

Superwarfarin (Rodenticide) Poisoning

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Features

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Extent of haematuria



Vit.K₁: 10mg daily → 50mg Q8H →
 FFP: 6 units 6 units

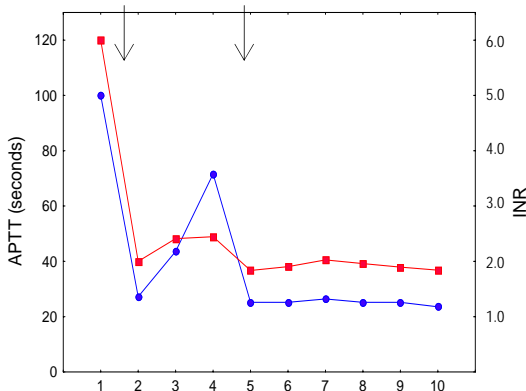


Figure 1 Change of international normalized ratio (INR), activated partial thromboplastin time (APTT) and bleeding symptoms in relation to treatment

Case Report

A 72-year-old gentleman presented to the Accident & Emergency Department complaining of gross haematuria for 3 days. There was no dysuria or frequency, and he denied any history of similar episodes. He also reported mild gum bleeding for one day but he had no other bleeding symptom. He had no significant past medical illness and denied any drug or herb use. He has already retired and lived with his wife and three children in a public housing estate in Shatin. There was no significant family history. His physical examination was unremarkable and he had no skin bruises. Blood tests showed a markedly prolonged prothrombin time (PT) of > 60 seconds (reference range: 10-14) with an international normalized ratio (INR) of >5 (reference range: 0.9-1.1) and an activated partial thromboplastin time (APTT) of > 120 seconds (reference range: 24-37). Other initial investigations including complete blood counts, electrolytes, urea, creatinine and liver function tests were all normal. He was given 6 units of fresh frozen plasma (FFP) and intravenous vitamin K₁ 10mg daily. His clotting profile improved immediately after FFP transfusion but there were progressive prolongation of INR and APTT despite vitamin K₁ 10mg daily and the required further FFP transfusion (Figure 1). Further studies confirmed deficiency of vitamin K-dependent clotting factors: factor II 11% (50-200), factor VII:C 82% (50-200), factor IX 4% (40-160) and factor X 2% (50-200). He was switched to oral vitamin K₁ 50mg thrice daily with prompt normalization of his clotting profile and resolution of bleeding symptoms. Assay performed by the Hospital Authority Toxicology Reference Laboratory confirmed the presence of bromadiolone, a superwarfarin, in the patient's blood sample collected a day after admission. The case was reported to the Centre for Health Protection (CHP) of the Department of Health for further investigation. The patient denied intentional ingestion of superwarfarin/rodenticides and the reason for exposure to bromadiolone remains a mystery. The dosage of vitamin K₁ supplement was gradually tapered with close monitoring of his clotting profile. The patient remained well with normal clotting profile upon his last follow-up visit.

Superwarfarin (Rodenticide) Poisoning (Cont')

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Discussion

Superwarfarins are a class of rodenticides developed in the 1970s to overcome warfarin resistance in rats. Examples include brodifacoum, bromadiolone, chlorophacinone, difenacoum and difethialone. These long acting, fat-soluble anticoagulants are colourless, tasteless, odourless compounds.

Superwarfarins are much more potent and have very long half-lives varying from weeks to months compared with warfarin.^{1,2} All of the superwarfarins work by blocking the formation of activated vitamin K (vitamin K₁) via inhibition of vitamin K 2,3-epoxide reductase enzyme complex.³ When vitamin K₁ is not regenerated, the clotting factors II, VII, IX and X cannot be activated and a coagulopathy will develop.

Clinical Features

Most exposures result in no clinical effects as the dose of warfarins and superwarfarins is low in the preparations of anticoagulant rodenticides in Hong Kong. Bleeding is the most common clinical feature of superwarfarin poisoning due to either chronic exposures or massive overdose, and may occur from any mucosal site or organ. Patients may present with skin petechiae, ecchymoses, epistaxis, gum bleeding, haematemesis, haematuria, haemoptysis, melaena and vaginal bleeding. More than one system is usually involved.^{3,4} Patients may also present with vague gastrointestinal symptoms, such as nausea, vomiting and abdominal pain after acute exposures.

Investigations

Laboratory studies show elevated PT and APTT that are corrected on a 1:1 mixing study with normal plasma; depleted levels of vitamin K-dependent clotting factors (factors II, VII, IX, X) and presence of superwarfarin in blood on special assays. Superwarfarin exposure should be suspected in patients who present with a coagulopathy consistent with vitamin K deficiency in the absence of warfarin therapy, liver disease, or the use of an inhibitor, and whose conditions show a transient or no response to standard doses of vitamin K therapy.³ PT and INR may be normal up to 48 hours after exposure and PT checked at 48-72 hours post-acute exposure should identify all patients at risk of bleeding. If patients have pre-existing liver disease or bleeding tendency, PT should be monitored at baseline, 24 and 48 hours. PT/INR should be repeated every 6-12 hours if any prolongation occurs until the level plateaus.

Management

Activated charcoal can be considered for patients with intentional overdose, large intake and presenting within 1-2 hours of superwarfarin poisoning. Vitamin K₁ (phytonadione) is the specific antidote for superwarfarin poisoning and can be given orally or intravenously. Prophylactic vitamin K₁ supplement immediately after exposure to superwarfarin in an asymptomatic patient with no laboratory evidence of coagulopathy is not indicated as this may affect the monitoring of clotting profile. In patients with coagulopathy, a starting dose of vitamin K₁ 100mg per day given in four divided doses orally should be used. A less frequent dosing regimen may not be effective. Dose of vitamin K₁ should be titrated to correct the PT/INR. The daily dose required may be up to 600mg depending on the severity of coagulopathy and the duration of therapy may vary from 2 months to a year.^{2,5,6} Vitamin K₄ (acetomenaphthone) is ineffective and should not be used. In patients with active bleeding, treatment should involve administration of fresh frozen plasma and/or coagulation factor concentrates, in addition to vitamin K₁ supplement.

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Superwarfarin (Rodenticide) Poisoning

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Alert

In the past 6 months, five confirmed cases of superwarfarin (rodenticide) poisoning were admitted to two Hospital Authority hospitals. Apart from two patients with deliberate self-poisoning, the reasons for exposure to superwarfarin were obscure. They all presented with major bleedings and severe, prolonged clotting abnormalities.

Superwarfarins are readily absorbed through the gastrointestinal tract, skin and respiratory system. Repeated exposure may lead to cumulative effect, due to the prolonged duration of action. Superwarfarins act by the same mechanism as warfarin but are 100 times more potent and have much longer plasma and tissue half-lives (weeks to months). In acute bleeding, administering fresh frozen plasma affords rapid correction (within hours) of clotting defect, but the effect is not durable. Therefore, vitamin K₁, NOT vitamin K₄ (acetomenaphthone), is also required. Initially, vitamin K₁ is given slowly by the intravenous route. It should be administered every 6 hours as the effect becomes much shortened in the presence of superwarfarins, which inhibit the regeneration of inactive vitamin K to the active moiety. Subsequently, it is given by the oral route in divided daily doses. Patients may require up to 600 mg of vitamin K₁ daily for weeks to months.

Superwarfarin poisoning should be suspected if there is a severe, prolonged clotting defect (of unknown aetiology) with a transient or lack of response to standard treatment. The reasons for exposure can be obscure. Management and investigations of these patients require experts' inputs. For these reasons, kindly let our Teams know of such cases. The Toxicology Reference Laboratory of Hospital Authority provides measurement for warfarin and all the registered superwarfarins in Hong Kong. Requests can be arranged via individual hospital laboratory.



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Vitamin K₁ as the Antidote for Warfarin and Superwarfarin Poisoning

Mr Ken WS Lee, Pharmacist, Hospital Authority

Antidote

Vitamin K, an essential vitamin, is a broad term which entails at least two natural forms, K₁ and K₂. Major forms of vitamin K are listed in Table 1. Vitamin K₃ was found to have caused haemolytic anaemia and jaundice in newborns, hence its use has been banned by the Food and Drug Administration (FDA).³ The only advantage of vitamin K₄ is that it is absorbed directly from the intestine by a passive process which does not require the presence of bile salts. *While it can be used to replenish depleted patients, vitamin K₄, lacking the phytyl side chain of the parent vitamin K compound, possesses almost no antagonistic effects against coumarin compounds.^{4,5} Hence, vitamin K₄ is neither interchangeable with vitamin K₁ nor a substitute for vitamin K₁, when oral anticoagulants are responsible for the coagulopathies.⁶*

Vitamin K₁ (Phytomenadione)

Indications:⁷

- Coagulation disorders: Coagulopathies due to faulty formation of factors II, VII, IX, and X when caused by vitamin K deficiency or interference with vitamin K activity.
 - ★ **Anticoagulant-induced prothrombin deficiency** caused by coumarins or indandione derivatives found in long-acting anticoagulant rodenticides (LAARs);
 - ★ Hypoprothrombinaemia secondary to factors limiting absorption or synthesis of vitamin K, e.g. obstructive jaundice, biliary fistula, cystic fibrosis of the pancreas OR factors interfering with the metabolism of vitamin K (i.e. drugs such as salicylates and antibacterials);
- Prophylaxis and treatment of haemorrhagic disease of the newborn.

Table 1 Major analogues of Vitamin K

Vitamin	Synonyms ^{1,2}	Source ^{1,2}	Uses ^{1,2}
K ₁	Phylloquinone	Naturally synthesized by plants and algae	A cofactor in the synthesis of active clotting factors II, VII, IX, and X
	Phytomenadione or phytonadione	Chemically synthesized	Treatment of impaired coagulation due to decreased production of coagulation factors secondary to acquired aetiologies
K ₂	Menaquinone	Naturally synthesized by bacteria in the intestines	A cofactor in the synthesis of active clotting factors II, VII, IX, and X
	Menatetrenone	Chemically synthesized	Prevention or reduction of bone loss in osteoporosis
K ₃	Menadione	Chemically synthesized	Poultry feed and as an intermediate in biosynthesis of vitamin K ₁
K ₄	Acetomenaphthone or menadiol sodium diphosphate	Chemically synthesized	Prevention of vitamin K deficiency in patients with malabsorption syndromes

Vitamin K₁ as the Antidote for Warfarin and Superwarfarin Poisoning (Cont')

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Antidote

Pharmaceutical forms:

- ★ Formulations for vitamin K₁ (phytomenadione as the only active ingredient) registered in Hong Kong include solution for injection which is available in 3 different strengths, 10mg/ml, 2mg/0.2ml, and 1mg/0.5ml.⁸ This solution for injection may be given by mouth.
- ★ Formulations for vitamin K₁ not registered with the Department of Health (e.g. phytomenadione oral tablets 5mg/10mg) are available in the market and may be purchased on a named patient basis. Currently, these unregistered vitamin K₁ oral tablets are available at public hospitals in Hong Kong.
- ★ *The oral formulation of vitamin K registered in Hong Kong contains vitamin K₄ only. This preparation should not be used for the treatment of coagulopathies due to faulty formation of factors II, VII, IX, and X when caused by vitamin K deficiency or interference with vitamin K activity.*

Dosages.^{6,7,9,10,11,12,13}

- ★ Over anticoagulation with drugs of the coumarin type: 1 – 5mg by mouth. This should be given only when discontinuation or reduction of the interfering drugs failed to lower the International Normalized Ratio (INR) substantially in 24 hours. Monitor the INR more frequently and repeat dose(s) if the response has been inadequate.

- ★ LAAR-induced prothrombin deficiency: 25-50mg three to four times daily by mouth, may be preceded by a subcutaneous dose of 10-25mg if necessary. Doses of up to 600 mg per day have been reported for initial management of severe coagulopathies. Patients who have overdosed on LAARs may require months of vitamin K therapy.

Cautions:^{4,6,14}

- ★ For patients deficient in bile salts who require oral vitamin K₁, exogenous bile salts such as ursodeoxycholic acid should be given with each dose of vitamin K₁.¹⁴
- ★ The oral route is preferred whenever possible because this route is virtually free of unwanted effects.⁶ It is preferred over subcutaneous route since the oral route offers more rapid onset of action and greater patient acceptability (free of pain and avoidance of bruising at injection site).
- ★ Although the intravenous (I/V) administration of vitamin K₁ offers rapid and reliable therapeutic effect, this route should be reserved for life-threatening situations since this route may rarely cause fatal anaphylactoid reactions (see below).
- ★ The intramuscular route is seldom used due to the risk of haematoma formation.⁶

A literature review by Fiore L.D. et al showed a total of 23 cases (3 fatal) of anaphylactoid reactions from I/V vitamin K₁. A review on the US Food and Drug Administration Spontaneous Reporting System Adverse Reactions (SRSAR) files revealed that 69% of patients who received I/V vitamin K₁ had an anaphylactoid reaction, with 24 fatalities (18%) attributed to the vitamin K₁ reaction; while there were 18% of patients who received vitamin K₁ via a non-intravenous route and developed the same reaction, with 1 fatality (3%) attributed to the drug. The onset of symptoms was either during or within minutes of I/V administration. These data reinforce that such anaphylactoid reactions to I/V vitamin K₁ are real and are often life-threatening although the incidence is rare. Fatalities were reported even when the drug is diluted and infused slowly. To prevent anaphylactoid reactions, it is recommended that a starting dose of 10mg of vitamin K₁ be dissolved in a 5% dextrose or 0.9% sodium chloride solution and be administered slowly via an infusion pump. Product literature should be consulted with respect to the rate of infusion.^{4,6,7}

Vitamin K₁ as the Antidote for Warfarin and Superwarfarin Poisoning (Cont')

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Antidote

Onset of action:^{9,15}

- ★ A minimum of 1 to 2 hours irrespective of dose. It may take 8-12 hours or longer to reach the target INR if inadequate doses are given. The INR should be monitored and the dose of vitamin K₁ adjusted accordingly.
- ★ Also depends on the route; a drop in the INR will be noted in several hours in most cases.

Adverse effects:^{4,7,9}

- ★ The parenteral route is responsible for the majority of adverse events, with the I/V route having the highest incidence and fatality due to anaphylactoid reactions such as chest pain, dyspnoea, cyanosis and cardiovascular collapse.
- ★ Other effects include pain, swelling, phlebitis and necrosis at the injection site.

- * *Vitamin K₁ (phytomenadione) is the only vitamin K compound used to reverse hypoprothrombinaemia and haemorrhage caused by oral anticoagulant therapy.*
- * *For patients deficient in bile salts who require oral vitamin K₁, exogenous bile salts such as ursodeoxycholic acid should be given with each dose of vitamin K₁.*
- * *Vitamin K₄ is neither interchangeable with vitamin K₁ nor a substitute for vitamin K₁, when oral anticoagulants are responsible for the coagulopathies.*
- * *The oral route is preferred whenever possible.*

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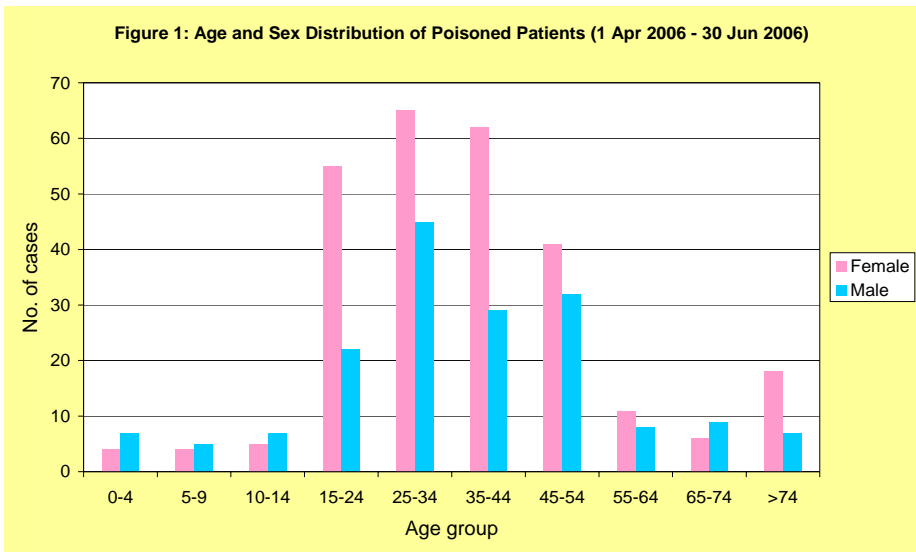
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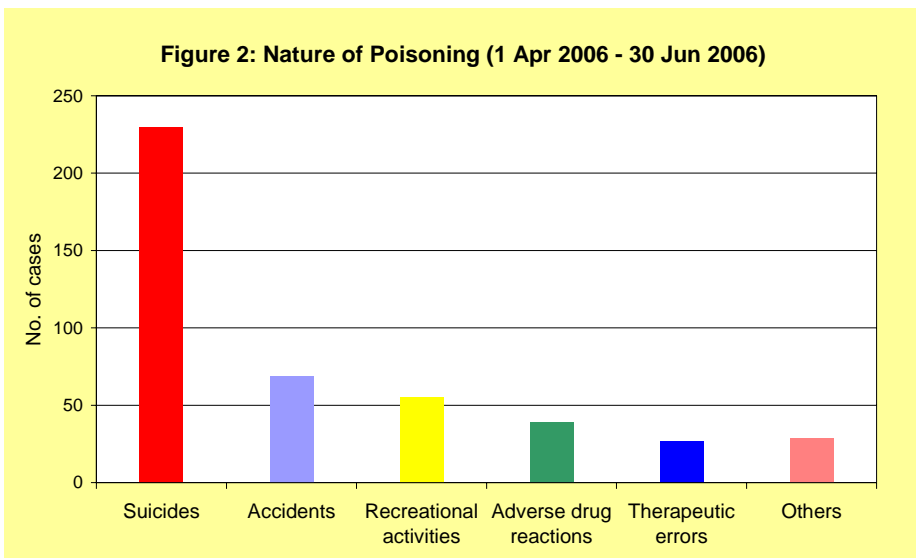


Toxicological Surveillance

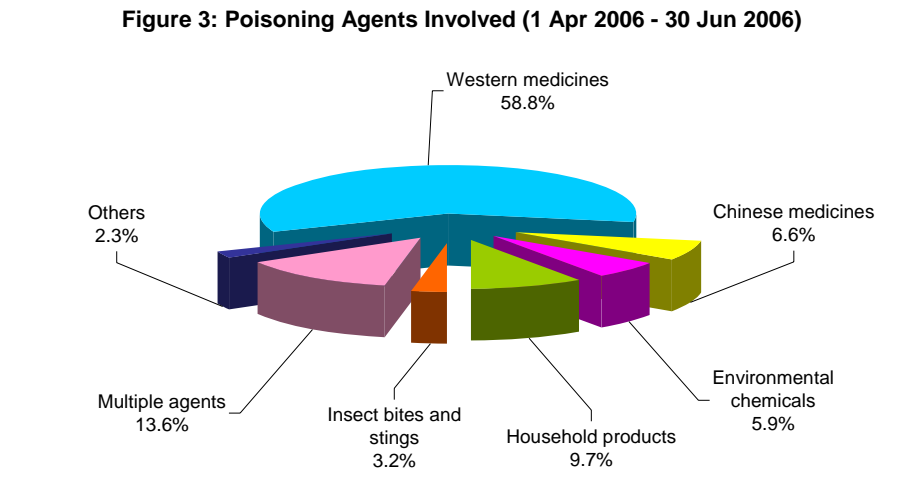
Between the period of 1 April and 30 June 2006 there were 442 cases of poisoning (excluding infective food poisoning) recorded by the Accident & Emergency Departments of six acute regional hospitals (QMH, PYNEH, UCH, PWH, PMH & TMH). The male to female ratio is approximately 2:3. The age and gender distribution of poisoned patients is shown in Figure 1.



Over two hundred cases of poisoning (53%) occurred at home, while fourteen cases (3%) occurred at workplaces and 129 cases (29%) happened at other places such as school, shopping centre and car park. The place of exposure for the rest of the cases (15%) was unknown.



With respect to the nature of poisoning, 230 cases were due to suicides (52%), 62 cases were accidental in nature (14%), 55 cases involved use of drugs for recreational purposes (12%), and 39 cases arose from undesirable effects of drugs (9%). (Figure 2)

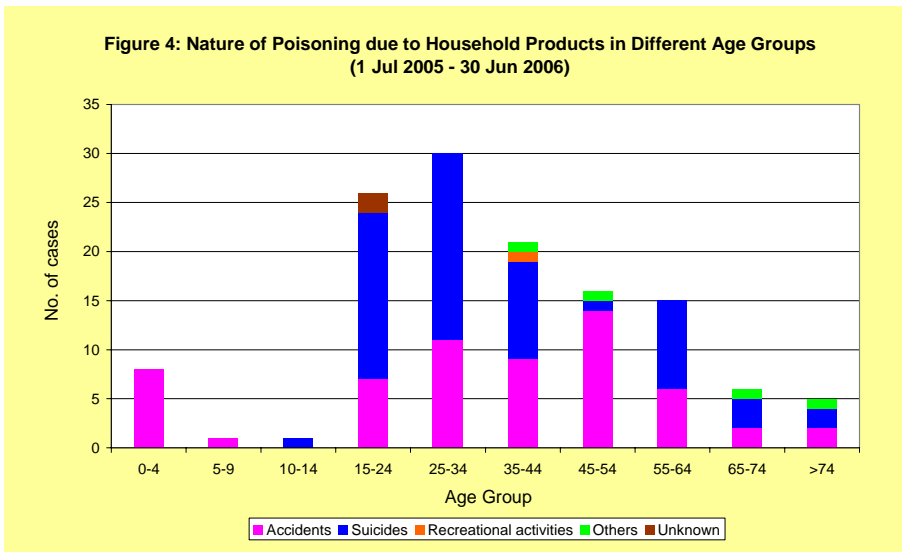


Whilst western medicines remained the most common substances involved in poison exposures (Figure 3), accounting for 260 cases (58.8%), the number of cases involving chinese medicines and household products had increased from 5.1% to 6.6% and 6.1% to 9.7% respectively when compared to the previous quarter.

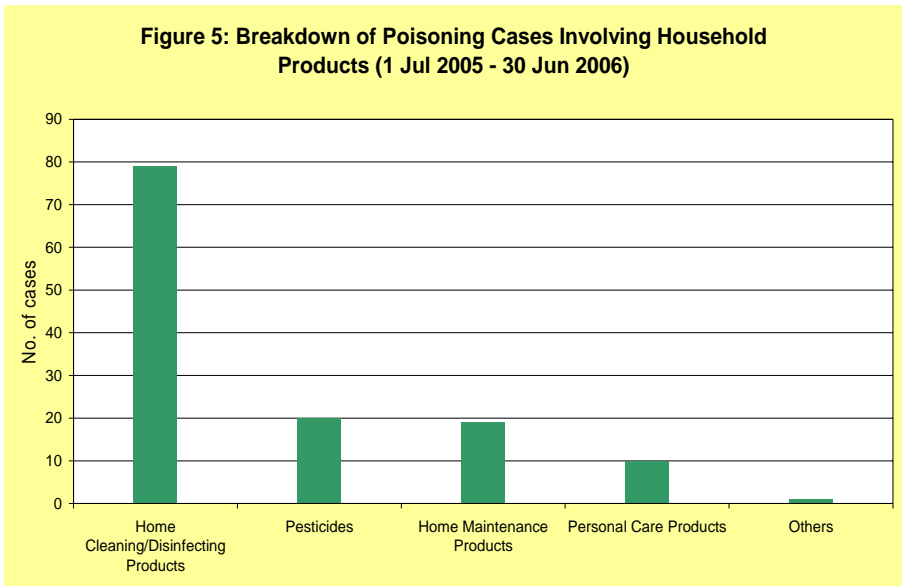


Toxicological Surveillance

During the twelve-month period between July 05 and June 06, a total of 129 cases of household product poisoning were recorded by the Accident & Emergency Departments of six acute regional hospitals (QMH, PYNEH, UCH, PWH, PMH & TMH). Nearly half of the cases (48%) were suicidal whereas 47% of the cases were accidental in nature. Majority of the suicidal cases (56) involved the age groups between 15 and 64. For children less than ten years of age, all of the cases (9) were accidental in nature, involving bubble bath, silica gel and stainless steel cleaner (Figure 4).



The type of substances involved in household product exposures included home cleaning/disinfecting products (61%) such as disinfectants, bleaching agents and multipurpose cleaning agents; pesticides (16%) like insecticides and herbicides; home maintenance products (15%) such as caustic drain cleaner; and personal care products (8%), for examples, shampoo, baby oil and mouthwash (Figure 5).



Two cases of death were reported. The first case involved an elderly woman who was found to have aspirin overdose. The other was a case of multi-organ failure, but the cause of death has not yet been ascertained.

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