ingestions of either immediate- or modified-release selective serotonin reuptake inhibitors, we suggest against multiple-dose AC administration (2, D).

Sulfonylureas

Evidence to decision rationale

Sulfonylureas are generally well adsorbed to AC. In one *in vitro* study, the following maximum adsorption capacities were determined: carbutamide, 460 mg/g AC; chlorpropamide, 420 mg/g AC; tolazamide,

450 mg/g AC; tolbutamide, 470 mg/g AC; glipizide, 500 mg/g AC [287]. In the same study, glibenclamide was reported to be well adsorbed to AC, but the maximum adsorption capacity was not given [287]. When healthy volunteers were randomized to ingestion of tolbutamide followed either by water or AC 5 min post-ingestion, the area under the plasma concentration-time curve was reduced by 89% (P <0.001) [288]. In a similar study, volunteers who ingested chlorpropamide were randomized to single-dose AC at 5 min post-ingestion or multiple-dose AC starting at 6 h post-ingestion and continuing every 6 h for 54 h. Compared to control, single-dose AC reduced the area under the plasma concentration-time curve by 81% (P <0.001), but multiple-dose AC reduced the area under the plasma concentration-time curve by 7.4% (P = not significant) [289]. Likewise, when volunteers were randomized to ingestion of glipizide followed immediately by water or single-dose AC, the area under the plasma concentration-time curve was reduced 81% by single-dose AC (P <0.01) [290]. The risks of prolonged or repeated hypoglycemia with potentially devastating neurological injury led the Workgroup to recommend the administration of single-dose AC in an attempt to lower the toxic burden, but recommend against additional-dose AC and multiple-dose AC because the ingested doses are usually small compared to the adsorptive capacity of AC.

- For ingestions of sulfonylureas with a dose threshold of five therapeutic doses, we recommend single-dose AC administration for up to 1 h post-ingestion (1, D).
- For ingestions of sulfonylureas with a dose threshold of five therapeutic doses, we suggest single-dose AC administration for up to 2 h post-ingestion (2, D).
- For ingestions of sulfonylureas with a dose threshold of five therapeutic doses, we suggest against single-dose AC administration beyond 6 h post-ingestion (2, D).
- For all other doses and time periods, an individualized risk assessment is required for single-dose AC administration.
- For ingestions of sulfonylureas with a dose threshold of less than or equal to nine therapeutic doses, we suggest against additional-dose AC administration (2, D).
- For ingestions of sulfonylureas, we suggest against multiple-dose AC administration (2, D).

Thallium

Evidence to decision rationale

Unlike many metals, thallium salts are well adsorbed to AC *in vitro* [291]. Rats given oral thallium sulphate eliminated 53% of the ingested dose in their faeces by day 8. When single-dose AC was added at an unreported time, faecal elimination increased to 93% by day 8 [292]. In a similar controlled study, there was no difference in faecal elimination between rats that were given thallium nitrate alone or those given AC at 6 h and 24 h post-ingestion [293]. Finally, rats given thallium sulphate were either given no antidotal therapy or multiple-dose AC twice per day for 5 days starting one day after ingestion. The rats given multiple-dose AC excreted 82% more thallium in their stool than the control rats [294]. In the same study, at a 20 mg/kg dose of thallous sulphate, lethality was decreased from 67% in the control group to 10% in the multiple-dose AC group [294]. At a greater thallium dose, the benefit of multiple-dose AC was lost. There are no human data to quantify either the clinical or pharmacokinetic numerical effects of single-dose AC, additional-dose AC, or multiple-dose AC. Although Prussian blue is an effective antidote in thallium poisoning, it has limited availability, and the sequelae of poisoning are severe. Based on the benchwork and animal data and a risk analysis the Workgroup concluded in favor of single-dose AC, additional-dose AC, and multiple-dose AC as reasonably safe methods to reduce the toxic burden of this poisoning. The Workgroup notes that no comparisons were made between AC and Prussian Blue because not only was that outside the scope of the mandated work but also because the availability of Prussian Blue differs worldwide.

- For ingestions of thallium with a dose threshold of 10 mg/kg, we suggest single-dose AC administration for up to 1 h post-ingestion (2, D).
- For all other doses and time periods, an individualized risk assessment is required for single-dose AC administration.
- For ingestions of thallium with a dose threshold of 50 mg/kg, we recommend additional-dose AC administration (1, D).
- For ingestions of thallium with a dose threshold of 10 mg/kg, we suggest multiple-dose AC administration (2, D).

Theophylline (and aminophylline)

Evidence to decision rationale

Ingested theophylline doses of greater than 10 mg/kg are associated with adverse clinical effects, with serious effects or death occurring at ingested doses of greater than 45 mg/kg. It should be noted that chronic poisonings resulting from repeated ingestions of lower doses are also associated with worse outcomes per given concentration than acute overdoses [295]. Several *in vitro* studies demonstrate strong adsorption of theophylline to AC [244,296–300]. Human volunteer studies demonstrated a statistically significant decrease in absorption of theophylline following single-dose AC when compared to no AC [296,301–303]. Administration of single-dose AC given 30–60 min post-ingestion reduced the area under the plasma concentration-time curve from 51% (P <0.001) [296] to 75% (P = 0.001) [303] compared with control. Although not formally studied, additional-dose AC may be beneficial in the setting of ingestions of theophylline in which AC is indicated because standard single-dose AC dosing may fail to achieve optimal binding ratios for preventing absorption. Multiple studies demonstrate that multiple-dose AC can significantly reduce the area under the plasma concentration-time curve, maximal plasma or serum concentration, time to maximum concentration, elimination half-life of theophylline, and increase its clearance of theophylline [296,301,304–314]. Once again, haemodialysis as the only definitive therapy in life-threatening cases. Unfortunately, haemodialysis is neither universally nor immediately available, and other therapies are required. Given that theophylline is well adsorbed to AC and that there is no specific antidote, and poisoning can be lethal, the Workgroup concluded that single-dose AC could decrease the overall toxic burden. Because lethal ingestions often exceed the adsorptive capacity of a standard dose of AC, the Workgroup concluded that theophylline ingestion was an ideal example of when additional-dose AC was indicated. Additionally, given the strong experimental data, the Workgroup was also supportive of multiple-dose AC to enhance the clearance of absorbed theophylline.

- For ingestions of immediate-release theophylline with a dose threshold of 20 mg/kg, we recommend single-dose AC administration for up to 2 h post-ingestion (1, C).
- For ingestions of immediate-release theophylline with a dose threshold of 20 mg/kg, we suggest single-dose AC administration for up to 3 h post-ingestion (2, C).
- For ingestions of immediate-release theophylline with a dose threshold of 20 mg/kg, an individualized risk assessment is required for single-dose AC administration beyond 3 h post-ingestion.

- For ingestions of modified-release theophylline with a dose threshold of 20 mg/kg, we recommend single-dose AC administration for up to 3 h post-ingestion (1, C).
- For ingestions of modified-release theophylline with a dose threshold of 20 mg/kg, we suggest single-dose AC administration for up to 6 h post-ingestion (2, C).
- For ingestions of modified-release theophylline with a dose threshold of 20 mg/kg, an individualized risk assessment is required for single-dose AC administration beyond 6 h post-ingestion.
- For ingestions of immediate-release theophylline with a dose threshold of 40 mg/kg, we suggest additional-dose AC administration (2, D).
- For ingestions of modified-release theophylline with a dose threshold of 50 mg/kg, we suggest additional-dose AC administration (2, D).
- For ingestions of either immediate- or modified-release theophylline with a dose threshold of 50 mg/kg, we recommend multiple-dose AC administration (1, C).

Toxic alcohols

Evidence to decision rationale

There is no evidence that any of the common toxic alcohols (methanol, isopropanol, and ethylene glycol) are significantly adsorbed to activated charcoal, and no animal or human data to support the administration of single-dose AC, additional-dose AC, or multiple-dose AC in patients with toxic alcohol poisoning. Taking into account the fast systemic absorption of toxic alcohols and the large doses required to produce toxicity, the lack of data in support of AC and the ready availability of antidotes, the Workgroup concluded that the balance of risks and benefits does not favour administration of AC in patients who have ingested toxic alcohols.

- For ingestions of toxic alcohols, we recommend against single-dose AC (1, D).
- For ingestions of toxic alcohols, we recommend against additional-dose AC (1, D).
- For ingestions of toxic alcohols, we recommend against multiple-dose AC (1, D).

Tricyclic antidepressants

Evidence to decision rationale

Tricyclic antidepressants are associated with a rapid onset of symptoms and high lethality in overdose. Several *in vitro* studies demonstrate adsorption of tricyclic antidepressants to AC [238,242,245,299,315–320]. In one trial, the incidence of toxic symptoms (systolic blood pressure <100 mmHg, dysrhythmias, Grade II coma, Grade IV coma, seizures, intubation, mechanical ventilation, intubation >8 h, patients needing >48 h in intensive care unit and >3 days at hospital) were more frequent in the patient group not receiving AC as part of treatment but was not statistically significant. Similarly, the difference in improvement measured using clinical outcome, such as the Glasgow Coma Scale, was non-significant (pooled results) in a group of patients overdosed on benzodiazepines, barbiturates or imipramine [321]. In actual overdose patients, there was a direct correlation between the time of AC administration and the reduction in the elimination half-life of amitriptyline [322]. The administration of multiple-dose AC reduced primarily pharmacokinetic parameters, the area under the plasma concentration-time curve, and elimination half-life for amitriptyline, nortriptyline, and doxepin compared with no AC [315,323–326]. For doxepin, the elimination half-life and maximal plasma or serum concentration, but not the area under the plasma concentration-time curve, were reduced compared to single-dose AC [326]. Actual patient cases showed great variation both inter- and intraindividual in elimination half-life of amitriptyline following overdose, but with patients also receiving orogastric lavage, the specific effect of AC treatment is difficult to extract [327,328]. In dothiepin overdoses, the elimination half-life was shorter in patients receiving multiple-dose AC (10.6 h-13.1 h) compared to single-dose AC (23.0 h-23.5 h) and no AC (28.6 h) [329].

- For ingestions of tricyclic antidepressants with a dose threshold of 10 mg/kg, we recommend single-dose AC administration for up to 2 h post-ingestion (1, D).
- For ingestions of tricyclic antidepressants with a dose threshold of 10 mg/kg, we suggest single-dose AC administration for up to 3 h post-ingestion (2, D).
- For ingestions of tricyclic antidepressants, suggest against single-dose AC administration beyond 6 h post-ingestion (2, D).
- For all other doses and time periods, an individualized risk assessment is required for single-dose AC administration.
- For ingestions of tricyclic antidepressants, an individualized risk assessment is required for additional-dose AC administration.
- For ingestions of tricyclic antidepressants, we suggest against multiple-dose AC administration (2, D).

Valproic acid

Evidence to decision rationale

Ingestion of valproic acid in doses greater than 50 mg/kg is associated with the risk of adverse clinical effects, and doses greater than 750 mg/kg with death. No studies demonstrating *in vitro* adsorption of valproate to AC were found. A human volunteer study demonstrated significant reductions in the maximal plasma or serum concentration and the area under the plasma concentration-time curve when single-dose AC was given immediately after ingestion ($P < 0.01$) [288]. There is no evidence evaluating additional-dose AC for valproic acid overdoses, but based on the fact that valproic acid is typically dosed in hundreds of mg, it is reasonable to expect that standard AC doses will not achieve optimal binding ratios. While the pharmacological properties of valproic acid suggest that large overdoses might benefit from multiple-dose AC, a human volunteer study of 300 mg valproic acid ingestions found no significant difference in pharmacokinetic parameters between groups receiving multiple-dose AC starting at 4 h post-ingestion or no AC [330]. As noted above for some other poisons, haemodialysis is useful in patients with the most severe forms of valproic acid poisoning, but it is not universally or immediately available.

- For ingestions of either immediate- or modified-release valproic acid at a dose threshold of 200 mg/kg, we recommend single-dose AC administration for up to 1 h post-ingestion (1, D).
- For ingestions of immediate-release valproic acid at a dose threshold of 200 mg/kg, we suggest single-dose AC administration for up to 3 h post-ingestion (2, D).
- For ingestions of immediate-release valproic acid at a dose threshold of 200 mg/kg, we suggest against single-dose AC administration beyond 6 h post-ingestion (2, D).

- For ingestions of modified-release valproic acid at a dose threshold of 200 mg/kg, we suggest single-dose AC administration for up to 4 h post-ingestion (2, D).
- For ingestions of either immediate or modified release valproic acid at other doses and time intervals, an individualized risk assessment is required for single-dose AC administration.
- For ingestions of either immediate or modified release valproic acid at a dose threshold of >400 mg/kg, we suggest additional-dose AC administration (2, D).
- For ingestions of either immediate- or modified-release valproic acid, an individualized risk assessment is required for multiple-dose AC administration.

Venlafaxine

Evidence to decision rationale

Venlafaxine doses >5.5 mg/kg are associated with risk of adverse clinical effects; In adults, doses >1,500 mg risk seizures, and doses >8,000 mg risk ventricular dysrhythmias [331,332]. The Workgroup did not identify any *in vitro* models describing the adsorption of venlafaxine to AC. In addition, no animal studies were identified. One study used toxicokinetic modelling based on 339 blood concentrations obtained in 76 venlafaxine overdose events to determine the role of single-dose AC in poisoning [333]. Compared to patients who received no decontamination, venlafaxine clearance was increased by 35% (*P* not reported) in those treated with single-dose AC. Although reductions in the area under the plasma concentration-time curve and the maximal plasma or serum concentration are noted, values are not provided [333]. Although uncommon, venlafaxine overdose can be severe, and no specific antidote exists.

- For ingestions of immediate-release venlafaxine at a dose threshold of 25 mg/kg, we recommend single-dose AC for up to 30 min (1, D).
- For ingestions of immediate-release venlafaxine at a dose threshold of 25 mg/kg, we suggest single-dose AC for ingestions between 30 min and 2 h (2, D).
- For ingestions of immediate-release venlafaxine at a dose threshold of 25 mg/kg, an individualized risk assessment for single-dose AC is required between 2 h and 6 h.
- For ingestions of immediate-release venlafaxine at a dose threshold of 25 mg/kg, we suggest against single-dose AC beyond 6 h (2, D).
  - For ingestions of modified-release venlafaxine at a dose threshold of 25 mg/kg, we recommend single-dose AC for up to 1 h (1, D).
  - For ingestions of modified-release venlafaxine at a dose threshold of 25 mg/kg, we suggest single-dose AC for ingestions between 1 h and 3 h (2, D).
  - For ingestions of modified-release venlafaxine at a dose threshold of 25 mg/kg, an individualized risk assessment for single-dose AC is required after 3 h.
  - For ingestions of both immediate- and modified-release venlafaxine at any dose, an individualized risk assessment is required for additional-dose AC.
  - For ingestions of both immediate- and modified-release venlafaxine at any dose, an individualized risk assessment is required for multiple-dose AC.

Warfarin

Evidence to decision rationale

In one study, the *in vitro* adsorption of warfarin to AC ranged from a maximum adsorption capacity of 536 mg/g AC to 636 mg/g AC depending on the commercial brand of AC used [334]. In another study, a maximum adsorption capacity of 434 mg/g AC was reported [335]. The Workgroup was unable to find any animal or human evidence to support the administration of AC in poisoning. However, given that warfarin overdose poses an increased risk of bleeding and patients would likely require ongoing monitoring for an extended period of time, the Workgroup concluded that significant ingestion could benefit from single-dose AC administration, but the pharmacokinetic properties did not justify additional-dose AC or multiple-dose AC.

- For ingestions of warfarin at a dose threshold of 0.7 mg/kg, we recommend single-dose AC for up to 1 h (1, D).
- For ingestions of warfarin beyond 1 h, an individualized risk assessment for single-dose AC is required.
- For ingestions of warfarin at any dose, we suggest against additional-dose AC (2, D).
- For ingestions of warfarin at any dose, we recommend against multiple-dose AC (1, D).

Appendix 2. Summary of the findings for the 43 poisons or poison categories selected for appraisal in the recommendations based on the systematic review of the literature on the administration of activated charcoal: Human studies, single-dose activated charcoal

		Single-dose activated charcoal for gastrointestinal decontamination: human studies		
Poison	Study outcomes	Total number of studies and level of evidence (GRADE)	Number of studies showing benefit and level of evidence (GRADE)	Longest time delay between poison dosing/ingestion and activated charcoal administration, and the level of evidence (GRADE)
Anticoagulants (warfarin)	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Antidysrhythmics (Class I, except disopyramide and quinidine, and Class III)	Pharmacokinetics-toxicokinetics	Low (C): $n=4$ [92,93,102,153]. Very low (D): $n=1$ [336].	Low (C): $n=4$ [92,93,102,153]. Very low (D): $n=1$ [336].	Low (C): 1.5 h [92]. Very low (D): 0 min [336].
	Clinical	No studies included.		
Barbiturates (phenobarbital)	Pharmacokinetics-toxicokinetics	Moderate (B) phenobarbital: $n=3$ [110,226,337]; other barbiturates: no studies included. Low (C) phenobarbital: $n=1$ [230]; other barbiturates: no studies included. Very low (D) phenobarbital: no studies included; other barbiturates: $n=2$ [321,338].	Moderate (B) phenobarbital: $n=3$ [110,226,337]; other barbiturates: no studies included. Low (C) phenobarbital: $n=1$ [230]; other barbiturates: no studies included. Very low (D) phenobarbital: no studies included; other barbiturates: $n=2$ [321,338].	Moderate (B) phenobarbital: 1h [110]. Low (C) phenobarbital: not reported [230]. Very low (D) other barbiturates: >7h post-ingestion [321].
	Clinical	No studies included.		
Benzodiazepines	Pharmacokinetics-toxicokinetics	Moderate (B): $n=1$ [72]. Low (C): $n=3$ [97–99]. Very low (D): $n=1$ [321].	Low (C): $n=3$ [97-99]. Very low (D): $n=1$ [321].	Low (C): 30 min [99]. Very low (D): >7 h [321].
	Clinical	No studies included.		
Beta-adrenergic antagonists (antidysrhythmic Class II)	Pharmacokinetics-toxicokinetics	Low (C): $n=3$ [102,339,340].	Low (C): $n=3$ [102,339,340].	Low (C): sotalol, atenolol, pindolol: 5 min [102,339,340].
	Clinical	Low (C): $n=1$ [101].	Low (C): $n=1$ [101].	Low (C): atenolol, propranolol: 15 min [101].
Bupropion	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Calcium-channel blockers (non-dihydropyridines Group 1/3, and dihydropyridines Group 2)	Pharmacokinetics-toxicokinetics	Low (C) : $n=6$: Group 1/3, $n=4$ [98,99,106,303,341]; Group 2, $n=2$ [107,342].	Low (C) : $n=6$: Group 1/3, $n=4$ [98,99,106,303,341]; Group 2, $n=2$ [107,342].	Low (C) : Group 1/3: 2 h (IR) [106]; 4 h (modified release) [106]; Group 2: 30 min [342].
	Clinical	No studies included.		
Carbamazepine, oxcarbazepine	Pharmacokinetics-toxicokinetics	Moderate (B): carbamazepine: $n=4$ [109–111,303]. Low (C): oxcarbazepine: $n=1$ [115]. Very low (D): carbamazepine: $n=1$ [343].	Moderate (B): carbamazepine: $n=4$ [109–111,303]. Low (C): oxcarbazepine: $n=1$ [115]. Very low (D): carbamazepine: $n=1$ [343].	Moderate (B): carbamazepine: 1 h [110,303]. Low (C): oxcarbazepine: 30 min [115]. Very low (D): carbamazepine: time not reported [343].
	Clinical	Low (C): carbamazepine: $n=1$ [111].	Low (C): carbamazepine: $n=1$ [111].	Low (C): carbamazepine: time not reported [111].
Cardiac glycosides (digoxin)	Pharmacokinetics-toxicokinetics	Digoxin: Moderate (B): $n=3$ [109,119,120].	Digoxin: Moderate (B): $n=3$ [109,119,120].	Moderate (B): 1 h [120].
	Clinical	No studies included.		
Cardiac glycosides (oleander)	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	Moderate (B): $n=2$ [73,129].	Moderate (B): $n=1$ [129].	Time not reported [129].
Chloroquine	Pharmacokinetics-toxicokinetics	Low (C): $n=2$ [133,134].	Low (C): $n=2$ [133,134].	Low (C): 5 min [133].
	Clinical	No studies included.		
Cocaine	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Colchicine	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Cyanide	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		

(*Continued*)

Appendix 2. Continued.

Poison	Study outcomes	Single-dose activated charcoal for gastrointestinal decontamination: human studies		
		Total number of studies and level of evidence (GRADE)	Number of studies showing benefit and level of evidence (GRADE)	Longest time delay between poison dosing/ingestion and activated charcoal administration, and the level of evidence (GRADE)
Dapsone	Pharmacokinetics-toxicokinetics	Very Low (D): $n=1$ [344].	Very Low (D): $n=1$ [344].	Very Low (D): Approximately 5 h [344].
	Clinical	No studies included.		
Diphenhydramine and other antihistamines	Pharmacokinetics-toxicokinetic	Low (C): diphenhydramine: $n=2$ [150,151]; other antihistamines: $n=3$ [85,340,345]. Very low (D): diphenhydramine: no studies included; other antihistamines: $n=2$ [346,347].	Low (C): diphenhydramine: $n=2$ [150,151]; other antihistamines: $n=2$ [85,340]. Very low (D): other antihistamines: $n=1$ [346].	Low (C): diphenhydramine: 5 min (60 min was non-significant) [150]; other antihistamines: 15 min [85]. Very low (D): other antihistamines: 2 h [346].
	Clinical	Very low (D): diphenhydramine: No studies included; other antihistamines: $n=2$ [346,347].	Very low (D): other antihistamines: $n=2$ [346,347].	Very low (D): other antihistamines: <4 h [347].
Disopyramide (antidysrhythmic Class I)	Pharmacokinetics-toxicokinetics	Low (C): $n=2$ [152,153].	Low (C): $n=2$ [152,153].	Low (C): 9 min [152,153].
	Clinical	No studies included.		
Ethanol	Pharmacokinetics-toxicokinetics	Moderate (B): $n=1$ [156].	No studies included.	Moderate (B): 30 min [156].
	Clinical	No studies included.		
Factor Xa Inhibitors	Pharmacokinetics-toxicokinetics	Low (C): $n=2$ [157,158].	Low (C): $n=2$ [157,158].	Low (C): apixaban: 6 h [158]; rivaroxaban 8 h [157].
	Clinical	No studies included.		
Iron	Pharmacokinetics-toxicokinetics	Moderate (B): $n=1$ [165].	No studies included.	
	Clinical	No studies included.		
Isoniazid	Pharmacokinetics-toxicokinetics	Low (C): $n=2$ [170,171].	Low (C): $n=1$ [170].	Low (C): 0 min [170].
	Clinical	No studies included.		
Lamotrigine	Pharmacokinetics-toxicokinetics	Low (C): $n=1$ [115]. Very low (D): $n=1$ [173].	Low (C): $n=1$ [115]. Very low (D): $n=1$ [173].	Low (C): 30 min [115]. Very low (D): 30 min [173].
	Clinical	No studies included.		
Lithium	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Metals	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Metformin (other antidiabetics: see sulfonylureas below)	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Methotrexate	Pharmacokinetics-toxicokinetics	Low (C): $n=1$ [190].	No studies included.	
	Clinical	No studies included.		
Moclobemide	Pharmacokinetics-toxicokinetics	Very low (D): $n=2$ [98,99].	Very low (D): $n=2$ [98,99].	Very low (D): 30 min [99].
	Clinical	No studies included.		
Nonsteroidal anti-inflammatory drugs (ibuprofen and others)	Pharmacokinetics-toxicokinetics	Low (C) $n=8$: ibuprofen: $n=1$ [97]; other: $n=7$ [93,110,152,153,253,348,349].	Low (C) $n=8$: ibuprofen: $n=1$ [97]; other: $n=7$ [93,110,152,153,253,348,349].	Low (C): Ibuprofen: 30 min [97]; Other: 1 h (mefenamic acid and phenylbutazone) [110,349].
	Clinical	No studies included.		
Opioids	Pharmacokinetics-toxicokinetics	Low (C): $n=5$, dextropropoxyphene [196, 197], pholcodine [198], codeine [151], oxycodone [209].	Low (C): $n=5$, dextropropoxyphene [196, 197], pholcodine [198], codeine [151], oxycodone [209].	Low (C): 2 h, pholcodine [198], oxycodone [209].
	Clinical	No studies included.		
Organophosphorus insecticides	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	Moderate (B): $n=1$, pesticides: [73]. Very Low (D): $n=1$, organophosphate insecticides: [200].	Moderate (B): No studies included. Very Low (D): No studies included.	
Paracetamol	Pharmacokinetics-toxicokinetics	Moderate (B): $n=23$ [72,201,202,205–209,341,350–363]. Low (C): $n=3$ [151,364,365]. Very Low (D): $n=3$ [204,366,367].	Moderate (B): $n=21$ [201,202,205–209,341,350–362]. Low (C): $n=2$ [151,364]. Very Low (D): $n=1$ [366].	Moderate (B): 3 h [208]. Low (C): 2 min [151]. Very Low (D): 10 h [366].
	Clinical	Moderate (B): $n=5$ [72,201,202,210,363]. Very Low (D): $n=2$ [204,367].	Moderate (B): $n=3$ [202,210,363]	Moderate (B): <4 h [202].

(*Continued*)

Appendix 2. Continued.

Poison	Study outcomes	Single-dose activated charcoal for gastrointestinal decontamination: human studies		
		Total number of studies and level of evidence (GRADE)	Number of studies showing benefit and level of evidence (GRADE)	Longest time delay between poison dosing/ingestion and activated charcoal administration, and the level of evidence (GRADE)
Paraquat	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Phenytoin	Pharmacokinetics-toxicokinetics	Low (C): $n=1$ [120]. Very Low (D): $n=1$ [232].	Low (C): $n=1$ [120]. Very Low (D): No studies included.	Low (C): 1 h [120].
	Clinical	Very Low (D): $n=1$ [232].	No studies included.	
Quinine and quinidine (antidysrhythmic Class I)	Pharmacokinetics-toxicokinetics	Low (C): $n=1$ [238].	Low (C): $n=1$ [238].	Low (C): 5 min [238].
	Clinical	No studies included.		
Salicylates	Pharmacokinetics-toxicokinetics	Moderate (B): $n=25$ [80,81,83,120,238,252,266–270,368–381]. Low (C): $n=3$ [93,152,339]. Very low (D): $n=1$ [338].	Moderate (B): $n=25$ [80,81,83,120,238,252,266–270,368–381]. Low (C): $n=3$ [93,152,339]. Very low (D): $n=1$ [338].	Moderate (B): 4 h [380]. Low (C): 5 min [339]. Very low (D): 1-12 h [338].
	Clinical	No studies included.		
Selective serotonin reuptake inhibitors	Pharmacokinetics-toxicokinetics	Low (C): $n=4$, fluoxetine [282], paroxetine [285], citalopram [97], mianserin [382]. Very low (D): $n=3$, citalopram [286], sertraline [284], escitalopram [283].	Low (C): $n=3$, fluoxetine [282], paroxetine [285], citalopram [97]. Very low (D): $n=3$, citalopram [286], sertraline [284], escitalopram [283].	Low (C): fluoxetine: 2 h [282], paroxetine: 40 min [285], citalopram: 30 min [97], mianserin: time not reported [382]. Very low (D): citalopram: 2-4 h [286], sertraline: median 3 h (1.5-4 h) [284], escitalopram: median 1.9 h [283].
	Clinical	Moderate (B): $n=1$, mianserin [382]. Low (C): $n=1$, citalopram [67].	Moderate (B): No studies included. Low (C): $n=1$, citalopram [67].	Low (C): citalopram: mean delay 2.0 h [67].
Sulfonylureas	Pharmacokinetics-toxicokinetics	Low (C): $n=3$, glipizide [290], tolbutamide [288], chlorpropamide [289].	Low (C): $n=3$, glipizide [290], tolbutamide [288], chlorpropamide [289].	Low (C): glipizide <5 min [290], tolbutamide <5 min [288], chlorpropamide <5 min [289].
	Clinical	No studies included.		
Thallium	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Theophylline and aminophylline	Pharmacokinetics-toxicokinetics	Moderate (B) $n=5$ [296,301–303,362]. Low (C) $n=1$ [383]. Very Low (D) $n=2$ [384,385].	Moderate (B) $n=5$ [296,301–303,362]. Low (C) $n=1$ [383]. Very Low (D) $n=2$ [384,385].	Moderate (B): moderate release 1 h [296,301,303]; immediate release 1 h [362]. Low (C): moderate release 2 h [383]. Very Low (D): 6 h [385].
	Clinical	No studies included.		
Toxic alcohols	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Tricyclic antidepressants	Pharmacokinetics-toxicokinetics	Low (C): $n=6$, amitriptyline [324,325], nortriptyline [315,323], doxepin [326], various tricyclic antidepressant group data (including amitriptyline, clomipramine, imipramine, dothiepin, doxepin, nortriptyline) [382]. Very low (D): $n=3$, amitriptyline [322], imipramine [321], maprotiline [386].	Low (C): $n=5$, amitriptyline [324,325], nortriptyline [315,323], doxepin [326]. Very low (D): $n=3$, amitriptyline [322], imipramine [321], maprotiline [386].	Low (C): amitriptyline: 5 min [324,325], nortriptyline: 4 h [323], doxepin: 30 min [326]. Very low (D): amitriptyline: 145 min [322], imipramine: >7 h [321], maprotiline: 20 h [386].
	Clinical	Moderate (B): $n=1$, various TCAs [382]. Very low (D): $n=1$, various TCAs [387].	Moderate (B): incidence of toxic symptoms, patients needing >48 h in ICU and >3 days at hospital were less frequent in the single-dose AC group (non-significant). Very low (D): No studies included.	Moderate (B): time not reported [382].

(*Continued*)

Appendix 2. Continued.

Poison	Study outcomes	Single-dose activated charcoal for gastrointestinal decontamination: human studies		
		Total number of studies and level of evidence (GRADE)	Number of studies showing benefit and level of evidence (GRADE)	Longest time delay between poison dosing/ingestion and activated charcoal administration, and the level of evidence (GRADE)
Valproic acid	Pharmacokinetics-toxicokinetics	Low (C): $n=1$ [288].	Low (C): $n=1$ [288].	Low (C): <5 min [288].
	Clinical	No studies included.		
Venlafaxine	Pharmacokinetics-toxicokinetics	Very Low (D): $n=1$, venlafaxine [333].	Very Low (D): $n=1$, venlafaxine [333].	Very Low (D): venlafaxine: >4h [333].
	Clinical	No studies included.		

Appendix 3. *summary of the findings for the 43 poisons or poison categories selected for appraisal in the recommendations based on the systematic review of the literature on the administration of activated charcoal: Human studies, additional-dose activated charcoal

Poison	Study outcomes	Additional-dose activated charcoal for gastrointestinal decontamination, human studies		
		Total number of studies and level of evidence (GRADE)	Number of studies showing benefit and level of evidence (GRADE)	Longest time delay between poison dosing/ ingestion and activated charcoal administration, and level of evidence (GRADE)
Benzodiazepines	Pharmacokinetics-toxicokinetics	Very low (D): $n=1$ [388].	No studies included.	Very low (D): 24 h [388].
	Clinical	No studies included.		
Carbamazepine, oxcarbazepine	Pharmacokinetics-toxicokinetics	Very low (D): carbamazepine: $n=2$ [388,389].	Very low (D): carbamazepine: $n=2$ [388,389].	Very low (D): carbamazepine: 3 h [389] and 24 h [388].
	Clinical	No studies included.		
Paracetamol	Pharmacokinetics-toxicokinetics	Very low (D) $n=1$ [204].	No studies included.	
	Clinical	No studies included.		
Phenytoin	Pharmacokinetics-toxicokinetics	Very low (D): $n=1$ [390].	Very low (D): $n=1$ [390].	Very low (D): Time for the initial dose not reported, repeated dose at 6h [390].
	Clinical	No studies included.		
Theophylline and aminophylline	Pharmacokinetics-toxicokinetics	Very low (D): $n=3$ [391–393].	Very low (D): $n=3$ [391–393]	Very low (D): Time not reported [391–393].
	Clinical	No studies included.		

*For the following poisons or poison categories there were no studies included: Anticoagulants (warfarin), antidysrhythmics (Class I, except disopyramide and quinidine, and Class III), barbiturates (phenobarbital), beta-adrenergic antagonists (antidysrhythmic Class II), bupropion, calcium-channel blockers, cardiac glycosides (digoxin), cardiac glycosides (oleander), chloroquine, cocaine, colchicine, cyanide, dapsone, diphenhydramine and other antihistamines, disopyramide (antidysrhythmic Class I), ethanol, factor Xa Inhibitors, iron, isoniazid, lamotrigine, lithium, metals, metformin, methotrexate, moclobemide, nonsteroidal anti-inflammatory drugs (ibuprofen and other), opioids, organophosphorus insecticides, paraquat, quinine and quinidine (antidysrhythmic Class I), salicylates, selective serotonin reuptake inhibitors, sulfonylureas, thallium, toxic alcohols, tricyclic antidepressants, valproic acid, venlafaxine.

Appendix 4. Summary of the findings for the 43 poisons or poison categories selected for appraisal in the recommendations based on the systematic review of the literature on the administration of activated charcoal: Human, multiple-dose activated charcoal

Poison	Study outcomes	Multiple-dose activated charcoal for enhanced elimination, human studies		
		Total number of studies and level of evidence (GRADE)	Number of studies showing benefit and level of evidence (GRADE)	Longest time delay between poison dosing/ingestion and activated charcoal administration, and level of evidence (GRADE)
Anticoagulants (warfarin)	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Antidysrhythmics (Class I, except disopyramide and quinidine, and Class III)	Pharmacokinetics-toxicokinetics	Low (C): $n=2$ [102,394]. Very low (D): $n=1$ [395].	Low (C): $n=1$ [394]. Very low (D): $n=1$ [395].	Low (C): minus 10 min, and x3/day for 48 h [394]. Very low (D): 1 h from admission, repeated every 4 h for 24 h [395].
	Clinical	No studies included.		

(*Continued*)

Appendix 4. Continued.

Poison	Study outcomes	Multiple-dose activated charcoal for enhanced elimination, human studies: Total number of studies and level of evidence (GRADE)	Number of studies showing benefit and level of evidence (GRADE)	Longest time delay between poison dosing/ingestion and activated charcoal administration, and level of evidence (GRADE)
Barbiturates (phenobarbital)	Pharmacokinetics-toxicokinetics	Moderate (B) phenobarbital: $n=6$ [227–230,396,397]; other barbiturates: no studies included Low (C) phenobarbital: $n=1$ [230]; other barbiturates: no studies included. Very low (D) phenobarbital: $n=8$ [100,398–404]; other barbiturates: no studies included.	Moderate (B) phenobarbital: $n=5$ [227–230,397]; other barbiturates: no studies included. Low (C) phenobarbital: no studies included; other barbiturates: no studies included. Very low (D) phenobarbital: $n=8$ [100,398–404]; other barbiturates: no studies included.	Moderate (B) phenobarbital: 6 h, then at 12 h, 18 h, 24 h, 30 h, 42 h [397]. Very low (D) phenobarbital: >10 h [100,401,404].
	Clinical	No studies included.		
Benzodiazepines	Pharmacokinetics-toxicokinetics	Very low (D): $n=3$ [100,405,406].	No studies included.	Very low (D): (adult) first dose not reported, then /4 h [405]; (pediatric) first dose not reported, then 1 g/kg every 6 h for 5 days [406].
	Clinical	No studies included.		
Beta-adrenergic antagonists (antidysrhythmic Class II)	Pharmacokinetics-toxicokinetics	Low (C): $n=2$ [102,103].	Low (C): $n=2$ [102,103].	Low (C): nadolol: 3 h, then at 4 h, 5 h, 6 h, 7 h, 8 h, 9 h, 10 h, 11 h, 12 h [103]; sotalol: 6 h, then at 12 h, 18 h, 24 h, 30 h, 36 h, 42 h, 48 h, 54 h [102].
	Clinical	No studies included.		
Bupropion	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Calcium-channel blockers (non-dihydropyridines Group 1/3, and dihydropyridines Group 2)	Pharmacokinetics-toxicokinetics	Very low (D): Group 3, $n=1$ [108].	Very low (D): Group 3, $n=1$ [108].	Very low (D): Group 3: 7 h [108].
	Clinical	No studies included.		
Carbamazepine, oxcarbazepine	Pharmacokinetics-toxicokinetics	Moderate (B): carbamazepine: $n=1$ [111]. Low (C): oxcarbazepine: $n=1$ [115]. Very low (D): carbamazepine: $n=6$ [112–114,402,407,408].	Moderate (B): carbamazepine: $n=1$ [111]. Low (C): oxcarbazepine: $n=1$ [115]. Very low (D): carbamazepine: $n=6$ [112-114,402,407,408].	Moderate (B): carbamazepine: first dose not reported, then every 6 h [111]. Low (C): oxcarbazepine: 30 min, then doses within 12-48 h [115]. Very low (D): carbamazepine: time not reported or unknown
	Clinical	Low (C): carbamazepine: $n=2$ [111,409].	Low (C): carbamazepine: $n=2$ [111,409].	Low (C): carbamazepine: first dose not reported, then every 4 h [409].
Cardiac glycosides (digoxin)	Pharmacokinetics-toxicokinetics	Digoxin: Moderate (B): $n=2$ [124,410]. Low (C): $n=1$ [411]. Very low (D): $n=5$ [121,122,124–126]. Digitoxin: Very low (D): $n=2$ [123,412].	Digoxin: Moderate (B): $n=2$ [124,410]. Low (C): no studies included. Very low (D): $n=5$ [121,122,124–126]. Digitoxin: Very low (D): $n=2$ [123,412].	Digoxin: Moderate (B): 0 h, then at 4 h, 8 h, 12 h, 16 h, 20 h, 24 h, 28 h, 32 h, 36 h, 48 h, 60 h, 72 h, 84 h, 96 h [124]. Low (C): Minus 10 min, and x3/day for 48 h [411]. Very low (D): 30 h [121]. Digitoxin: Very low (D): 7 h [412].
	Clinical	No studies included.		
Cardiac glycosides (oleander)	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	High (A): $n=1$ [74]. Moderate (B): $n=2$ [73,129].	High (A): $n=1$ [74]. Moderate (B): $n=1$ [129].	High (A): first dose not reported, then every 6 h x3 daily, to total dose 600 g [74]. Moderate (B): first dose not reported, then at 4 h, 8 h, 12 h, 16 h, 20 h [129].
Chloroquine	Pharmacokinetics-toxicokinetics	Low (C): $n=1$ [133].	Low (C): $n=1$ [133].	Low (C): 5 min, then at 4, 8, 12 h [133].
	Clinical	No studies included.		

(*Continued*)

Appendix 4. Continued.

Poison	Study outcomes	Multiple-dose activated charcoal for enhanced elimination, human studies		
		Total number of studies and level of evidence (GRADE)	Number of studies showing benefit and level of evidence (GRADE)	Longest time delay between poison dosing/ingestion and activated charcoal administration, and level of evidence (GRADE)
Cocaine	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Colchicine	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Cyanide	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Dapsone	Pharmacokinetics-toxicokinetics	Low (C): $n=1$ [147]. Very low (D): $n=3$ [147,148,413].	Low (C): $n=1$ [147]. Very low (D): $n=3$ [147,148,413].	Low (C): first dose not reported, then every 12 h at 10-58 h [147]. Very low (D): 5 days [147,413].
	Clinical	No studies included.		
Diphenhydramine and other antihistamines	Pharmacokinetics-toxicokinetics	Very low (D): diphenhydramine: no studies included; other antihistamines: $n=2$ [414,415].	Very low (D): other antihistamines: $n=2$ [414,415].	Very low (D): Other antihistamines: 9.2 h [414].
	Clinical	Very low (D): diphenhydramine: no studies included; other antihistamines: $n=2$ [414,415].	Very low (D): other antihistamines: $n=1$ [414].	Very low (D): other antihistamines: 9.2 h, then x4/day for 2 days [414].
Disopyramide (antidysrhythmic Class I)	Pharmacokinetics-toxicokinetics	Low (C): $n=1$ [154].	Low (C): $n=1$ [154].	Low (C): 4 h, then at 6, 8, 12 h [154].
	Clinical	No studies included.		
Ethanol	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Factor Xa Inhibitors	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Iron	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Isoniazid	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Lamotrigine	Pharmacokinetics-toxicokinetics	Low (C): $n=1$ [115]. Very low (D): $n=1$ [173].	Low (C): $n=1$ [115]. Very low (D): $n=1$ [173].	Low (C): 30 min, then multiple during 6-72 h [115]. Very low (D): 30 min, then at 6 h, 12 h, 24 h, 36 h and 48 h [173].
	Clinical	No studies included.		
Lithium	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Metals	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Metformin	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Methotrexate	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Moclobemide	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Nonsteroidal anti-inflammatory drugs (ibuprofen and others)	Pharmacokinetics-toxicokinetics	Low (C): $n=3$, ibuprofen: no studies included. Other: $n=3$ [348,416,417].	Low (C): $n=2$, other: $n=2$ [348,417].	Low (C): other: piroxicam: 24 h, then x4 Day 1, and x3 Day 2 [417].
	Clinical	No studies included.		
Opioids	Pharmacokinetics-toxicokinetics	Low (C): $n=2$, dextropropoxyphene [196], pholcodine [198].	Low (C): $n=1$, dextropropoxyphene [196].	Low (C): 6 h, then 12 h, 18 h, 24 h, 30 h, 36 h, 42 h, 48 h, 52 h [196].
	Clinical	No studies included.		
Organophosphorus insecticides	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	Moderate (B): $n=1$, pesticides [73]. Very low (D): $n=1$, organophosphorus insecticides [418].	Very low (D): $n=1$, organophosphorus insecticides [418].	Very low (D): time not specified [418].
Paracetamol	Pharmacokinetics-toxicokinetics	Very low (D): $n=3$ [204,419,420].	Very low (D): $n=2$ [419,420].	Very low (D): 2-8 h, specific h for the paracetamol case unclear in [420].
	Clinical	No studies included.		

(*Continued*)

Appendix 4. Continued.

Poison	Study outcomes	Multiple-dose activated charcoal for enhanced elimination, human studies: Total number of studies and level of evidence (GRADE)	Number of studies showing benefit and level of evidence (GRADE)	Longest time delay between poison dosing/ingestion and activated charcoal administration, and level of evidence (GRADE)
Paraquat	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Phenytoin	Pharmacokinetics-toxicokinetics	Low (C): $n=3$ [234–236]. Very low (D): $n=6$ [232,400,403,421–423].	Low (C): $n=3$ [234–236]. Very Low (D): $n=5$ [400,403,421–423].	Low (C): 0 h, then 2 h, 4 h, 8 h, 12 h, 24 h, 30 h, 36 h, 48 h [234]. Very Low (D): 2 days, repeated x10 every 4 h [422].
	Clinical	Low (C): $n=1$ [236].	No studies included.	
Quinine and quinidine (antidysrhythmic Class I)	Pharmacokinetics-toxicokinetics	Low (C): $n=1$ [240]. Very Low (D): $n=1$ [424].	Low (C): $n=1$ [240]. Very Low (D): $n=1$ [424].	Low (C): 4 h, then x 3 over 12 h [240]. Very Low (D): <4-34 h, then x3-7 every 4 h [424].
	Clinical	No studies included.		
Salicylates	Pharmacokinetics-toxicokinetics	Moderate (B): $n=6$ [269,271–274,368]. Very low (D): $n=2$ [403,420].	Moderate (B): $n=3$ [269,274,368]. Very low (D): $n=2$ [403,420].	Moderate (B): 4 h, then 6 h, 8 h, 10 h [273], and 4 h, then 8 h, 12 h, 16 h, 20 h, 24 h, 28 h [274]. Very low (D): 2-8 h, then every 4 h x3 [420], and initial dose not reported, then every 4 h for 48 h [403].
	Clinical	No studies included.		
Selective serotonin reuptake inhibitors	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Sulfonylureas	Pharmacokinetics-toxicokinetics	Low (C): $n=1$, chlorpropamide [289].	Low (C): $n=1$, chlorpropamide [289].	Low (C): chlorpropamide: 1 h, then 6 h, 12 h, 18 h, 24 h, 30 h, 36 h, 42 h, 48 h, 54 h [289].
	Clinical	No studies included.		
Thallium	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Theophylline and aminophylline	Pharmacokinetics-toxicokinetics	Moderate (B): $n=13$ [296,301,304–314]. Low (C): $n=1$ [425]. Very low (D): $n=15$ [310,391–393,425–435].	Moderate (B): $n=13$ [296,301,304–314]. Low (C): $n=1$ [425]. Very low (D): $n=15$ [310,391–393,425–435].	Moderate (B): 6 h [307,312]. Low (C): 0 h [425]. Very low (D): 30 h (immediate release) [428]; >18 h (modified release) [393].
	Clinical	No studies included.		
Toxic alcohols	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Tricyclic antidepressants	Pharmacokinetics-toxicokinetics	Low (C): $n=5$, amitriptyline [324,325]; nortriptyline [315]; doxepin [326]; imipramine [436]. Very low (D): $n=5$, amitriptyline [327,328,437]; clomipramine [438]; dothiepin [329].	Low (C): $n=3$, amitriptyline [324,325]; nortriptyline [315]; doxepin: no studies included; imipramine: no studies included. Very low (D) $n=4$, amitriptyline [327,328,437]; clomipramine: no studies included; dothiepin [329].	Low (C): amitriptyline: 5 min, then 6 h, 12 h, 18 h, 24 h, 30 h, 36 h, 42 h, 48 h [325]; nortriptyline: 30 min, then 120 min, 240 min, 360 min [315]. Very low (D): amitriptyline: 1 h, then every 4 h up to 23 h [328]; dothiepin: initial dose not reported, then variable dose every 4-12 h [329].
	Clinical	Very low (D): $n=1$, amitriptyline [327].	Very low (D): $n=1$, amitriptyline [327].	Very low (D): amitriptyline: time not reported [327].
Valproic acid	Pharmacokinetics-toxicokinetics	Moderate (B): $n=1$ [330]. Very low (D): $n=2$ [415,439,440].	Moderate (B): no studies included. Very low (D): $n=2$ [415,439,440].	Very low (D): 3 h, then multiple at 13-19 h [440].
	Clinical	No studies included.		
Venlafaxine	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		

Appendix 5. Summary of the findings for the 43 poisons or poison categories selected for appraisal in the recommendations based on the systematic review of the literature on the administration of activated charcoal: Animal studies, single-dose activated charcoal

		Single-dose activated charcoal for gastrointestinal decontamination, animal studies		
Poison	Study outcomes	Total number of studies	Number of studies showing benefit	Longest time delay between poison dosing/ingestion and activated charcoal administration
Anticoagulants	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	$n=1$, rats (Bromadiolone) [143].	No studies included.	0 min in rats (Bromadiolone) [143].
Antidysrhythmics (Class I, except disopyramide and quinidine, and Class III)	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Barbiturates (phenobarbital)	Pharmacokinetics-toxicokinetics	Phenobarbital: $n=3$, rabbits [441], rats [261], dogs [442].	Phenobarbital: $n=3$, rabbits [441], rats [261], dogs [442].	Phenobarbital: 50 min in rabbits [441], 15 min in rats [261], 30 min in dogs [442].
		Other barbiturates: $n=10$, pigs [443,444], rats [169,260,445–447], dogs [246,442,448].	Other barbiturates: $n=10$, pigs [443,444], rats [169,260,445–447], dogs [246,442,448].	Other barbiturates: 2 h in pigs [443], 5 min in rats [445], 30 min in dogs [442].
	Clinical	Phenobarbital: no studies included.	Phenobarbital: no studies included.	Other barbiturates: 5 min in rats [445], 30 min in dogs [246].
		Other barbiturates: $n=2$, rats [445], dogs [246].	Other barbiturates: $n=2$, rats [445], dogs [246].	
Benzodiazepines	Pharmacokinetics-toxicokinetics	$n=1$, rats [96].	$n=1$, rats [96].	0 min in rats [96].
	Clinical	No studies included.		
Beta-adrenergic antagonists (antidysrhythmic Class II)	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Bupropion	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Calcium-channel blockers (antidysrhythmic Class IV)	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Carbamazepine, Oxcarbazepine	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Cardiac glycosides (digoxin)	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Cardiac glycosides (oleander)	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	$n=1$, sheep [449].	$n=1$, sheep [449].	1 h in sheep [449].
Chloroquine	Pharmacokinetics-toxicokinetics	$n=4$, rats [169,246,446,447], dogs [246].	$n=4$, rats [169,246,446,447]	1 min in rats [246].
	Clinical	$n=1$, dogs [246].	$n=1$, dogs [246].	30 min in dogs [246].
Cocaine	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	$n=1$, mice [137].	$n=1$, mice [137].	1 min in mice [137].
Colchicine	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Cyanide	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	$n=1$, rats [145].	$n=1$, rats [145].	0 min in rats [145].
Dapsone	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Diphenhydramine and other antihistamines	Pharmacokinetics-toxicokinetics	Diphenhydramine: no studies included.	Diphenhydramine: no studies included.	Other antihistamines: 1 min in rats [246,260], 2 min in dogs [450,451].
		Other antihistamines: $n=6$, rats [246,260,446,447], dogs [450,451].	Other antihistamines: $n=6$, rats [246,260,446,447], dogs [450,451].	
	Clinical	No studies included.		
Disopyramide (antidysrhythmic Class I)	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Ethanol	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Factor Xa Inhibitors	Pharmacokinetics-toxicokinetics	Apixaban: $n=1$, dogs and rats [452].	Apixaban: $n=1$, dogs and rats [452].	Apixaban: 3 h in dogs [452], dosing time in rats not reported.
		Rivaroxaban: $n=1$, mice [453].	Rivaroxaban: $n=1$, mice [453].	Rivaroxaban: 1 h in mice [453].
	Clinical	No studies included.		
Iron	Pharmacokinetics-toxicokinetics	$n=2$, rats [454,455].	$n=1$, rats [455].	0 min in rats [455].
	Clinical	No studies included.		

(*Continued*)

Appendix 5. Continued.

		Single-dose activated charcoal for gastrointestinal decontamination, animal studies		
Poison	Study outcomes	Total number of studies	Number of studies showing benefit	Longest time delay between poison dosing/ingestion and activated charcoal administration
Isoniazid	Pharmacokinetics-toxicokinetics	$n=2$, rabbits [168], rats [169].	$n=2$, rabbits [168], Rats [169].	0 min in rabbits [168], 0 min in rats [169].
	Clinical	No studies included.		
Lamotrigine	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Lithium	Pharmacokinetics-toxicokinetics	$n=1$, mice [176].	No studies included.	
	Clinical	No studies included.		
Metals	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	Arsenic: $n=2$, rats [456], mice [457]. Mercury: $n=1$, horse [458].	No studies included.	
Metformin	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Methotrexate	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Moclobemide	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Nonsteroidal anti-inflammatory drugs (ibuprofen and others)	Pharmacokinetics-toxicokinetics	Ibuprofen: no studies included. Other: $n=3$, dogs [159–161].	Ibuprofen: no studies included. Other: $n=3$, dogs [159–161].	Other: 1 h in dogs (carboprofen) [159].
	Clinical	No studies included.		
Opioids	Pharmacokinetics-toxicokinetics	$n=3$, [193–195]: Diphenoxylate: $n=1$, mice [193] Morphine: $n=1$, rabbits [194]. Dextropropoxyphene: $n=1$, rats [195].	$n=3$, [193–195].	30 min in mice and rats [193,195].
	Clinical	No studies included.		
Organophosphorus insecticides	Pharmacokinetics-toxicokinetics	$n=6$, dichlorvos: rats [459], mice [460–462]. VX: sheep [463]. Thimet: sheep [464].	$n=1$, dichlorvos: rats [459].	Dichlorvos: 0-1 min in rats [459].
	Clinical	$n=6$, dichlorvos: rats [459], mice [460–462]. VX: sheep [463]. Thimet: sheep [464].	$n=6$, dichlorvos: rats [459], mice [460–462]. VX: sheep [463]. Thimet: sheep [464].	Dichlorvos: 0-1 min in rats [459], and mice [460–462]. VX: 0-1 min in sheep [463]. Thimet: 0-1 min in sheep [464].
Paracetamol	Pharmacokinetics-toxicokinetics	$n=6$, pigs [444], rats [465–467], dogs [448,468].	$n=5$, pigs [444], rats [465,466], dogs [448,468].	1 h in pigs [444].
	Clinical	$n=1$, mice [468].	$n=1$, mice [468].	1 min in mice [468].
Paraquat	Pharmacokinetics-toxicokinetics	$n=1$, rabbits [218].	$n=1$, rabbits [218].	2 h in rabbits [218].
	Clinical	$n=3$, rats [216,217], mice [214].	$n=3$, rats [216,217], mice [214].	0 min in rats [216,217], 30 min in mice [214]-
Phenytoin	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Quinine-quinidine (antidysrhythmic Class I)	Pharmacokinetics-toxicokinetics	$n=1$, rabbits [239].	$n=1$ (quinidine only), rabbits [239].	0 min in rabbits [239].
	Clinical	No studies included.		
Salicylates	Pharmacokinetics-toxicokinetics	$n=8$, dogs [246,248,257,261], rats [258–260,447].	$n=8$, dogs [246,248,257,261], rats [258–260,447].	45-60 min in Dogs [261], 2 h in rats [258].
	Clinical	No studies included.		
Selective serotonin reuptake inhibitors	Pharmacokinetics-toxicokinetics	Fluoxetine: $n=1$, rats [281].	Fluoxetine: $n=1$, rats [281].	Fluoxetine: 15 min in rats [281].
	Clinical	No studies included.		
Sulfonylureas	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Thallium	Pharmacokinetics-toxicokinetics	$n=1$, rats [292].	$n=1$, rats [292].	1 h in rats [292].
	Clinical	No studies included.		
Theophylline and aminophylline	Pharmacokinetics-toxicokinetics	$n=1$, rabbits [469].	$n=1$, rabbits [469].	4 h in rabbits [469].
	Clinical	No studies included.		
Toxic alcohols	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		

(*Continued*)

Appendix 5. Continued.

		Single-dose activated charcoal for gastrointestinal decontamination, animal studies		
Poison	Study outcomes	Total number of studies	Number of studies showing benefit	Longest time delay between poison dosing/ingestion and activated charcoal administration
Tricyclic antidepressants	Pharmacokinetics-toxicokinetics	Amitriptyline: $n=3$, rats [470,471], pigs [444].	Amitriptyline: $n=2$, rats [470,471], pigs: no studies included.	Amitriptyline: 30 min in rats [471].
	Clinical	No studies included.		
Valproic acid	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Venlafaxine	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		

Appendix 6. Summary of the findings for the 43 poisons or poison categories selected for appraisal in the recommendations based on the systematic review of the literature on the administration of activated charcoal: Animal studies, additional-dose activated charcoal.*

		Additional-dose activated charcoal for gastrointestinal decontamination, animal studies		
Poison	Study outcomes	Total number of studies	Number of studies showing benefit	Longest time delay between poison dosing/ ingestion and activated charcoal administration
Paracetamol	Pharmacokinetics-toxicokinetics	$n=1$, rats [472].	$n=1$, rats [472].	0 min, and 2 h in rats [472].
	Clinical	No studies included.		

* For the following poisons or poison categories there were no studies included: anticoagulants (warfarin), antidysrhythmics (Class I, except disopyramide and quinidine, and Class III), barbiturates (phenobarbital), benzodiazepines, beta-adrenergic antagonists (antidysrhythmic Class II), bupropion, calcium-channel blockers, carbamazepine, cardiac glycosides (digoxin), cardiac glycosides (oleander), chloroquine, cocaine, colchicine, cyanide, dapsone, diphenhydramine and other antihistamines, disopyramide (antidysrhythmic Class I), ethanol, factor Xa Inhibitors, iron, isoniazid, lamotrigine, lithium, metals, metformin, methotrexate, moclobemide, nonsteroidal anti-inflammatory drugs (ibuprofen and other), opioids, organophosphorus insecticides, paraquat, phenytoin, quinine and quinidine (antidysrhythmic Class I), salicylates, selective serotonin reuptake inhibitors, sulfonylureas, thallium, theophylline and aminophylline, toxic alcohols, tricyclic antidepressants, valproic acid, venlafaxine.

Appendix 7. Summary of the findings for the 43 poisons or poison categories selected for appraisal in the recommendations based on the systematic review of the literature on the administration of activated charcoal: Animal studies, multiple-dose activated charcoal

		Multiple-dose activated charcoal for enhanced elimination, animal studies		
Poison	Study outcomes	Total number of studies	Number of studies showing benefit	Longest time delay between poison dosing/ingestion and activated charcoal administration
Anticoagulants (warfarin)	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	$n=1$, rats (Bromadiolone) [143].	No studies included.	0 min (Bromadiolone) in rats [143].
Antidysrhythmics (Class I, except disopyramide and quinidine, and Class III)	Pharmacokinetics-toxicokinetics	$n=2$, rats [473,474].	$n=1$, kidney failure rats [473].	0 h, 1 h, 2 h, 3 h, 4 h in rats [473].
	Clinical	No studies included.		
Barbiturates (phenobarbital)	Pharmacokinetics-toxicokinetics	Phenobarbital: $n=3$, rats [475,476], mice [477].	Phenobarbital: $n=1$, rats [475,476].	Phenobarbital: 0 h, 6 h, 12 h, 24 h, 48 h, 54 h in rats [475].
		Other barbiturates: $n=1$, dogs [246].	Other barbiturates: No studies included.	
	Clinical	Phenobarbital: $n=1$, mice [477].	Phenobarbital: $n=1$, mice [477].	Phenobarbital: pre-dose 20 min, then post-dose every 20 min for 1 h in mice [477].
		Other barbiturates: No studies included.	Other barbiturates: No studies included.	
Benzodiazepines	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Beta-adrenergic antagonists (antidysrhythmic Class II)	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Bupropion	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Calcium-channel blockers (antidysrhythmics Class IV)	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		

(*Continued*)

Appendix 7. Continued.

Poison	Study outcomes	Multiple-dose activated charcoal for enhanced elimination, animal studies		
		Total number of studies	Number of studies showing benefit	Longest time delay between poison dosing/ingestion and activated charcoal administration
Carbamazepine, oxcarbazepine	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Cardiac glycosides (digoxin)	Pharmacokinetics-toxicokinetics	Digoxin: $n=3$, rats [478], dogs [479], pigs [480].	Digoxin: $n=3$, rats [478], dogs [479], pigs [480].	Digoxin: rats, 0 min, then x4/day for 2-3 days [478]. Dogs, Pre-dose 15 min; post-dose 2 h [479]. Pigs, 5 min, then 2 h, 4 h, 6 h, 12 h, 18 h, 24 h, 30 h [480].
	Clinical	No studies included.		
Cardiac glycosides (oleander)	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Chloroquine	Pharmacokinetics-toxicokinetics	$n=1$, rats [474].	No studies included.	48-264 h in rats [474].
	Clinical	No studies included.		
Cocaine	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Colchicine	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Cyanide	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Dapsone	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Diphenhydramine and other antihistamines	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Disopyramide (antidysrhythmic Class I)	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Ethanol	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Factor Xa Inhibitors	Pharmacokinetics-toxicokinetics	Apixaban: $n=1$, dogs and rats [452].	Apixaban: $n=1$ [452].	Apixaban: dogs, 10 min, then at 90 min, 180 min, 420 min [452]. Rats, pre-dose 30 min, then post-dose at 5 min, 90 min, 180 min [452].
	Clinical	No studies included.		
Iron	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Isoniazid	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Lamotrigine	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Lithium	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Metals	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	Lead: $n=1$, rats [481].	Lead: $n=1$, rats [481].	Lead: day 1 and day 28 in rats [481].
Metformin	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Methotrexate	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Moclobemide	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Nonsteroidal anti-inflammatory drugs (ibuprofen and others)	Pharmacokinetics-toxicokinetics	Ibuprofen: no studies included. Other: $n=2$, dogs [159,162].	Ibuprofen: no studies included. Other: $n=2$, dogs [159,162].	Other: dogs, first dose 1 h, then every 6 h (carboprofen) [159], and <2 min, then every 8 h for 272 h [162].
	Clinical	No studies included.		
Opioids	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Organophosphorus insecticides	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	Fenithrothion: $n=1$, rats [199]. Dichlorvos: $n=1$, rats [459].	Fenithrothion: $n=1$, rats [199]. Dichlorvos: $n=1$, rats [459].	Fenithrothion: 1.5 h in rats [199].
Paracetamol	Pharmacokinetics-toxicokinetics	$n=1$, pigs [480].	$n=1$, pigs [480].	5 min, 2 h, 4 h, 6 h, 12 h, 18 h, 24 h, 30 h in pigs [480].
	Clinical	No studies included.		

(*Continued*)

Appendix 7. Continued.

		Multiple-dose activated charcoal for enhanced elimination, animal studies		
Poison	Study outcomes	Total number of studies	Number of studies showing benefit	Longest time delay between poison dosing/ingestion and activated charcoal administration
Paraquat	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	$n=1$, rats [216].	$n=1$, rats [216].	0.5 h, then 1 h, 2 h, or 3 h in rats [216].
Phenytoin	Pharmacokinetics-toxicokinetics	$n=1$, rats [233].	$n=1$, rats [233].	0 h, then 1 h, 2 h, 3 h, 4 h, 6 h in rats [233].
	Clinical	No studies included.		
Quinine-quinidine (antidysrhythmic Class I)	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Salicylates	Pharmacokinetics-toxicokinetics	$n=5$, pigs [262,263], dogs [265,482], rabbits [264].	$n=2$, no studies included in pigs, dogs [265,482], no studies included in rabbits.	Dogs: first dose after infusion, then every 1 h for 2 h and every 1 h for 4 h [265,482].
	Clinical	No studies included.		
Selective serotonin uptake inhibitors	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Sulfonylureas	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Thallium	Pharmacokinetics-toxicokinetics	$n=1$, rats [293].	$n=1$, rats [293].	6 h, then 24 h in rats [293].
	Clinical	No studies included.		
Theophylline and aminophylline	Pharmacokinetics-toxicokinetics	$n=8$, rats [476,483,484], dogs [485–487], pigs [69,480],	$n=8$, rats [476,483,484], dogs [485–487], pigs [69,480].	5 min in pigs [480].
	Clinical	No studies included.		
Toxic alcohols	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	Methanol: $n=1$, rats [488].	Methanol: $n=1$, rats [488].	Time not specified.
Tricyclic antidepressants	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		
Valproic acid	Pharmacokinetics-toxicokinetics	$n=1$, pigs [480].	$n=1$, pigs [480].	5 min, then 25 g at 2 h, 4 h, 6 h, 12 h, 18 h, 24 h, 30 h in pigs [435].
	Clinical	No studies included.		
Venlafaxine	Pharmacokinetics-toxicokinetics	No studies included.		
	Clinical	No studies included.		

Appendix 8. In vitro studies on adsorption to activated charcoal

Poison	Total number of studies	Number of studies showing poison adsorption to activated charcoal
Anticoagulants (warfarin)	$n=2$ (Warfarin) [334,335].	$n=2$ (Warfarin) [334,335].
Antidysrhythmics (Class I, except disopyramide and quinidine, and Class III)	$n=5$ [90,91,153,299,489].	$n=5$ [90,91,153,299,489].
Barbiturates (phenobarbital)	Phenobarbital: $n=13$ [142,222,223,237,244,245,300,337,490–494]. Other barbiturates: $n=12$ [142,155,223–225,237,242,245–247,260,490].	Phenobarbital: $n=13$ [142,222,223,237,244,245,300,337,490–494]. Other barbiturates: $n=12$ [142,155,223–225,237,242,245–247,260,490].
Benzodiazepines	$n=3$ [94,95,245].	$n=3$ [94,95,245].
Beta-adrenergic antagonists (antidysrhythmic Class II)	$n=1$ [340].	$n=1$ [340].
Bupropion	No studies included.	
Calcium-channel blockers	No studies included.	
Carbamazepine, oxcarbazepine	Carbamazepine: $n=1$ [495].	Carbamazepine: $n=1$ [495].
Cardiac glycosides (digoxin)	$n=1$ [118].	$n=1$ [118].
Cardiac glycosides (oleander)	$n=2$ (oleander, oleandrin, oleandrigenin) [127,128].	$n=2$ (oleander, oleandrin, oleandrigenin) [127,128].
Chloroquine	$n=3$ [132,246,494].	$n=3$ [132,246,494].
Cocaine	$n=2$ [135,136].	$n=2$ [135,136].
Colchicine	No studies included.	
Cyanide	$n=1$ [142].	$n=1$ [142].
Dapsone	No studies included.	No studies included.
Diphenhydramine and other antihistamines	Diphenhydramine: $n=1$ [150]. Other antihistamines: $n=7$ [155,242,246,300,340,496,497].	Diphenhydramine: $n=1$ [150]. Other antihistamines: $n=7$ [155,242,246,300,340,496,497].
Disopyramide (antidysrhythmic Class I)	$n=2$ [152,153].	$n=2$ [152,153].
Ethanol	$n=3$ [142,155,211].	$n=2$ [142,155].

(*Continued*)

Appendix 8. Continued.

Poison	Total number of studies	Number of studies showing poison adsorption to activated charcoal
Factor Xa Inhibitors	No studies included.	
Iron	*n* = 2 [155,164].	*n* = 2 [155,164].
Isoniazid	*n* = 1 [167].	*n* = 1 [167].
Lamotrigine	No studies included.	
Lithium	*n* = 2 [174,175].	*n* = 1 [175].
Metals	*n* = 5, mercury [142,179,180], copper [177], lead [177], caesium [178].	*n* = 4, mercury [142,179,180], copper [177], lead [177], caesium: no studies included.
Metformin	*n* = 1 [13].	No studies included.
Methotrexate	No studies included.	No studies included.
Moclobemide	No studies included.	No studies included.
Nonsteroidal anti-inflammatory drugs (ibuprofen and others)	Ibuprofen: no studies included. Other: *n* = 6 [152,153,253,498–500].	Ibuprofen: no studies included. Other: *n* = 6 [152,153,253,498–500].
Opioids	*n* = 6, tilidine [191], tramadol [192], diphenoxylate [193], morphine [142,237], dextropropoxyphene [245].	*n* = 6, tilidine [191], tramadol [192], diphenoxylate [193], morphine [142,237], dextropropoxyphene [245].
Organophosphorus insecticides	*n* = 3, various organophosphorus insecticides [199,501,502].	*n* = 3, various organophosphorus insecticides [199,501,502].
Paracetamol	*n* = 22 [82,84,211,231,242–244,299,316,317,334,335,467,503–511].	*n* = 22 [82,84,211,231,242–244,299,316,317,334,335,467,503–511].
Paraquat	*n* = 3 [214–216].	*n* = 3 [214–216].
Phenytoin	*n* = 2 [231,244].	*n* = 2 [231,244].
Quinine-quinidine (antidysrhythmic Class I)	*n* = 4 [237,238,299,512].	*n* = 4 [237,238,299,512].
Salicylates	*n* = 22 [81,142,152,155,237,238,242–247,250–252,254–256,513–516].	*n* = 22 [81,142,152,155,237,238,242–247,250–252,254–256,513–516].
Selective serotonin reuptake inhibitors	*n* = 4, fluoxetine [277–280].	*n* = 4, fluoxetine [277_280].
Sulfonylureas	*n* = 1, carbutamide, chlorpropamide, tolazamide, tolbutamide, glibenclamide/glyburide, glipizide [287].	*n* = 1, carbutamide, chlorpropamide, tolazamide, tolbutamide, glibenclamide/glyburide, glipizide [287].
Thallium	*n* = 1 [291].	*n* = 1 [291].
Theophylline and aminophylline	*n* = 7 [244,296,297,299,300,517,518].	*n* = 7 [244,296,297,299,300,517,518].
Toxic alcohols	*n* = 2, ethylene glycol [519], isopropanol and acetone [520].	*n* = 1, isopropanol and acetone [520].
Tricyclic antidepressants	*n* = 15, imipramine [299,319,320], desipramine [299,319], amitriptyline [238,245,299,316–318], nortriptyline [242,299,315], doxepin [299].	*n* = 15, imipramine [299,319,320], desipramine [299,319], amitriptyline [238,245,299,316–318], nortriptyline [242,299,315], doxepin [299].
Valproic acid	No studies included.	
Venlafaxine	No studies included.	