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Abstracts of the European Association of Poisons Centres and Clinical Toxicologists XIX International Congress

1 PESTICIDES—WHAT TOXICOLOGICAL DATA ARE REQUIRED FOR REGULATORY APPROVAL?

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In Europe at the present time, new and existing pesticides are subject to regulation at both national and European Community (EC) levels. The EC has prioritized long-standing pesticides for review and designated countries to undertake the evaluations. The toxicology package required to support active ingredients, old and new, and their various formulations is voluminous, expensive to generate and expensive to evaluate. Indeed, the costs may be such that manufacturers may not be prepared to finance the studies required to support products that have limited sales, thus creating problems of pest control for niche markets. Regulation aims to ensure that a pesticide is effective in the circumstances under which it will be used. Any risks posed to non-target organisms, the wider environment, pesticide operators and consumers (including high-risk groups such as pregnant women, young children, and the elderly) must be acceptable and minimized as far as possible. Clearly, the amount of data required for approval to investigate a new active ingredients that will not find its way into the food chain (the restricted amount of crop treated with an experimental pesticide would normally be destroyed) is much less than for one which is to be marketed commercially. Much of the data package is standard and addresses the pesticide's physico-chemical properties, plant and mammalian metabolism, fate in the environment, efficacy, mammalian toxicology, its impact on non-target species, soil and water and the levels to which operators and consumers are likely to be exposed. The remainder of the package, however, is flexible, constantly evolving in the light of scientific advances and tailored to individual needs. Data requirements additional to those submitted for evaluation may be set in discussion between the regulators' scientific advisors and the manufacturers to elucidate perceived areas of concern, the principle underlying such requests being a ''need to know'' rather than ''it would be interesting to know.'' Human data are clearly preferable to animal data in risk assessment but are commonly either not available or are unhelpful, often because the magnitude of exposure cannot be quantified. Poisons information enquiries can be of value in identifying the frequency with which acute exposure to a pesticide is a matter for health concern and reports of accidental and intentional poisonings are useful in identifying end-points that might be used to set acute reference doses. Rarely, experience in humans may overturn a conclusion reached on the basis of animal studies (e.g., that a pesticide is an irritant or a skin sensitizer). On the other hand, the absence of data indicating a problem cannot be interpreted as meaning there is no problem.

2 HERBICIDE FORMULATIONS—WHAT TO EXPECT

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Background: Herbicides comprise 55% of the 25 million tons of pesticide active ingredients used worldwide annually. The active ingredient is rarely used commercially as a single agent preparation but must be formulated with other ingredients to allow mixing, dilution, application, and stability. The final product is often carefully designed, not only for chemical compatibility but also to optimize the effectiveness of the active ingredient. In most world areas, the identity of the formulation ingredients is not disclosed outside the business team and regulatory agency, often under the outmoded notion of ''trade secret'' protection. Secrecy protection is still desired, but frequently to deflect inquiries from consumer safety groups and environmentalists. Health professionals often seem at a loss in dealing clinically with the concept of a formulated pesticide, either totally discounting the non-active ingredients, or assigning an inappropriate level of concern to them. An understanding of the basic types of herbicide formulations and the ingredients they may

contain is helpful background for the medical toxicologist. Review: The basic modes of application of herbicides are spray and solid broadcast. Certain novel application routes are seen, e.g., bullets to shoot into trees. Formulations for spray application include: water soluble liquids, water soluble powders, emulsifiable concentrates, wettable powders, water dispersible liquids or "flowables," and water dispersible granules. These formulations carry the highest concentration of active pesticidal ingredient (25–65%) because they are intended for dilution prior to application except certain products sold to the home and garden market as "ready-to use." Solid formulations for broadcast directly out of the bag include granules and pellets. They are characteristically of lower concentration (2–25%) because they are not diluted prior to use, but are adsorbed onto a carrier solid in the proper concentration. The first ingredient to consider in any formulation is the carrier, which is water, an organic solvent or oil, or a clay-like solid such as attapulgite. The carrier may be deduced based on the solubility characteristics of the active ingredient. Special effort must be made to ascertain whether the entity actually contained in the formulation is in a salt or the parent form. The chemical form can dramatically change the solubility and the thus the polarity of the carrier. Co-solvents may be necessary to optimize solubility and stability (e.g., *N* methyl pyrrolidone, alcohols, glycols). The trend is toward ultra-low-use-rate chemicals that are carried and/or diluted with water. Surfactants are nearly universally present in herbicide formulations or added prior to application, an exception being use in natural water areas. Surfactant aids uniform spreading of the spray droplet on the leaf and penetration of its waxy cuticle by the active ingredient. In solvent-based formulations it permits a stable oil-in-water emulsion to form when diluted with water for actual use. There are many major classes of agricultural surfactants, some of which are also used in other industrial segments. Because of their critical role in performance enhancement, surfactant systems are currently of intense competitive importance. Other formulation ingredients include pH adjusters (e.g., sodium or potassium hydroxide, sulfuric acid, phosphoric acid); buffers (e.g., sodium acetate); milling aids (e.g., amorphous silica); antifoaming agents (e.g., dimethylpolysiloxane); acid scavengers (e.g., epoxidized soybean oil); dyes to mark areas already treated, to standardize color if the active agent is chromogenic, to indicate extreme toxic hazard (e.g., methyl violet, FDC colors); suspending agents (e.g., sodium alginate, xanthum gum); preservatives (e.g., sodium sulfite, benzisothiazalone, propionic acid, sorbic acid); dispersant/emulsifier (e.g., lignosulfonate); densifier (e.g., sodium chloride, aluminum sulfate); antifreeze (e.g., ethylene glycol, propylene glycol); and crystal promoters (e.g., sugar, salt). In highly regulated environments, the other formulation components in pesticides are receiving scrutiny. Since they are directly applied to the environment in immense quantities, their acute and chronic toxicity must be understood and factored into the regulatory process. In the US, the strategy has been to categorize currently used formulation ingredients into four lists based on their toxicology profile. List 1, agents of toxicological concern, has been reduced from 37 to 8 chemicals over the last decade. Examples of voluntarily withdrawn List 1 inerts include aniline, carbon tetrachloride, *n*-hexane, TDI, and asbestos. Currently used List 1 ingredients include formaldehyde, diethylhexylphthalate, and nonyl phenol. Interestingly, alkyl phenol exthoxylate surfactants, which are suspected of endocrine disruption, are on List 4, agents of minimal concern. List 4 ingredients are generally regarded as safe or have current use patterns that do not pose an unreasonable risk to human or environmental health.

3 PESTICIDES—ARE THE CURRENT EC AND WHO LIMITS FOR DRINKING WATER TOXICOLOGICALLY SOUND?

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Background: In 1980, European legislation in the form of the EC Council Directive 80/778/EEC[1] laid down standards relating to the quality of water intended for human consumption. Specifically, a uniform Maximum Admissible Concentration (MAC) of 0.1 μg/L was applied for individual pesticides in drinking water, irrespective of their toxicity, together with a limit of 0.5 μg/L for total pesticides. The MAC for individual pesticides was based on the analytical detection limits for organochlorine pesticides achievable at the time, and its implementation reflects an ethos that pesticides should not be present in drinking water. Review: The derivation of these MACs has been criticized widely as having no toxicological basis. Except in the event of massive accidental contamination of the water supply, pesticides are unlikely to be present at concentrations sufficient to give rise to acute toxicity. The major concern regarding pesticides as contaminants of drinking water is the potential exposure of large populations to low concentrations of compounds over long periods of time. Of particular concern are substances that may be carcinogenic, and those which have a tendency to bioaccumulate. Given the diversity of chemical classes of pesticides and their widely varying toxicity, concentrations in drinking water that constitute a health hazard can only be established by evaluating the toxicity of individual com-

pounds. This approach has been adopted by the WHO, which has published guideline values for individual pesticides.[2] For the majority of pesticides, it is generally believed that there is a threshold dose below which no adverse health effects will occur. WHO guidelines for these compounds are based on Tolerable Daily Intakes (TDIs), values that are derived mainly from animal studies. In general, insecticides are more toxic to man than herbicides and consequently they have higher TDIs. In the case of genotoxic carcinogens, it is likely that no such threshold exists, and guideline values are derived using a mathematical model that combines toxicological data with the concept of 'acceptable levels of risk'. The guideline values set by the WHO vary over several orders of magnitude for different pesticides. Most exceed the EC limit of 0.1 μg/L, some considerably so (e.g., 100 μg/L for dichlorprop), but in a few cases lower limits have been set (e.g., 0.03 μg/L for aldrin). Guideline values for pesticides such as those published by the WHO were developed to safeguard health on the basis of lifelong consumption, and incorporate safety factors of 1000 or more. Small or transient breaches of the limit such as may occur following heavy rainfall are not considered, therefore, to represent a threat to public health, but rather are taken to be a signal that investigative and remedial action may be necessary. In contrast, to comply with the EC Directive, drinking water must meet pesticide standards for every sample analyzed. Thus, every breach of a pesticide standard represents a breach of European law. Given the very low risk to health of any short-term exceedances, this absolute approach is widely regarded as untenable, both in terms of science and public policy. Clearly, it is desirable that drinking water quality is maintained at as high a level as possible. However, standards must be feasible to implement as well as protective to public health. In order to achieve compliance with current EC standards, water providers may incur excessive costs in limiting concentrations of compounds that may be of no real toxicological significance. In addition, some restrictions may have to be placed on the use of highly effective pesticides of relatively low toxicity that may be present in water at slightly elevated concentrations. In deriving standards for pesticides in drinking water, it is essential that sound toxicological criteria are utilized. Conclusion: The stringent and uniform pesticide standard applied by the EC Directive is not toxicologically sound, based as it is on analytical and not toxicological criteria, and may only serve to increase public concern unnecessarily. On the contrary, the WHO guideline values for pesticides were developed to safeguard public health on the basis of lifelong consumption and are therefore more toxicologically robust. References: [1]*EC Directive Relating to the Quality of Water Intended for Human Consumption, 80/778/EEC*. Luxembourg: Office for Official Publications of the European Communities, 1980. [2]WHO. *Guidelines for Drinking Water Quality. Volume 1. Recommendations*. 2nd ed. Geneva: World Health Organization, 1993.

4 PESTICIDES—IS ROUTINE MONITORING IN DRINKING WATER COST-EFFECTIVE?

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Background: The EC "Drinking Water Directive" (80/778/EEC)[1] sets a Maximum Admissible Concentration (MAC) for individual pesticides in drinking water of 0.1 μg/L and a total concentration for all pesticides of 0.5 μg/L. These limits were not based on any toxicological criteria, but on the analytical limit of detection for the organochlorine insecticides at the time of the Directive. As the Directive was based on analytical criteria it may be thought that the routine analysis of pesticides in drinking water would be straightforward. However, the organochlorine insecticides are relatively easy to analyse as they extract readily into organic solvents, separate well chromatographically and can be detected by sensitive and selective methods. The majority of pesticides pose great difficulties in analysing at the 0.1 μg/L MAC, and some cannot be monitored routinely at the required limit of detection of 0.01 μg/L. In the UK water companies are not required to monitor routinely for all pesticides.[2] Companies need monitor only those pesticides that are used within their catchment areas and which could reach water sources. However, atrazine and simazine have been used widely in non-agricultural situations and all companies have been advised to monitor for these herbicides. Review: Data from England and Wales, where comprehensive audits of the public water suppliers are published annually, show that in 1997 there were 788,880 determinations for individual pesticides[2] at an estimated cost of well over £1 million. In addition, the water industry is still required to install additional treatment to remove pesticides at a cost of some £1 billion,[2] with ongoing operating costs estimated at a further 10% of this figure. To view these data in context, only 157,245 determinations were made for faecal coliforms, yet it is widely accepted that the main threat to public health is from microbial contamination and the World Health Organization stresses that microbial quality should always be viewed as being of paramount importance.[3] The resources put into monitoring other chemical species are also at a much lower level than those invested into pesticide monitoring, even where the standards set are based on substantial toxicological knowledge. For example, 30,403 determinations were carried out for nitrate, 36,685 for nitrite and 29,237

for lead. The MAC for lead has since been reduced from 50 μg/L to 25 μg/L with the provision for a further lowering of the limit to 10 μg/L in line with the WHO Guidelines for Drinking Water Quality. It would seem reasonable to place a greater emphasis on identifying and remediating households with potential lead problems rather than on what is only a theoretical threat from pesticides. Despite such comprehensive monitoring of pesticides in drinking water, only 292 (0.04%) of 788,880 analyses were found to have concentrations above the 0.1 μg/L limit, representing 15 individual species.[2] Of these 15 compounds health based exposure limits published by the WHO and US EPA are available for eleven, and in every case the concentration reported is well below these guidelines. In the UK at least, there is no evidence that pesticides in drinking water pose any threat to public health. The current legislation also poses the question of what is a pesticide? Trichloroacetic acid (TCA) is used in some pesticide formulations and so under the terms of the current legislation needs to be analysed for at the 0.1 μg/L level. However, TCA is also produced in concentrations well in excess of the pesticide standard as a by-product of chlorination. This can lead to the situation where TCA is required to be analysed as a pesticide in raw waters, even though it will be present in the final chlorinated supply at a much higher concentration. Additionally, health based guidelines have been published by the WHO[3] and US EPA[4] of 100 μg/L and 300 μg/L respectively, making the monitoring of TCA at 0.1 μg/L seem even more futile. Conclusions: No one would advocate that pesticides are desirable constituents of drinking water and, in an ideal world, the concentrations in all supplies would be zero. However, the available UK data indicate that there are very few breaches of the pesticide standard and that the concentrations that have been found are well below published health based guidelines and are not of public health concern. The concentrations found in drinking water would also seem to contribute a small percentage of total exposure and do not justify the expense of such widespread monitoring and remediation. It would be more reasonable to advocate standards, and subsequently monitoring strategies, that are based on toxicological data. If this approach were to be adopted the monitoring of pesticides in drinking water would be more cost-effective. However, given the political pressures associated with drinking water quality in general, and pesticide contamination in particular, such a change is unrealistic at the present time. References: [1]*EC Directive Relating to the Quality of Water Intended for Human Consumption, 80/778/EEC.* Luxembourg: Office for Official Publications of the European Communities, 1980. [2]Drinking Water Inspectorate. *Drinking water 1997.* London: The Stationery Office, 1998. [3]WHO. *Guidelines for drinking-water quality. Volume 1. Recommendations.* 2nd ed. Geneva: World Health Organization, 1993. [4]US Environmental Protection Agency. *Drinking Water Regulations and Health Advisories.* Washington, DC, Office of Water, 1996.

5 PESTICIDES—OCCUPATIONAL USE AND MISUSE

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Introduction: Pesticide exposure can occur orally, by inhalation or via the skin. Most pesticides have relatively low volatility and the droplet size generated by typical spray equipment is generally too large to be respirable. Therefore, the skin is the main route of absorption into the body for most pesticide formulations and applications. Dependent on the inherent toxicity of the pesticide formulation and the magnitude and duration of exposure there may be a risk of adverse health effects. These can either be localized (irritation of skin, eyes or mucous membranes; skin sensitization), or systemic. The term 'poisoning' should be restricted to the latter category. Health effects from acute exposure: There are no reliable data on the global extent of acute pesticide poisoning. There is a lack of consistent definitions and data collection formats and the widely used WHO estimate is based on extrapolation of data from a small number of countries. This is now being addressed by a new project under the auspices of the International Programme on Chemicals Safety (IPCS) and supported by the Global Crop Protection Federation (GCPF). Two points can, however, already be made with relative certainty. Firstly, severe acute pesticide poisoning is largely associated with suicide, both in the developed and the developing world. Secondly, despite the fact that industrialized countries use some 80% of the world production of pesticides, acute pesticide poisoning is an uncommon cause of hospital admission and fatalities in those countries. Health effects from chronic exposure: Here, the biggest problem is that exposure estimates dating back some 30 or 40 years are virtually impossible to quantify. Nevertheless, a review of 440 research papers published between 1975 and 1991 has shown some interesting results. For example, when compared to the general population, total mortality has been found to be consistently lower among pesticide manufacturers and applicators, and non-cancer causes of deaths were generally less frequent than expected. There was a strikingly consistent reporting of a low overall cancer risk among agricultural workers; life-style, clean air and low prevalence of smoking have been hypothesized to explain these observations. Some studies have shown an increased risk for certain types of cancer such as soft tissue sarcoma

and myelolymphoproliferative disorders. However, many of the reported associations with pesticide exposure remain controversial and other potential aetiological agents (e.g., viruses) have often not been exhaustively taken into account. Protection of pesticide applicators: Pesticides should be sold in appropriate containers and pack sizes to prevent decanting into unmarked containers. Labels should be clear and concise and give adequate information about risks and protective measures. The use of pictograms is of particular value in countries with low literacy. Protective clothing must be appropriate to the risks involved, but should not be so cumbersome to prevent its use in practice. Basic hygiene measures must be encouraged. Access to pesticides should be restricted to *bona fide* users who have a basic knowledge of safe storage and use of pesticides. Conclusions: Prevention of adverse health effects must be of prime importance in the occupational use of pesticides. This is the responsibility of all parties involved: manufacturers, regulators, distributors, users, and health workers. Organizations such as IPCS, companies and manufacturers associations have developed their own education and training schemes, often in conjunction with government extension services. Hospitals and poison centres are critical elements of toxicovigilance and should be encouraged to collect data, preferably in a harmonized format which can form an important basis for public health initiatives.

6 CHLOROPHENOZY HERBICIDES—MECHANISMS OF TOXICITY

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Background: Chlorophenoxy herbicides are used widely for the control of broad-leaved weeds in pastures, cereal crops, and along public rights of way. Structurally, they consist of a simple aliphatic carboxylic acid moiety attached via an ether linkage to a chlorine- (and, in some cases, methyl-) substituted aromatic ring. The most commonly used herbicide of this class is 2,4-D (2,4-dichlorophenoxyacetic acid). Chlorophenoxy herbicides are of limited persistence in the environment, and are considered to be of low to moderate mammalian toxicity. Review: Although the precise mechanisms of toxicity have not been elucidated, experimental studies indicate the involvement of the following: (i) Interference in cellular metabolic pathways involving acetylcoenzyme A (acetyl-CoA) leading to disruption of (a) cholinergic transmission, (b) the citric acid cycle, (c) cholesterol synthesis, and (d) increased β-oxidation of fatty acids; (ii) uncoupling of oxidative phosphorylation (potentially as a consequence of (i) or following disruption of cellular membranes by the herbicide), and (iii) (other) membrane associated effects; all potentially leading to cytotoxicity. *Interference with cellular metabolic pathways*: The formation of acetyl-CoA is a vital step in several important biochemical pathways. Since chlorophenoxy herbicides are structurally related to acetic acid, they are able to form corresponding coenzymes (e.g., 2,4-D-CoA) which could interfere with cellular metabolic pathways involving acetyl-CoA. They may enter the acetylcholine (ACh) synthetic pathway, with the subsequent formation of choline esters (e.g., 2,4-D-ACh). These phenoxy acid derivatives can act as false cholinergic messengers in nerve and muscle at muscarinic and nicotinic synapses causing neuromuscular blockade upon electrical stimulation of the nerve. This mechanism could account, in part, for the development of myotonia, a widely reported feature of chlorophenoxy herbicide poisoning in experimental animals, and for muscle twitching and cardiac arrhythmias. Chlorophenoxy derivatives of CoA can alternatively enter other acetyl-CoA metabolic pathways and interfere with energy metabolism, with the utilization of two-carbon fragments in the citric acid cycle, with the β-oxidation of fatty acids, and with the synthesis of cholesterol. 2,4-D exposure has also been observed to reduce myelin production in chick embryos. The fatty acid pattern of the individual myelin lipids was significantly altered, with a decrease in long chain fatty acids and an increase in saturated fatty acids. *Uncoupling of oxidative phosphorylation*: There is evidence that chlorophenoxy herbicides alter energy metabolism in rat liver mitochondria by uncoupling oxidative phosphorylation, possibly via disruption of the phospholipid bilayer structure of mitochondrial membranes after entry into the cell. Electron microscopy studies have demonstrated swelling and degradation of muscle mitochondria following administration of 2,4-D. As a consequence of this uncoupling, severe and rapid depletion of ATP supply occurs, and a variety of cellular activities are compromised, including the ability of the cell to maintain ionic gradients through the function of ATP-dependent translocases (e.g., Na^+/K^+ ATPase), DNA and protein synthesis, and the polymerization of microfilaments and mictrotubules that may lead to disruption of the cytoskeletal system and maintenance of cell shape. *Membrane associated effects*: Inhibition of some ion channels has been demonstrated, with the potential to disrupt severely the regulation and maintenance of cellular functions. For example, 2,4-D has been shown to inhibit the compartmentalization of Ca^{2+} in rat muscle tissue, leading to long-lasting and finally irreversible activation of the actin-myosin system and degeneration of myofibrils. The depletion of hepatic protective agents such as glutathione and protein thiols has been demonstrated, and there is evidence for the occurrence of

lipid peroxidation, although it is not known whether this is a primary or secondary event in the cellular toxicity of chlorophenoxy herbicides. The CNS and organs such as the kidney are particularly susceptible to chlorophenoxy herbicide toxicity, since they accumulate the herbicide via active transport mechanisms. Experimental studies have shown that 2,4-D and mecoprop [2-(2-methyl-4-chlorophenoxy) propionic acid] cross the blood-brain barrier (BBB) of rats by active transport. At low doses of 2,4-D, only small amounts are found in the brain. At high doses, saturation of plasma protein binding sites occurs, and increased levels of unbound herbicide are available to cross the BBB. Thus the rate of influx into the brain or other target sites is increased significantly. CNS toxicity may occur due to the resulting inhibition of organic acid transport mechanisms, which causes the accumulation of endogenous acidic metabolites and of the herbicide itself. In support of this mechanism, it has been demonstrated that metabolites of the neurotransmitters dopamine and serotonin accumulate in the CNS of rats following 2,4-D administration. Selective damage has been reported to occur in regions of the medulla oblongata, principally dorsal to the corticospinal tract, an area that is rich in motor and sensory fibers. It has been speculated that damage to this region might contribute to symptoms of poisoning such as lethargy and myotonia.

7 POISONING WITH CHLOROPHENOXY HERBICIDES: CLINICAL FEATURES

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Background: Chlorophenoxy herbicides are compounds which contain a chlorinated phenol group attached to a simple carboxylic acid, ester or alkyl moiety via an ether linkage. Examples include 2,4-D, 2,4,5-T, MCPA, mecoprop and dichlorprop. The chemically related herbicide, dicamba, is also often included in this group. Chlorophenoxy herbicides are used primarily to control weeds in lawns, pastures, cereal crops and along public rights of way. Epidemiology: Chlorophenoxy herbicide poisoning is rare but may produce severe sequelae. Among over two million human toxic exposures recorded by the AAPCC Toxic Exposure Surveillance System (TESS) in 1996, only 2503 (0.1%) involved 2,4-D or 2,4,5-T; at least one quarter of these involved children under six years old. Three patients developed life-threatening or "significant residual" effects but there were no fatalities. Some 66 case reports of chlorophenoxy herbicide ingestion have been published in the literature in the last 37 years; 22 of these 66 cases died. Review: Published data indicate that severe effects follow substantial ingestion rather than dermal exposure or inhalation. Vomiting is a prominent early feature (occurring in at least one third of all reported ingestions) and may be accompanied by burning in the mouth, abdominal pain, diarrhea and occasionally gastrointestinal hemorrhage (although severe corrosive effects probably are contributed to by other chemicals in the formulation). Gastrointestinal fluid loss may precipitate hypovolemic shock and, in at least three reported cases, this has led to death from cardiogenic shock or multi-organ failure and its associated complications including disseminated intravascular coagulation and cerebral edema. Hypotension, which often cannot be explained solely by intravascular volume loss, is a prominent early feature in approximately one third of reports and may reflect direct myocardial toxicity. Gastrointestinal features are followed in severe cases by the onset of coma (within the first few hours), which may be preceded by a period of agitation and confusion. Coma is an almost invariable feature of fatal cases and occurs in over two thirds of reported non-fatal ingestions. Coma was associated often (in at least 21 of 66 published cases) with respiratory distress (tachypnea, hypoxia and occasionally pulmonary edema). In some patients ventilatory insufficiency appears to be part of a generalized myopathy with weakness and/or fasciculation, loss of reflexes and increased creatine kinase activity. Some degree of peripheral muscle involvement occurred in approximately one third of reported cases though the presentation was variable. For example, complete loss of reflexes was reported in at least seven cases, twitching or fasciculation in at least five, weakness in at least four and myotonia in three. Occasionally there was evidence of primary peripheral neuronal damage with electromyographic evidence of a peripheral neuropathy in at least two cases. Upper motor neurone involvement is recognized also, with hypertonia, hyperreflexia or clonus described in some 10 reports and extensor plantar responses in at least one case. Evidence of CNS demyelination at post-mortem has been reported. Other reported neurological features include miosis (which is described in approximately 10 per cent of all cases), nystagmus, ataxia, hallucinations and convulsions. Metabolic acidosis is recognized and is contributed to by circulatory failure. Pyrexia in the absence of infection is noted occasionally, sometimes in association with hyperventilation, which may reflect chlorophenoxy herbicide-induced uncoupling of oxidative phosphorylation. Renal failure may occur secondary to rhabdomyolysis or, less commonly, reflect primary renal injury. Other uncommon features include ECG T wave and QT interval changes, cardiac arrhythmias and liver function test abnormalities. Although the prognosis is poor in patients who rapidly become shocked and

comatose, full recovery may ensue over weeks to months despite initial severe myopathy and neuropathy. There are few reports of significant toxicity following inhalational and/or dermal exposure, and in these cases it is often difficult to be sure that the observed features were caused by the herbicide, or that ingestion did not also occur; but none of these reports are substantiated by measurement of herbicide concentrations in biological fluids. There is no confirmed evidence that chronic occupational exposure to chlorophenoxy herbicides is associated with adverse health effects.

8 CHLOROPHENOXY HERBICIDES: MANAGEMENT—HOW EFFECTIVE IS URINE ALKALINIZATION?

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Background: Acute poisoning with chlorophenoxy herbicides usually involves 2,4-dichlorophenoxyacetic acid (2,4-D) and mecoprop. It is rare, potentially lethal and survival may be complicated by impaired mobility that takes weeks to recover. Review: Though only a small number of cases have been published, the toxicokinetics of 2,4-D, mecoprop and dichlorprop have been reported. These herbicides are acidic compounds (pKa 3.31 and 2.8 for 2,4-D and mecoprop respectively), have long plasma half-lives and are mainly eliminated in the urine. Urine alkalinization could, therefore, be a logical approach to enhancing elimination. Prescott *et al.*[1] clearly showed the dependence of elimination on urine pH in human poisoning. Renal clearance of 2,4-D was only 0.14 mL/min at pH 5.1 but increased to 63 mL/min at pH 8.3. Each increase of urine pH of 1 unit increased the renal clearance of 2,4-D five-fold. The renal clearance of mecoprop also increased but less dramatically; each increase of urine pH of 1 unit only doubled the clearance. In view of this, it is not surprising that alkalinization of the urine also shortened the plasma half-lives from 143 to 3.7 h and 24 to 11 h for 2,4-D and mecoprop respectively. Friesen *et al.*[2] confirmed these results; the plasma half-life of 2,4-D was reduced from 39.5 to 2.7 h by alkalinizing the urine. Durakovic *et al.*[3] used hemodialysis and a combination of hemodialysis and resin (Amberlite XAD-4) hemoperfusion to enhance the elimination of 2,4-D. Clearances of the order of 64 mL/min were obtained during hemodialysis alone and 66 mL/min during combined hemodialysis and hemoperfusion. The addition of resin hemoperfusion to hemodialysis therefore does not significantly improve the clearance of 2,4-D. Conclusion: Urine alkalinization is as effective as hemodialysis and is the treatment of choice in serious poisoning with chlorophenoxy herbicides. The target urine pH is 8 or higher. References: [1]Prescott LF, Park J, Darrien I. *Br J Clin Pharmacol* 1979;**7**:111–116. [2]Friesen EG, Jones GR, Vaughan D. *Drug Safety* 1990;**5**:155–159. [3]Durakovic Z, Durakovic A, Durakovic S, Ivanovic D. *Arch Toxicol* 1992;**66**:518–521.

9 DIQUAT—MECHANISMS OF TOXICITY, CLINICAL FEATURES AND MANAGEMENT

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Background: Diquat (1,1′-ethylene-2,2′-bipyridyldiylium) is a non-selective contact herbicide which is structurally related to paraquat. Compared with paraquat it is used less widely and thus poisoning is very uncommon. Over the period 1969–1998, some 27 cases of diquat poisoning have been reported, of which 12 were fatal. Most cases reported to date have followed deliberate, usually suicidal, ingestion. Mechanisms of toxicity: Diquat is a potent redox cycler and has been shown to undergo conversion to a free radical form in the presence of glutathione reductase and NADPH-cytochrome P450 reductase. The diquat cation is reformed on reaction with molecular oxygen, a process which generates superoxide anion radicals (O_2^-), and subsequently other reactive oxygen species. These redox products induce lipid peroxidation in cell membranes, compromising cell structure and function, and causing cell death. The oxidative stress induced by diquat is associated with the depletion of glutathione and protein thiols, of NADPH and NADH, and with the release of iron from hepatic ferritin. Some protection against the toxic effects of diquat is provided by catalase, especially in the presence of the iron chelator desferrioxamine. This suggests that iron and hydrogen peroxide may have important roles in the cytotoxicity of diquat. Clinical features: Local and systemic effects have been observed following diquat exposure, systemic features being associated primarily with cases of acute ingestion. Ocular burns, corneal scarring and epistaxis have been reported following eye and nasal exposure to diquat-containing formulations; prolonged skin contact with diquat may cause full thickness skin burns, disturbance of nail growth and shedding of the nail. Ingestion causes oral mucosal irritation and is followed by abdominal pain, epigastric tenderness, diarrhea and hepatic dysfunction. Paralytic ileus may contribute to hypovolemic shock via fluid accumulation in distended bowel loops. Circulatory collapse may cause acute tubular necrosis, although acute renal failure has been described in the absence of hypovolemia, suggesting a direct renal toxic effect. Proteinuria is also well documented. Coma occurs in

severe cases. Post mortem examination of the brain has demonstrated areas of hemorrhage and small, sometimes confluent, areas of infarction. Death may follow hypovolemic shock or ventricular tachycardia/fibrillation; respiratory arrest has complicated the development of bronchopneumonia or the adult respiratory distress syndrome. The ingestion of a substantial amount of diquat (> 6 g) may cause death within 24 hours. Management: After confirmation of the diagnosis, there are three approaches to treatment. Firstly, gut decontamination may be considered in patients who present within one hour of diquat ingestion, although there is no published evidence to support this approach. Secondly, supportive measures including fluid and electrolyte replacement should be employed. Thirdly, although hemodialysis/hemofiltration is of proven value if renal failure supervenes, there is no evidence that hemodialysis, hemofiltration or hemoperfusion remove clinically significant amounts of diquat, thereby reducing the risk of organ failure and preventing a fatal outcome in severe cases.

10 A CASE OF FATAL DIQUAT POISONING: TOXICOKINETIC DATA AND AUTOPSY FINDINGS

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Case report: A 37-year-old man was admitted to a regional hospital one hour after having ingested about 300 mL (equivalent to 60 g) of a diquat solution. On arrival, he was found conscious but agitated. Arterial blood pressure was 140/80 mm Hg, heart rate was 68/min. Gastric lavage was productive and activated charcoal (30 g) was administered. Diuresis was maintained through fluid replacement and mannitol infusion. The patient was referred to our University hospital for further management. At admission, 4 hours after poisoning, the first arterial blood gas analysis revealed: pH 7.57, pO_2 118 mm Hg, pCO_2 14 mm Hg, total CO_2 13 mmol/L, lactate 3.1 mmol/L (<2). The initial diquat serum level was 64 μg/mL. Supportive therapy included vigorous fluid therapy, dopamine and mannitol infusion. Fuller's earth (60 g) was administered and 60 g of activated charcoal 4 hours later. Urinary output was 150 mL over the first 2 hours. Arteriovenous hemoperfusion on activated charcoal was considered to enhance diquat epuration and was initiated (6 h) for 3 hours. Thereafter, continuous venovenous hemofiltration combined with hemoperfusion on activated charcoal was prolonged for 15 hours. About 1 g diquat was recovered in the ultrafiltrated fluid (4300 mL). Urinary output felt gradually (610 mL within 10 hours) and the patient became anuric 14 hours after poisoning. Urea and creatinine serum levels remained within normal range. Despite dialysis and bicarbonate administration, lactic metabolic acidosis worsened. Arterial blood pressure was also decreasing (10 h) and high doses of dopamine had to be infused. As hypoxia developed, the patient was intubated (14 h) for mechanical ventilation. Chest X-ray was unchanged. A widening of the QRS duration was noted on the ECG. A Swan-Ganz catheter was inserted for hemodynamic measurements (vasoplegia with high cardiac index). Electroencephalogram was performed and sustained episodes of seizure waves were noted in both temporal areas, evolving to status epilepticus which was initially refractory to intravenous pentobarbital administration. Hemodynamic status worsened dramatically 22 hours after intoxication. Despite the administration of high doses catecholamines and vasopressin, the patient remained hypotensive and died from refractory cardiocirculatory collapse 26 hours after poisoning. An autopsy was performed. The lesions predominated in the renal tubules. The pancreas appeared partially necrotic. Some degree of interstitial edema was observed into the lungs and the myocardium. The highest diquat concentration was found in the kidney>lung>liver. Discussion: Compared to paraquat, fatal diquat poisoning is less frequently reported. Cardiocirculatory failure with acute tubular necrosis is observed in the severe forms. The mechanism of toxicity is similar to that of paraquat, but the lungs are not damaged.

11 PARAQUAT: MECHANISMS OF TOXICITY, CLINICAL FEATURES AND MANAGEMENT

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Mechanisms: The precise mode of toxicity of paraquat is unknown[1]. It is irritant to tissues and poorly but rapidly absorbed from the GI tract. Tissue concentrations are highest in the lungs and kidneys. Only the lungs are able to accumulate paraquat against a concentration gradient, indicating involvement of an energy-dependent process, possibly involving transport systems for amines. Paraquat then undergoes redox cycling generating superoxide radicals, hydrogen peroxide and hydroxyl radicals that cause lipid peroxidation. Type I alveolar cells are the first to show signs of damage closely followed by Type II cells leading to loss of alveolar epithelium and an acute inflammatory response and edema that provoke rapid and extensive fibrosis, both in the alveoli and between them. Features of local toxicity: The local effects of paraquat on the cornea, conjunctiva, skin, upper alimentary tract (particularly the esophagus) and larynx depend on the concentration of the herbicide in the contaminating fluid. Inhalation of spray may cause pain in the throat

and epistaxis. Splashes in the eye cause blepharospasm, lacrimation and ulceration. Dermal exposure may cause burns. Painful ulcers on the mouth and tongue are common after ingestion and in combination with laryngeal contamination make it difficult to swallow, speak, and cough. Perforation of the esophagus and its complications may develop. Features of systemic toxicity: Nausea, vomiting and diarrhea are common features of ingestion of virtually any quantity of paraquat. Subsequent developments are dose-related. Ingestion of amounts exceeding 6 g is likely to be fatal within 24 to 48 h as a result of peripheral circulatory failure, metabolic acidosis, impaired consciousness, convulsions and increasing breathlessness and cyanosis secondary to acute pneumonitis. Amounts of 3 to 6 g are less likely to cause cardiovascular and CNS features but death is still the likely outcome. Escalating breathlessness, tachypnea, widespread crepitations and central cyanosis commonly lead to death from hypoxia after 5 to 10 days. Mild jaundice and renal failure may be seen in these cases. With smaller amounts (1.5 to 2.0 g), respiratory involvement may not appear for 10 to 21 days after ingestion but respiratory failure may still develop causing death after 5–6 weeks. Management: There is no effective treatment for paraquat poisoning.[1,2] Gut decontamination, measures to reduce uptake of absorbed paraquat by the lungs or minimize free radical damage, the use of techniques to enhance paraquat elimination and treatment aimed at preventing pulmonary fibrosis do not alter the outcome. References: [1]Bismuth C, Hall AH, eds., *Paraquat Poisoning*. New York: Marcel Dekker Inc, 1995. [2]Second European Symposium on Paraquat Poisoning. *Hum Toxicol* 1987;**6**:3–98.

12 PYRETHROIDS—WHY IS THEIR USE INCREASING?

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Background: During the half century since DDT was developed as the primordial synthetic insecticide, only four classes of chemicals have dominated worldwide markets for the control of insect pests and disease vectors of agricultural and public health importance. After the organochlorines (OCls) (e.g., DDT, HCH), came organophosphates (OPs) (e.g., fenitrothion, malathion), carbamates (e.g., carbaryl, propoxur) and currently pyrethroids predominate. Leading synthetic pyrethroids include cyfluthrin, cypermethrin, deltamethrin, fenvalerate, lambda-cyhalothrin and formerly permethrin (the first photostable synthetic pyrethroid discovered in 1974). The world market value exceeds $10 billion per annum for production and use of pyrethroids totalling >100,000 tonnes of active ingredients. The global market value for insecticides exceeds $25 billion, of which over 90% goes on agriculture. Effectiveness and safety of pyrethroids: The main reasons why pyrethroid insecticides are preferred is because they provide unrivalled speed of insect knock-down and kill at minimal dosages. Effective treatment rates for pyrethroids are 10–100x less than for DDT or OPs. When applied correctly, pyrethroids have negligible side-effects on operators or the environment and they are not bioaccumulative. Hence pyrethroids avoid the most serious sequelae incurred by OCls (bioaccumulation) or carbamates and OPs (vertebrate toxicology). Thanks to the wide range of pyrethroids available from manufacturers in most industrialized countries, they are competitively priced and supplied in many formulations for specific applications. To avoid using costly hydrocarbons and other undesirable solvents in emulsion concentrates (ECs), modern pyrethroid products are formulated as aqueous suspension concentrates (SCs), microencapsulated suspension (CS) or wettable grains (WGs) for crop spraying. Role and value of pyrethroids: During the 1990s vector-borne disease control programmes in tropical countries have been revolutionized by the introduction of pyrethroids to replace DDT and OPs. This has led to major advances against malaria, leishmaniasis, trypanosomiasis and onchocerciasis as well as drastically reducing problems of livestock caused by ectoparasites that can be eliminated by pyrethroids. Proof that sleeping under pyrethroid-impregnated bednets quickly reduces mortality from malaria by up to 60% among children has led UNICEF to set a timetable for providing this simple protection for all children in malarious situations. Resistance: Unfortunately, resistance to pyrethroids has developed in various pests and vectors (e.g., *Bemisia, Heliothis, Musca*), but this can be avoided and/or limited by various management strategies. Conclusion: In the foreseeable future, pyrethroid usage is expected to continue increasing as a mainstay of modern pest control practices worldwide.

13 PYRETHROID INSECTICIDES: MECHANISMS OF TOXICITY, POISONING SYNDROMES AND SYNERGIES

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Background: Pyrethroid insecticides have been used since the 1970s, and represent an increasing proportion of world pesticide sales. Fortunately there have been relatively few reports of acute poisoning, but these have shown that pharmacotherapy is difficult, and that the duration of poisoning can be unexpectedly long. Mechanisms of toxicity: Pyrethroids

are sodium channel toxins, prolonging excitation with relatively little blocking effect. Animal studies have shown that the only hazard presented by pyrethroids to adults is acute excitation; no lasting adverse effects being reported other than a possible developmental effect in neonatal mice. Two basic poisoning syndromes are seen, although some pyrethroids produce both syndromes simultaneously. Type I pyrethroids produce reflex hyperexcitability and fine tremor. Type II pyrethroids produce salivation, hyperexcitability, choreoathetosis, and seizures. Both classes produce a potent activation of the sympathetic system. In addition local effects are seen: skin contamination producing paresthesia, and ingestion producing gastrointestinal irritation. Both classes have a similar range of potency but, for commercial pesticides, the type II pyrethroids such as deltamethrin and cypermethrin are both more potent and more toxic than the type I pyrethroids such as permethrin. Poisoning syndromes and synergies: The blood half-life of pyrethroids is of the order of hours, and intoxication by the oral route is correspondingly short lasting. Inherent toxicity can be high (intravenous LD_{50}s range from 0.5 to >250 mg/kg), but this is limited in practice by rapid detoxification via ester hydrolysis in blood and liver. Hence the relatively slow absorption of pyrethroids across the skin presents little risk of systemic poisoning although, in cases of very severe skin contamination, intoxication has lasted for more than a week, probably due to a reservoir of pyrethroid bound to the epidermis. Since our resistance is based upon rapid detoxification, impaired carboxyesterase capacity (seen with co-exposure to certain organophosphates such as the cotton defoliant DEF) can enhance toxicity. Similarly, sufficiently large exposures to pyrethroids to saturate carboxyesterase capacity can enhance organophosphate toxicity. As yet these interactions have only been reported in experimental studies, but unauthorized pyrethoid/organophosphate mixtures are being marketed in some parts of the world. The paresthesia produced by pyrethroids can be treated by decontamination of the skin by vegetable oil, but if type II poisoning advances to central hyperexcitation it is difficult to control with anticonvulsants such as diazepam in man or animals. Our own experimental studies with rats have however shown that pentobarbitone is anomalously effective as therapy against type II poisoning. This is probably due to pentobarbitone's action both as a chloride channel agonist and as a membrane stabilizer, since type II pyrethroids act on both voltage-gated chloride and sodium channels.

14 PYRETHROID EXPOSURE—CLINICAL FEATURES

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Objective: To review the clinical manifestations of acute pyrethroid poisoning. Methods: All clinical reports of acute pyrethroid poisoning published in the Chinese medical literature from 1983 to 1997 were obtained and analyzed. Results: Among 1580 reported cases of acute pyrethroid poisoning, occupational poisoning accounted for one third of the total cases; two thirds were intentional ingestions. The majority of cases of poisoning were due to deltamethrin, followed by fenvalerate, cypermethrin and other pyrethroids (cyfluthrin, fenpropathrin). Nearly 100 cases resulted from exposure to pyrethroid-organophosphate mixtures. The initial symptoms of acute occupational pyrethroid exposure were burning and itching sensations in the face or dizziness which usually developed 4–6 h after exposure. After pyrethroid ingestion, epigastric pain, nausea and vomiting usually occurred within 10 minutes to one hour. Systemic symptoms included dizziness, headache, nausea, anorexia, fatigue, increased stomal secretion, and muscle fasciculation. Severe cases often developed seizures, disturbance of consciousness as well as dyspnea, cyanosis and moist rales indicating pulmonary edema. Blood cholinesterase activity was normal except in those cases where poisoning was due to a pyrethroid-organophosphate mixture. In these patients, the clinical manifestations were mainly due to cholinergic crisis. EEG, ECG, and EMG showed abnormalities in some patients. The prognosis was good even in patients with severe pyrethroid poisoning. A few fatal cases were reported due to misdiagnosis and inappropriate treatments, including those poisoned by pyrethroid-organophosphate mixtures who were treated with insufficient atropine, and those with pure pyrethroid poisoning who died of atropine poisoning. Diagnostic criteria for acute pyrethroid poisoning have now been introduced in China. Conclusions: The features of acute pyrethroid poisoning include dizziness, headache, nausea, anorexia, fatigue, increased stomal secretion, and muscle fasciculation, in addition to burning and itching of the face. Seizures, coma and pulmonary edema may occur in severe cases. The diagnosis of pyrethroid poisoning should be made on the basis of verified exposure history, relevant symptoms and signs, and reasonable exclusion of other exposures and diseases. Poisoning with pyrethroid-organophophate mixtures should be treated with appropriate doses of atropine and cholinesterase reactivators.

15 PYRETHROID-INDUCED PARESTHESIA—A CENTRAL OR LOCAL TOXIC EFFECT?

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Background: Pyrethroid induced paresthesia is the most frequently described adverse effect resulting from dermal expo-

sure to pyrethroids, particularly (but not exclusively) those with an α-cyano group. The face is the most commonly affected area, but paresthesia has been described in other body areas, particularly those with a high density of nerve endings. It appears that large differences exist in individual susceptibility to paresthesia. Affected individuals experience a sensation of burning, tingling, itching or numbness. This reaction occurs 1–2 hours after beginning of exposure and resolves spontaneously without treatment, usually within 24 hours. No long-term effects are known. Mechanisms: Paresthesia is not associated with an inflammatory response although a temporary erythema has occasionally been described. The most likely explanation for this is mechanical irritation through rubbing and scratching. An animal model using the guinea pig has been developed to study and quantify paresthesia. The sensory effects are thought to be related to a reversible, temporary fixing of the gates in nerve cell membrane sodium channels leading to repetitive firing. Paresthesia occurs as a result of a direct effect on intracutaneous nerve endings at very low pyrethroid doses. It is related to potency of the pyrethroid with permethrin generally showing the weakest effect. However, no direct comparative study of the potency of the major pyrethroids relative to each other has been carried out. Conclusion: Since dermal penetration of most pyrethroids is poor and metabolism rapid, doses sufficient to cause paresthesia are far too small to cause central or systemic toxicity. Paresthesia is therefore considered to be a localized nuisance effect. The best advice to affected individuals is to prevent paresthesia from occurring through appropriate hygiene measures and personal protection. Indeed, it has been suggested that it can act as an early warning signal of exposure before there is a risk of toxicity, prompting affected individuals to seek better protection.

16 MANAGEMENT OF PYRETHROID EXPOSURE

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Background: Pyrethrins are naturally occurring pesticides derived originally from the chrysanthemum family. The pyrethroids are synthetic analogues derived from this group. Synthetic pyrethroids are widely used insecticides. The compounds all have a three membered (cyclopropane carboxylic acid) ring with a variety of esters attached to it. Synthetic pyrethroids are divided chemically into those which do not have a cyano group substitution (Type 1 pyrethroids) and those which do have a cyano substitution (Type 2 pyrethroids). The pyrethroids themselves have at least four stereoisomers, and some isomers are marketed separately. *Clinical features*: Clinical features in man depend on the route of administration. Skin exposure results in paresthesiae, probably related to repetitive firing of sensory nerve endings. There appear to be individual differences in the propensity of pyrethroids to cause this symptom complex. Paresthesiae usually start 30 minutes to 2 hours after exposure, are maximal at about 6 hours, and recover completely by 24 hours. Exposure to the eye, and by inhalation, results in local irritation of the affected membranes. In the case of the upper respiratory tract this may include cough, rhinorrhea and dyspnea. Systemic effects of pyrethroids are seen more commonly in areas where these agents are used widely in agriculture, the largest case series comes from He *et al.*[1] who reviewed 573 cases. Within this series there were only seven fatalities. Of the seven cases who died, four had convulsions, one died from non-cardiogenic pulmonary edema, one was thought to have developed atropine intoxication, and one patient had taken a combination of pyrethroid and organophosphate. A more recent death[2] was related to aspiration pneumonia and subsequent renal failure. Ingestion of pyrethroids tend to cause vomiting as a prominent symptom. Anorexia was reported in 45% of He *et al.*'s cases. Dizziness, headache, fatigue and increased salivation are also common. Cardiovascular toxicity has also been reported with ECG changes in the sinus tachycardia and ventricular atopics being reported, which resolve over 2–14 days. Management: Management of patients depends on the dose and route of exposure. There is some evidence that topical vitamin E will reduce the severity of paresthesia for a range of pyrethroids. The mechanism of this effect has not been clarified and vitamin E is not a medicinal product in the United Kingdom. In the case of more severe toxicity it is important to differentiate the effects of pyrethroids from other insecticides, in particular organophosphates. Hypersalivation and convulsions may obviously confuse the clinical picture. In the case of pyrethroids brief convulsions may not require treatment, but intravenous diazepam will be required if seizures are prolonged. For patients who have hypersalivation intravenous atropine is the treatment of choice. It is also possible that bronchorrhea may be a component of pyrethroid exposure, although this does not seem to have been formally studied, and the case reports refer to pulmonary edema. Animal data suggests propranolol will protect against tremor, but it is not clear how frequently this is a significant problem in man. Skin decontamination procedures should routinely be carried out for dermal exposure. Pyrethroids are formulated in organic solvents, and may bind to activated charcoal—data are lacking. References: [1]He F, Wang S, Liu L, Chen S, Zhang Z, Sun J. Clinical manifestations and

diagnosis of acute pyrethroid poisoning. *Arch Toxicol* 1989;**63**:54–58. [2]Peter JV, John G, Churian AM. Pyrethroid poisoning. *J Assoc Phys India* 1996;**44**:343–344.

17 RISK ASSESSMENT REGARDING CHRONIC EXPOSURE TO PESTICIDES: DICHLORVOS, A SCIENTIFICALLY BASED REGULATORY DECISION

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Objective: Being confronted with quite contradictory, regulatory decisions in different European and American countries concerning the carcinogenic risk of dichlorvos, and with urgent calls for its total ban in Belgium, the *Hoge Gezondheids-raad–Conseil Supérieur d'Hygiène* (HGR-CSH)—the Belgian Pesticide Safety Authority—started an open, formal risk assessment procedure. Methods: Following the procedures of the systematic review, developed within the context of evidence based medicine, a review was performed of the data concerning the long term toxicity and carcinogenicity of dichlorvos which could be retrieved from the open literature or from expert panel reports. Each paper was assessed, directly or indirectly, for its quality, and the studies qualified as having a low or moderate risk of bias were than judged for the positive association between cancer endpoints and dichlorvos administration. The final conclusion was based on IARC criteria. Having made our conclusion public, a meeting was organized with all stakeholders, the discussions leading to a final decision and regulatory advice. Results: The conclusion of the review was that there was *sufficient evidence* for carcinogenicity in the animal—only two studies were classified as showing a moderate risk of bias, and they were positive—and that there was *inadequate evidence* for carcinogenicity in man. Therefore, dichlorvos had to be classified as a *possible carcinogen for man* (IARC class 2B). At and after the public meeting, an in-depth scientific discussion followed, among others with a US Blue Ribbon Panel of independent experts. The data base taken into account was broadened by including some of the negative animal studies that had initially been classified as presenting a high risk of bias, and by taking into account new data, obtained with metrifonate, which non-metabolically transforms into dichlorvos in the organism. As a result *sufficient evidence for carcinogenicity in the animal* was changed into *limited evidence in the animal*, leading the HGR-CSH to downgrade its classification of dichlorvos towards *non classifiable with regard to cancer and man* (IARC class 3). The regulatory decision issued was then based on the cholinesterase inhibitory properties of dichlorvos, and its resulting neurotoxicity. The most important steps followed in this regulatory decision process will be presented.

18 SEVERE POISONING BY QUELLADA H, A γ-HCH-CONTAINING SHAMPOO IN A HUMAN—MONITORING OF LINDANE AND ITS METABOLITES IN SERUM AND URINE

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Case report: A 24-year-old male caucasian ingested 100 mL of Quellada hair shampoo in a suicidal attempt. One gram of the shampoo contains 9.85 mg lindane. The total amount of lindane taken was 1035 g. The emergency physician found the patient 20 minutes after the ingestion, he was agitated, disorientated and developed generalized convulsions. He was sedated by midazolam and thiopental and transferred to our Toxicological Department three hours after ingestion. After mechanical ventilation for three days, while sedated with diazepam (680 mg) and midazolam (45 mg), the patient was weaned from the ventilator and left the ICU in good condition without sequelae. Results: Serial plasma levels of γ-HCH (18 times over 90 hours) were determined. At the same time lindane and all its metabolites were determined in eight hours urine fractions for 48 hours. At admission the lindane serum level was 42.69 μg/L (normal < 2 μg/L) which was relatively low compared to levels in other cases of severe lindane intoxication. The β-half-life of γ-HCH was around 15 hours, whereas the γ-half life was as long as several days. The volume of distribution for lindane in this case was very high with 300 L/kg b.w. The following amounts of lindane and its metabolites were detected in urine (cumulative up to 48 hours): 1349 μg trichlorophenol (2,4,5 -), 830 μg trichlorophenol (2,4,6 -), 127 μg dichlorophenol (2,5 -), 130 μg dichlorophenol (2,4 -), 170 μg tetrachlorophenol, 22 μg monochlorophenol, 0.68 μg lindane. Pentachlorophenol, a potentially more toxic compound than γ–HCH itself, could not be found. Conclusion: In humans the ingestion of 1 g γ-HCH can lead to convulsions at a level as low as 42 μg/L. The distribution half-life of lindane was 15 hours whereas the elimination half-life is several days. The main metabolites are the trichlorophenols followed by dichlorophenoles, tetrachlorophenol and monochlorophenol. Unmetabolized lindane appears in urine only in minute amounts. Pentachlorophenol is not a metabolite of γ-hexachlorocyclohexane.

19 A RETROSPECTIVE REVIEW OF TRIAGE CRITERIA OF ACCIDENTAL LONG-ACTING ANTICOAGULANT RODENTICIDE INGESTIONS IN CHILDREN

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Objective: To assess the safety of the Illinois Poison Center (IPC) triage criteria for the accidental ingestion of long-acting anticoagulant rodenticides in children and to compare the results to the published national TESS data. Methods: The IPC has triage criteria for the accidental pediatric ingestion of the long-acting anticoagulant rodenticides of 1) < mouthful, home observation 2) > mouthful and < one hour, home decontamination and 3) > mouthful and > one hour post-ingestion, refer to a health care facility (HCF). The general recommendations once at a HCF are activated charcoal (AC), baseline PT and follow up at 24 and 48 hours with a physician. For calls which originate at a HCF, the triage criteria are suggested, but most patients already at a HCF receive AC and a baseline PT is drawn. A retrospective review of all pediatric exposure calls for 1998 was performed. The records were reviewed for the number managed at home, the number managed at a HCF, and the results of documented prothrombin times were tabulated. The percentage of patients managed at a HCF by the IPC was compared to national TESS data. Results: There were 751 pediatric exposure calls in 1998. 618 (82%) of these were managed at home with no documented morbidity. 47 (6%) callers were referred to a HCF and 86 (12%) calls originated from a HCF for a total of 18% of calls managed at a HCF. In contrast, approximately 30% of accidental ingestions in the TESS data were managed at a HCF. Of the 133 patients receiving initial care at a HCF, 50 had documented prothrombin times. All were essentially normal. In addition, another 14 had PT documented as within normal limits though no number was recorded. Of the 751 cases, no adverse outcomes were noted. Conclusion: The IPC triage criteria manage more patients at home than the national TESS data average. However, in retrospect, the patients who were managed initially at a HCF were asymptomatic and probably did not need to be referred at that time. This data shows that long-acting anticoagulant rodenticide ingestions in children are of low toxicity and that initial labs are of no benefit. This follows other published reports from Washington and Denver. This is significant as the emergency department charges for nursing care, decontamination, laboratory work and physician charges are on the order of 550 dollars in the Chicago area. In the approximately 4000 cases treated in a HCF in the 1997 TESS data, this could represent a savings of over 2 million dollars.

20 CHILD ABUSE WITH α-CHLORALOSE

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Background: α-Chloralose is used as a rodenticide and in the control of bird pests. Its toxicity profile resembles that of chloral hydrate and strychnine. Most reported poisonings are suicidal. To our knowledge this is the first reported use associated with child abuse. Case report: A 10-year-old male was repeatedly admitted to hospital over an 11 month period after several similar episodes of headache and sudden drowsiness, rapidly followed by coma and myoclonus or generalized seizures; seizures were triggered by minimal stimulation such as touch, and required sedation with high doses of anticonvulsants (diazepam, clonazepam, phenobarbitone) and artificial ventilation. Bronchial hypersecretion, bilateral mydriasis reacting to light, facial flushing, and hypothermia were also observed. After 24–48 hours the child suddenly regained consciousness and recovery was complete after each episode. The EEGs performed during seizures showed abnormal diffuse discharge without evidence of focal abnormalities; EEG pattern was normal in the interseizure periods. Blood, CSF and urine electrolytes, liver enzymes, CT scan, MRI imaging were unremarkable. Cytogenetic and metabolic investigations (karyotyping, aminoacids and acylcarnitine assays and a neuromuscular biopsy) were unremarkable. The child was treated with long-term valproate, unsuccessfully. His father repeatedly had experienced the same clinical features and died at home 5 years earlier from coma and collapse. His younger sister had been also treated for "epilepsy" of unknown origin for two years. Diagnosis of "familial hemiplegic migraine" was considered, although ataxia and nystagmus were absent. Criminal poisoning was finally suspected when the child had another episode of generalized seizures after his mother visited him while still in the hospital. Intoxication was confirmed by the determination of α-chloralose in blood and urine (15.2 mg/L and 65 mg/L respectively, time after ingestion: about 5 hours) and the discovery of several packages of a rodenticide containing 80% α-chloralose in the garage of the family home. Conclusion: The diagnosis of child abuse associated with poisoning is certainly difficult and may be easily overlooked, as in this case where repeated administration of α-chloralose to several members of the same family over several years mimicked a genetic neurological disease.

21 MECHANISMS OF TOXICITY OF ORGANOPHOSPHORUS INSECTICIDES

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Consideration of mechanisms of toxicity of organophosphorus (OP) insecticides has traditionally focussed on the role of acetylcholine esterase (AChE, EC 3.1.1.7). The normal function of AChE is to destroy acetylcholine (ACh) in synaptic clefts and myoneural junctions, to terminate nerve impulse transmission. OP oxon phosphylates a serine hydroxyl group at the esteratic site of AChE, causing enzyme inhibition. Extent of inhibition depends on the rate constant for the reaction and on duration of AChE exposure. Stability of phosphylated enzyme is determined by the chemical structure of the OP and on the occurrence of "ageing," resulting from monodealkylation. Failure of AChE activity results in accumulation of ACh causing enhancement and prolongation of cholinergic effects and depolarization blockade. OPs also react with butyryl cholinesterase (BuChE, EC 3.1.1.8), carboxylesterases and OP-hydrolyzing enzymes. BuChE constitutes an alternative binding site for OPs but BuChE inhibition is not normally associated with toxicity. Carboxylesterase and OP-hydrolyzing enzyme activity is low in humans, though phenotypic variation may contribute to interindividual OP sensitivity. Some OPs, such as mipafox and triorthocresyl phosphate, cause OP-induced delayed neuropathy (OPIDN), characterized by central and peripheral axonal degeneration and ataxia and/or paralysis 2–3 weeks after exposure and attributed to phosphylation and subsequent ageing of a neural phenyl valerate esterase, so-called neuropathy target esterase (NTE). However, ageing is not an absolute requirement and esterases other than NTE may also be involved. Autophosphylation of Ca^{2+}/calmodulin-dependent kinase II and enhanced phosphorylation of cytoskeletal proteins is reported to be an early event. A third type of OP-induced neurotoxicity has been described, the "intermediate syndrome," occurring 24–96 hours after the original cholinergic crisis and characterized by weakness affecting neck flexors, proximal limb muscles and motor cranial nerves, accompanied by respiratory failure. Although originally attributed to muscle fibre necrosis, inadequate oxime dosing has been suggested as being contributory. A fourth chronic neurobehavioural syndrome has recently been proposed resulting from long-term (episodic or continual) low-dose OP exposure. Subtle cognitive impairment, greater psychiatric morbidity and minor sensory changes have been noted, but methodological weaknesses in studies reported hitherto render interpretation difficult. Underlying mechanisms for this type of toxicity are uncertain. Aside from the neurotoxic effects described above, OPs also exhibit cardiotoxicity, nephrotoxicity and immunotoxicity, and there is concern regarding potential carcinogenicity and developmental/reproductive toxicity. Perturbations in hematological and biochemical indices have also been reported, accompanying acute cholinergic crises. Of particular interest is the role of glutamate in sustained OP-induced seizure activity, and therefore the possible therapeutic use of non-selective glutamate receptor antagonists, such as felbamate, and of selective *N*-methyl-D-aspartate (NMDA) receptor-channel blockers, such as dizocilpine and procyclidine, in the management of OP poisoning.

22 ORGANOPHOSPHORUS INSECTICIDE POISONING: CLINICAL FEATURES

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Background: The clinical picture of organophosphorus insecticide poisoning results from accumulation of acetylcholine at nerve terminals. Due to the inhibition of junctional and non-junctional acetylcholinesterase (AChE) the biological activity of acetylcholine (ACh) is not terminated. As ACh is a neurotransmitter throughout the whole nervous system, poisoning with organophosphorus insecticides results in its excessive stimulation. Thus, the central nervous system, the somatic motor system, the parasympathetic system and even the sympathetic system are affected. In the CNS, ACh-containing interneurons exist within the striatum, the basal forebrain and the pontomesencephalotegmental complexes. ACh is released by all motor neurons, all preganglionic autonomic neurons, all postganglionic parasympathetic neurons and some postganglionic sympathetic neurons. Two distinct receptor groups have been identified for ACh, the nicotinic and the muscarinic groups. There are at least four subtypes of nicotinic and five subtypes of muscarinic receptors. The muscarinic receptors can be blocked by atropine whereas the nicotinic receptors can only be blocked by non-depolarizing muscle relaxants. The sympathetic ganglions and the parasympathetic ganglions exhibit a mixture of nicotinic and muscarinic receptors and react to cholinergic stimulation. As the adrenal gland is also sensitive to cholinergic stimulation, both autonomic systems are overstimulated if there is a surplus of ACh. Clinical features: In mild poisoning the muscarinic effects prevail. Stimulation of endocrine secretions with salivation, lacrimation, rhinorrhea, exocrine pancreatic secretion, and marked bronchial secretion can be observed. Tightness in the chest, bronchospasm and wheezing may also be found. Parasympathetic stimulation leads to gastrointestinal signs and symptoms such as nausea, vomiting,

abdominal cramps, tenesmus and diarrhea. Sympathetic stimulation results in hypertension and tachycardia. Mydriasis can be present. Local contamination of the eyes may result in headache and miosis and these may be the only symptoms of a mild intoxication by any route. In moderate poisonings major symptoms are somnolence, dysarthria, headache, bradycardia, dyspnea, nausea, vomiting, diarrhea, weakness, hypotension and miosis. Tachycardia and hypertension due to adrenergic depletion can precede circulatory depression. In addition, profuse perspiration, a sensation of numbness, crepitations over the lungs due to pseudo-lung edema may be observed. At this stage fasciculation of the fine skeletal muscles of the face and eyelids can be seen. Spontaneous or provoked muscle fibrillations and idiomuscular bulging may appear. In a further stage, this nicotinic overstimulation can lead to depolarization of the muscular endplate with weakness or paralysis of the respiratory muscles and a flaccid or rigid muscle tone. In severe poisoning, CNS symptoms and cardiovascular signs are predominant. Convulsions are followed by deep coma. The pupils are pinpoint and not reactive to light. There are life-threatening respiratory difficulties: a central block of the respiratory stimulus, relaxation of the peripheral respiratory muscles and the diaphragmatic innervation, and bronchorrhea that leads to near drowning. Even if mechanical ventilation and suction are performed there is still circulatory failure due to extreme bradycardia and conduction block. Organophosphorus insecticides have a direct cardiotoxic action on the myocardium and by pooling of venous blood, shock is enhanced, though the endogenous adrenergic drive is immense. These shock symptoms are increased by hypoxemia due to respiratory failure. If shock persists too long, the cascade of shock mediators are triggered and multiorgan failure ensues. Besides this, signs of shock, muscular twitching, wheezing, excessive bronchial secretion, pulmonary edema, loss of sphincter and urinary bladder control are characteristic criteria for severe organophosphate poisoning. Depending on the type and concentration of organophosphorus insecticides to which the individual is exposed, signs and symptoms can start within 15 minutes or be delayed for up to 24 hours.

23 ARE THERE LONG-TERM SEQUELAE FROM A SINGLE ACUTE ORGANOPHOSPHORUS INSECTICIDE EXPOSURE?

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Background: This review will examine the possibility that long-term sequelae can occur after acute and symptomatic exposure to organophosphorus (OP) insecticides. Since acute intoxication with OPs can cause major effects such as convulsions, respiratory failure and cardiac arrhythmias, all of which can result in cerebral anoxia, it would be surprising if severe acute OP poisoning was not associated with long-term neurological sequelae. The scientific value of epidemiological studies in this area are limited often by uncertainties in relation to the compounds involved, their quantity and exposure duration. For retrospective cohort studies it is often difficult, if not impossible, to identify these parameters. Hence, many studies do no more than generate hypotheses. Moreover, case reports describing effects observed in a few subjects would have to be very well defined before they could be generalized. Suspected effects based on such observations need to be confirmed in prospective studies or supported by animal studies. In considering published reports the evaluation of neurobehavioral effects by objective test methods is considered superior to the use of questionnaires or the evaluation of subjective complaints. Review: Four studies[1–4] are relevant. Rosenstock *et al.*[1] and McConnell *et al.*[2] investigated the neurophysiological effects[1] and, as an index of delayed neuropathy, measured vibrotactile thesholds[2] in 36 agricultural workers in Nicaragua who had been admitted to hospital between 10 and 34 months earlier with acute OP poisoning. It is probable that many of these subjects had been exposed repeatedly to OPs (though only 14% of cases had a history of recent pesticide exposure) and some may have suffered the features of OP poisoning on more than one occasion. Moreover, 21 of 36 workers had been poisoned with methamidophos, a recognized peripheral neurotoxin. In a battery of neuropsychological tests the exposed group performed significantly worse than the control group[1] and a significant decrease in vibrotactile sensitivity was also observed.[2] Despite the limitations of the design, these two studies provide evidence of long-term sequelae following acute poisoning with OP insecticides. Savage *et al.*[3] investigated the presence of chronic neurological or neuropsychological abnormalities in 100 subjects who had experienced at least one episode of acute OP poisoning confirmed by a physician. The authors found significant deficits in a wide range of neuropsychological variables, including visiomotor, attention and language function. Persistent abnormalities in affective behaviour, especially anxiety, were also found, though no differences on EEG or neurological examination were identified. However, the clinical severity of poisoning, the analytical confirmation of the diagnosis and the nature of other intercurrent diseases were not reported. As most observed differences between the exposed and

control groups were within normal variability, other factors such as education might have accounted for differences in comprehension, arithmetic and vocabulary. Interestingly, the blood concentrations of organochlorine pesticides in the study group were approximately twice that of controls which might be relevant in the interpretation of the neuropsychological tests. This study suggests that there are long-term neurological sequelae to acute poisoning with OPs, though these sequelae were sufficiently subtle that the clinical neurological examination and EEG could not discriminate poisoned subjects from controls. Steenland *et al.*[4] also investigated whether there were chronic neurological sequelae in 83 subjects who reported symptoms consistent with OP poisoning a mean of seven years earlier and who had a reduction in RBC or plasma cholinesterase activity of at least 20%; 36 of 83 had required hospitalization. Vibrotactile sensitivity of finger and toe and two neurobehavioral tests (sustained visual attention and mood scales) were significantly worse in the poisoned men, and several tests showed deficits which increased with the severity of poisoning. Nerve conduction tests and clinical examination, however, showed no differences. Conclusion: Despite some shortcomings in methodology, there is evidence that acute OP poisoning can produce subclinical damage to the central and peripheral nervous systems. It is important therefore that workers occupationally exposed to OP insecticides are adequately protected by appropriate clothing and practice to ensure that they do not develop features of acute poisoning. References: [1]Rosenstock L, Keifer M, Daniell WE, McConnell R, Claypole K and the Pesticide Health Effects Study Group. Chronic central nervous system effects of acute organophosphate pesticide intoxication. *Lancet* 1991;**338**:223–227. [2]McConnell R, Keifer M, Rosenstock L. Elevated quantitative vibrotactile threshold among workers previously poisoned with methamidophos and other organophosphate pesticides. *Am J Ind Med* 1994;**25**:325–234. [3]Savage EP, Keefe TJ, Mounce LM, Heaton RK, Lewis JA, Burcar PJ. Chronic neurological sequelae of acute organophosphate pesticide poisoning. *Arch Environ Health* 1998;**43**:38–45. [4]Steenland K, Jenkins B, Ames RG, O'Malley M, Chrislip D, Russo J. Chronic neurological sequelae to organophosphate pesticide poisoning. *Am J Public Health* 1994;**84**:731–736.

24 ARE THERE LONG-TERM SEQUELAE FROM REPEATED LOW DOSE ORGANOPHOSPHORUS INSECTICIDE EXPOSURES?

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Background: The toxicology of organophosphorus (OP) insecticides when taken in large doses is well-documented, and relates principally to the interaction between the compounds and acetylcholinesterase (AChE). Following significant poisoning two other neurological syndromes are recognized, the intermediate syndrome[1] and OP-induced polyneuropathy (OPIDPN). This syndrome is related to the ability of the organophosphorus agent to interact with neuropathy target esterase (NTE), and is a complication of poisoning of both pesticidal and non-pesticidal OP compounds that bind NTE. Severity of OPIDPN can be enhanced by so-called ''promoting'' compounds but is thought not to be a clinically important phenomenon. In view of this well-known range of toxicological effects it is not surprising that questions have arisen as to the dose threshold in man. There is thus debate about whether organophosphorus pesticides produce effects on the peripheral and central nervous systems following exposure to doses not associated with acute clinical poisoning. OP pesticides are used principally in agriculture, and exposure occurs potentially in the manufacturing process, during their use as insecticides in arable farming, and during their use as insecticides in animal husbandry, particularly in the United Kingdom in sheep farming where OP insecticides replaced organochlorines as dip products. Because of the very nature of agricultural practice it is often difficult to estimate dosing levels in exposed subjects. This is further complicated by the fact that the symptoms being investigated develop slowly and insidiously and follow some time after exposure. The techniques used to investigate the possibility of chronic neurological damage have therefore tended to involve investigations of cohorts of subjects, both exposed and unexposed. By comparing the outcome in a range of tests, investigators have attempted to attribute causation. Review: There are a number of epidemiological approaches to studying rare syndromes. A commonly applied one is a case-control study in which index cases are compared to controls with respect to exposure to potentially toxic agents. This approach has, for example, been used successfully in the investigation of Reye's syndrome. One problem in the use of this approach in pesticide exposure is that there are no clearly defined clinical syndromes to investigate and therefore no good case-control studies on pesticide sufferers. Case series, in which groups of individuals have been collected by interested physicians, are unhelpful in defining causation. Thus even if farmers using agricultural pesticides were to suffer peripheral nerve damage, since their working practices would mean they were exposed to a range of chemicals, for example petroleum distillate, organic solvents and OP insecticides, together with a range of other environmental factors, such as animal viruses, clear cause

and effect is difficult to establish. One way to try and do this is to establish a dose-response to a specific, well-defined, abnormality in relation to a specific toxin. Studies: There have been at least 20 studies investigating the potential neurological effects of low-level exposure to OP pesticides. Numbers of subjects involved ranged between 11[2,3] and over 100.[4,5] The techniques used included measurements of EEG, central neurological testing, neuropsychological testing, and neuromuscular investigations, particularly including EMG studies, in addition to investigations on mood disorders and suicide rate. From this range of tests it is clear that no specific syndrome has been identified. The largest study, that of Stevens *et al.*,[5] was carried out on a cohort of sheep dippers with a group of quarry workers as controls. Both short-term effects, based on measurements made before, 24 hours and 3 weeks after dipping and long-term effects, based on health and memory questionnaires and neuropsychological tests made up to one year later (3 months after dipping) were carried out. An estimate of exposure was taken from the number of sheep dipped over the subjects lifetime. This is imprecise in view of the different exposure rates to dip occurring in different aspects of sheep dipping. Nevertheless it was the best that could be done in the circumstances. The sheep dippers had generally fewer signs of ill-health than the quarry workers and none of them had experienced acute poisoning. Differences were found in only some of the psychological tests investigated. One potential confounding factor was the higher proportion of patients in the exposed group with clinical psychiatric disease. This did not show a dose-response relationship. In contrast, for tests of synaptic reasoning, there seemed to be a dose-response effect, although it is only apparent in the more complex tasks. Other tests, such as single-digit substitution and reaction time, did not show any evidence of a dose-response effect, although they were worse in the exposed group. The exposed group were, however, slightly older and this could perhaps account for some of these changes. Attempts to correct for age in a mathematical model could perhaps be criticized on the basis that the corrections were linear, rather than the normal exponential change as seen in an aging population. This study illustrated many of the difficulties in interpretation of toxicological studies in OP exposure. While there were clear statistical differences between the samples, the magnitude of the changes, and the fact that these were brought out following the use of covariant analyses, raises questions as to the relationship of the changes to OP exposure. Conclusions: Many of the social and economic pressures that apply to farmers, who often work under extreme stress and in isolated communities, has meant that it has not yet been possible to conclusively show an association between OP use at low doses and chronic neurological damage. Clearly high doses of OPs are potentially toxic, but a no effect level has yet to be established. Present evidence suggests that if OP insecticides do have an effect at low dose this is small, is likely to be in some way related to exposure to the chemicals themselves, and for this reason the most important public health measure is to protect individual operatives by reducing the overall use of OP insecticides where possible and when this is not practicable, by using appropriate personal protective equipment. Although claims have been made that organophosphates have other toxicological effects, including increased risk of malignant disease and cardiomyopathy, there is no good evidence in support of these suggestions. References: [1]Senanayake N, Karalliedde L. Neurotoxic effects of organophosphorus insecticides. An intermediate syndrome. *N Engl J Med* 1987;**316**:761–763. [2]Rayner MD, Popper JS, Carvalho EW, Hurov R. Hyporeflexia in workers chronically exposed to organophosphate insecticides. *Res Commun Chem Pathol Pharmacol* 1972;**4**:595–606. [3]Staolberg E, Hilton-Brown P, Kolmodin-Hedman B, Holmstedt B, Augustinsson K-B. Effect of occupational exposure to organophosphorus insecticides on neuromuscular function. *Scand J Work Environ Health* 1978;**4**:255–261. [4]Parrón T, Hernández AF, Pla A, Villanueva E. Clinical and biochemical changes in greenhouse sprayers chronically exposed to pesticides. *Hum Exp Toxicol* 1996;**15**:957–963. [5]Stephens R, Spurgeon A, Calvert IA, Beach J, Levy LS, Berry H, Harrington JM. Neuropsychological effects of long-term exposure to organophosphates in sheep dip. *Lancet* 1995;**345**:1135–1139.

25 THE ROLE OF ATROPINE AND OXIMES IN THE TREATMENT OF ORGANOPHOSPATE POISONING

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Introduction: For the abundant use of organophosphates (OP) to control disease vectors and crop pests we have to pay dearly, taking into account the some 100,000 victims recorded per year world-wide. In developing countries, exposure to moderate doses of OPs is often accidental due to inadvertent use of pesticides. In developed countries, however,

accidental exposure is rare, and the majority of OP poisonings result from suicidal attempts, usually with multiple lethal doses. Apart from decontamination and supportive care, accidentally poisoned patients may benefit favorably from atropine therapy alone, while suicidal patients are still a major challenge to clinical toxicologists. Due to the high poison load the life-threatening intoxication lasts for several days and requires intensive treatment facilities. Nevertheless, the lethality is high, amounting to some 30%. A third group may be discerned in nerve agent poisoning. Nerve agents are designed to quickly penetrate the respiratory epithelium, skin, and mucous membranes. Moreover, they are rapidly distributed in the body, including brain, and possess a particularly high toxic potency. These properties imply that intoxications become life-threatening within a few minutes, although the poison load is very low. While the toxic mechanisms are essentially the same with all OPs, the clinical picture may vary considerably, also depending on the route of entry into the body. Features: The signs and symptoms that characterize OP poisoning are generally thought to arise from inhibition of acetylcholinesterase (AChE) and the ensuing cholinergic crises elicited by excess acetylcholine at cholinergic receptors. The muscarinic signs and symptoms, e.g., central respiratory depression, bronchospasm, bronchial hypersecretion, pulmonary edema, bradycardia, and hypotension, may be counteracted by an antimuscarinic drug, usually atropine. Role of atropine: Although other cholinolytics with different distribution kinetics, for example dexetimide, may have distinct advantages, the role of atropine as a mainstay of therapy is essentially unchallenged. However, there is controversy as to the most appropriate dosage of atropine. Care must be taken in hot climates due to inhibition of sweating. Furthermore, hypoxic patients may develop ventricular fibrillation. To avoid long-lasting paralysis of the gut with risk of prolonged absorption of the poison, it appears prudent to carefully titrate atropine according to the following endpoints: no bronchorrhea, dry mucous membranes, no axillary sweating, heart rate at about 100/min. While atropine is suitable to antagonize the initial muscarinic effects of excess acetycholine, it is ineffective at nicotinic receptors. Role of oximes: To cope with the fatal neuromuscular dysfunction of respiratory muscles, antidotes reactivating inhibited AChE have been developed. Their effectiveness, however, is still a matter of debate. While some clinicians have observed a similar outcome in OP-poisoned patients, no matter if pralidoxime or obidoxime was given along with atropine, others have convincingly reported on benefits of oxime co-administration. There may be several reasons for this dichotomy: 1) The type and dose of poison is usually not reported and may vary widely. 2) The regimen of oxime administration may be different, including the time elapsing between ingestion of poison and oxime administration, oxime plasma concentration, and duration of oxime therapy. 3) The extent of decontamination, such as gastric lavage and administration of activated charcoal, may be affected by the action of atropine on intestinal motility. 4) Patients may vary with respect to enzyme polymorphism in toxifying phosphothioates (cytochrome P450 superfamily) and in hydrolytic detoxication (''paraoxonase status''). All these variables markedly influence the balance between reactivation and re-inhibition. Personal studies: To unravel this puzzling complexity, we have established a working group in Munich to follow the various reactions during intoxication and therapy. An intensive monitoring system has been elaborated to assess erythrocyte AChE activity (Ery-AChE), reactivatability of Ery-AChE *ex vivo*, plasma cholinesterase activity, the plasma concentrations of AChE-inhibiting compounds and their potential precursors, as well as those of obidoxime and atropine. Before transfer to the intensive care (ICU), all patients received primary care by an emergency physician, including improvement or restoration of vital functions, artificial ventilation and initiation of atropine therapy. In the ICU, atropine was continuously administered IV upon demand. Obidoxime was given as an IV bolus (250 mg) followed by continuous infusion of 750 mg/24 h, resulting in a steady-state plasma concentration of 10 to 20 μM. Obidoxime was administered until plasma cholinesterase activity increased definitely and AChE-inhibiting material was no longer detectable. On the other hand, obidoxime infusion was discontinued when reactivatability of Ery-AChE had faded due to complete ageing. Results: Our preliminary results ($n = 15$) allow the following conclusions: 1) Obidoxime was highly effective in life-threatening parathion poisoning when the dose absorbed was comparably low. 2) In poisoning with excessive doses of parathion, significant net reactivation was not achieved until several days after ingestion, when the concentration of paraoxon had declined below 0.2 μM. 3) Contrary to the current opinion, reactivatability of diethylphosphoryl-Ery-AChE *in vivo* lasted for longer periods than expected (up to 5 days). 4) In oxydemeton-methyl poisoning, which leads to dimethylphosphoryl-Ery-AChE, obidoxime was only effective when the time elapsing between ingestion of poison and onset of obidoxime therapy was shorter than 12 h. 5) The effectiveness of obidoxime was indicated by drastic reduction of the atropine demand. Usually, 1 mg atropine sulphate/h or less, resulting in plasma concentrations of approx. 20 nM, was sufficient to cope with muscarinic signs. Atropine could be discontinued when Ery-AChE was reactivated by $> 30\%$ of normal. 6) Signs of transiently impaired liver and kidney function were observed in severely poisoned patients with transient multi-organ failure. Conclusions: It is concluded that prolonged obidoxime treatment

may be of value in OP poisoning as long as reactivatability can be anticipated. In analogy, the same holds true for pralidoxime, provided the dose is high enough to correct for its higher volume of distribution and its much lower reactivating potency in comparison to obidoxime.

26 GULF-WAR SYNDROME AND ORGANOPHOSPHATES: IS THERE A CONNECTION?

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Background: Simultaneous to the history of warfare has been a record of medical symptoms in those returning from combat. These post-war syndromes following conflicts in the history of the United States has been chronicled in detail. [1] Among these syndromes are common diarrheal symptoms that probably related to the crowded and non-hygienic conditions of combat. However, the other common post-war symptoms of headache, fatigue, anxiety or nervousness, and sleeping problems are nearly identical to those seen in standard primary care medical practices. [1,2] In August of 1990 Iraq invaded Kuwait, an event which led to the deployment of over 700,000 soldiers from the United States, Great Britain, and Canada over the ensuing months. This culminated in the so-called Persian Gulf War (PGW) of February 1991. The entire PGW consisted of a 39-day air war and only 4 days of ground combat. The number of casualties in this war were markedly less than predicted. [3] However, soon after the return of United States troops, veterans of the PGW complained of symptoms of fatigue, muscle and joint pain, memory loss, headaches, diarrhea, rashes, shortness of breath, chest pain, sleep disturbances, impaired concentration, forgetfulness, irritability and depression. Because of these symptoms the United States Congress mandated the development of case registries and databases in an attempt to elucidate the cause of these symptoms. These have provided data to multiple governmental and independent commissions evaluating veterans of the PGW. However, despite all of these activities there has been no specific case definition that has been found to be applicable, nor any causal link between possible etiologic factors to which the PGW veterans were exposed and their symptoms. Review: Several epidemiologic studies have not been able to demonstrate evidence of increased disease in PGW veterans. There were many potential hazards to which individuals from the PGW were exposed. These include infectious diseases, oil well fires, pesticides, nerve agents, pyridostigmine bromide, sand particles, biologic warfare agents, multiple vaccinations, depleted uranium canisters, psychological stress, diesel exhaust, and chemoprophylactic agents. Recently a study on a single battalion serving in the PGW reported a variety of symptoms in PGW veterans and hypothesized that these individuals are suffering from an organophosphate induced delayed polyneuropathy. [4] It was further speculated that this syndrome was perhaps exacerbated by the simultaneous administration of the insect repellent *N,N*-Diethyl-*m*-toluamide (DEET). [5] However, empirical support for this hypothesis, based on our current databases and the existing scientific literature, is sparse. The study itself was symptom, not population, based and is thus vulnerable to ascertainment bias. The participation rate was 41%. Conclusion: The group of PGW veterans choosing to participate had a symptom prevalence rate of 70%, compared to 43% in the non-participants. In addition, there was minimal objective data, or verification of the self-reported exposure data. The acceptance of this hypothesis would also require long-term profound effects of these chemicals in the absence of an acute poisoning episode. The unlikely nature of this scenario, poorly supported by scientific data, render this theory a hypothesis in need of testing. References: [1]Hyams KC, Wignall FS, Roswell R. War syndromes and their evaluation: From the US Civil War to the Persian Gulf War. *Ann Int Med* 1996;**125**:398–405. [2]Lees-Haley PR, Brown RS. Neuropsychological complaint base rates of 170 personal injury claimants. *Arch Clin Neuropsych* 1993;**8**:203–209. [3]Congressional Research Service. Iraq-Kuwait crisis: a chronology of events, July 17, 1990–December 23, 1991. Washington, DC: Library of Congress, 1992. [4]Haley RW, Hom J, Roland PS, *et al.* Evaluation of neurologic function in Gulf War Veterans. A blinded case-control study. *JAMA* 1997;**277**:223–230. [5]Haley RW, Kurt TL. Self-reported exposure to neurotoxic chemical combinations in the Gulf War. A cross-sectional epidemiologic study. *JAMA* 1997;**277**:231–237.

27 PREVALENCE OF TOXIC EXPOSURES, SYMPTOMS, AND ILLNESSES AMONG US GULF WAR VETERANS

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Objective: To determine the prevalence of symptoms and medical conditions among those individuals who served in the Gulf War. Methods: Almost 697,000 U.S. military personnel were deployed to Southwest Asia during the Gulf War. Many veterans returned with multi-system complaints including fatigue, headache, memory loss, muscle pain, dizziness and numbness among other problems. Veterans were variably exposed to numerous potential toxins before,

during and after the conflict, including chemical warfare nerve agents, pesticides, depleted uranium, petroleum products, solvents, pharmaceutical products, etc. Several investigators have suggested that veterans' illness(es) resulted from toxic exposures during service. This study is a population-based health survey designed to estimate and compare the prevalence of symptoms and health conditions among Gulf War veterans and non-Gulf veterans. In Phase I, a structured health questionnaire was mailed to a randomly-selected sample of 15,000 Gulf War veterans and 15,000 similar-era veteran controls to obtain information on their exposures, symptoms, and medical conditions, recent clinic visits and hospitalizations. After three mailings, 15,825 veterans responded. In Phase II, telephone interviews were attempted on the 14,175 non-respondents using the same questionnaire as mailed in Phase I, with the addition of a question on reasons for the previous non-response. A total of 5,116 veterans participated in the telephone interviews increasing the overall response rate to 70%. Medical records were obtained on a sample of the respondents from Phases I and II, in order to validate self-reported health outcomes. The prevalence of symptoms and diagnoses for all Gulf War veterans was obtained from weighted estimates of individual military strata values from the samples using SUDAAN, a statistical program consisting of a family of procedures used to analyze data from complex surveys. This survey is complex in that the sampling design was stratified random sampling with unequal probabilities of selection in the various strata (gender, branch of service, reserve and National Guard unit status, and deployment status). Results: Rates of self-reported exposures, symptoms, and illnesses have been determined from veterans' survey responses and medical record review. Gulf War veterans report more fatigue, headaches, blurred vision, auditory symptoms, respiratory complaints, muscle ache/cramps, and numbness and tingling than the non-deployed controls. Prevalence rates of reported muscle disease, respiratory disease, skin problems, neuralgia/neuritis, and hypertension are increased in Gulf War veterans, while the prevalence of other serious illnesses such as cancer and stroke are equal in deployed and non-deployed individuals. Conclusion: The prevalence of certain toxic exposures, symptoms and illnesses are increased in U.S. military veterans who were deployed to the Gulf War compared to non-deployed controls.

28 HOW TOXIC ARE CARBAMATE INSECTICIDES?

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Background: Carbamate insecticides have the general formula $CH_3NHC(O)OR$ where R is an aromatic or aliphatic moiety. Examples include carbaryl, aldicarb, methomyl, carbofuran, bendiocarb, benfuracarb, butoxycarboxim, carbosulfan, ethiofencarb, methiocarb, oxamyl, pirimicarb, propoxur, thiodicarb and thiofanox. They are used extensively in agricultural, industrial, domestic and public health pest control. Epidemiological data: Carbamate insecticides are not a major cause of severe poisoning. For example, among just over two million human toxic exposures recorded in 1996 by the AAPCC Toxic Exposure Surveillance System (TESS) only 5000 were due to carbamate insecticides alone with only 3% of 5000 cases recorded as developing moderately severe or life threatening symptoms; only two patients (0.04%) died. As 45% of these 5000 exposures involved children under six years of age, it is probable that many were poison scares rather than true poisonings. Moreover, as TESS data include a substantial proportion of enquiries from members of the public, few of these cases are corroborated analytically. Even in countries where agriculture is the primary industry and pesticide ingestion is an important means of suicide, fatal carbamate poisoning is uncommon. Among 228 confirmed fatal poisonings in Northern Greece (population three million) between 1990 and 1995, carbamates were implicated in 24 of 85 cases of pesticide poisoning. There are several possible explanations for these observations. Firstly, carbamates could be relatively non-toxic, particularly when compared to OP insecticides. Secondly, those who ingest carbamate insecticides deliberately may only imbibe small quantities. Thirdly, carbamates could be ingested relatively infrequently because they are not perceived by the public generally as being toxic and therefore suitable for a suicidal attempt. Mechanisms of toxicity: Carbamates inhibit acetylcholinesterase (AChE). This occurs by carbamylation of a serine hydroxyl residue at the active site of the enzyme, a process that involves clevage of the carbamate molecule, which in effect is treated by the enzyme as an alternative substrate to acetylcholine (ACh). Therefore the AChE-carbamate interaction is not truly reversible, as the carbamate does not depart the encounter intact but rather as the products of hydrolysis. AChE activity is restored when spontaneous hydrolysis of the carbamylated enzyme occurs. This spontaneous reactivation, expressed as half-life, of carbamylated enzyme varies between 2–240 minutes depending on the carbamate and in part explains some of the observed differences between carbamates as regards their toxicity. The rate of regeneration of the carbamylated enzyme to AChE is relatively rapid when compared with that of an OP phosphorylated enzyme and, moreover, "aging" does not occur. Carbamates do not cross the blood-brain barrier readily, so the contributory effect on cerebral AChE is considerably less than that caused by OP insecticides. Hence,

there are mechanistic reasons why human exposure to carbamate insecticides is less dangerous than exposure to an OP insecticide. Review: Although carbamate poisoning is not frequently life-threatening, cholinergic symptoms have occurred in workers exposed inadvertently to excessive amounts of carbamates by skin contact or inhalation, usually following equipment malfunction or inadequate protective measures. In these cases the rapid (often within 30 minutes) onset of mild cholinergic features including nausea, sweating, lacrimation, salivation, bronchorrhea, weakness and diarrhea, serves to alert affected individuals to remove themselves from exposure, with resolution of symptoms within hours, often without the need for atropinization. Although there are isolated reports of severe sequelae following occupational carbamate exposure (including a pilot who died after crashing a plane following inhalation and dermal methomyl exposure within the cockpit), most cases of severe poisoning occur from deliberate ingestion. There are occasional reports, often involving the ingestion of methomyl, of severe cholinergic manifestations including agitation, profound weakness, muscle fasciculation, respiratory distress and coma; these features often develop within a few minutes. In untreated cases death has occurred within a few hours; pulmonary edema and evidence of cerebral hypoxia are the main findings at autopsy. In patients who survive, coma may persist for 18–24 hours. In less substantial ingestions, cholinergic symptoms are evident within two hours in most cases, and typically resolve within 24 hours though they may persist for up to two days. There is some evidence that central nervous system depression in moderate carbamate poisoning is more common in young children than adults, possibly due to a greater blood brain barrier permeability in infants. Conclusion: Although most carbamate insecticides are less toxic than OP insecticides, they should not be considered toxicologically benign. Severe cholinergic symptoms may ensue following ingestion and unless supportive care, often with atropinization, is instituted promptly, significant morbidity may ensue and deaths have been reported.

29 CARBAMATE INSECTICIDES: ARE OXIMES HARMFUL, BENEFICIAL OR UNNECESSARY?

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Background: Carbamate insecticides inhibit acetylcholinesterase (AChE) enzymes resulting in the characteristic features of acetylcholine (ACh) excess. Atropine is used to antagonize the effects of ACh at muscaranic receptors but does not affect nicotinic features. The use of oximes to reactivate carbamate-inhibited AChE is controversial. Many toxicology textbooks state that oximes are contraindicated in carbamate poisoning. What is the evidence for this? Review: Few cases of carbamate insecticide poisoning have been treated with oximes since Farago (1969) described a fatal case of carbaryl poisoning in a 39-year-old man, intoxicated with alcohol, who drank approximately 500 mL of an 80% solution of Sevin (carbaryl). He was treated with gastric lavage, drugs to stimulate the circulation and a total of 6 mg atropine. His symptoms of confusion, disturbed vision and pulmonary edema were slightly ameliorated by atropine but full atropinization was not achieved. About three hours after ingestion 250 mg 2-PAM was administered. Pulmonary edema progressed rapidly and the patient died six hours post-ingestion. Two adults poisoned with aldicarb and one with methomyl recovered following treatment with atropine and pralidoxime. In one of these cases muscle fasciculations stopped following administration of pralidoxime. Atropine and pralidoxime controlled cholinergic hyperactivity in a case of benfuracarb poisoning but the patient sustained permanent partial cortical blindness. A retrospective review of 26 children intoxicated with methomyl or aldicarb found that none of the children deteriorated or showed exacerbation of cholinergic symptoms following treatment with obidoxime (total dose 12 mg/kg). Tests in experimental animals indicate that oximes can increase the LD_{50} of aldicarb, neostigmine and physostigmine. When used in conjunction with atropine they may provide greater or equal protection to atropine alone. Pralidoxime accelerated the rate of decarbamylation of physostigmine and pyridostigmine-inhibited AChE *in vitro* and *in vivo*. However, pralidoxime did not reduce the toxicity of benfuracarb in rats and oximes had no significant effect on methomyl or aldicarb-inhibited enzyme activity *in vitro*. Pralidoxime alone increased the toxicity of carbaryl in experimental animals and combined atropine/oxime therapy provided less effective protection against carbaryl than atropine alone. Oximes virtually stopped spontaneous reactivation of carbaryl-inhibited rat erythrocyte AChE and enhanced inhibition of human serum cholinesterase by carbaryl *in vitro*. Although caution is necessary in applying results of animal and *in vitro* studies to humans, these findings indicate that oximes provide no additional benefit compared with atropine alone in cases of carbaryl poisoning and can in fact diminish the efficacy of atropine. Oxime therapy alone may increase carbaryl toxicity. There are limited and conflicting data on the role of oximes in poisoning due to other carbamate insecticides. Oximes reduced the toxicity of aldicarb but not of benfuracarb and they had no significant effect on methomyl or aldicarb-inhibited AChE activity. Conclusion: Oximes have a limited role in the treatment of carbamate insecticide poisoning. Oxime therapy, in addition to treatment with atropine, can be considered if life-threatening symptoms are present or if poisoning is due to a mixture of organo-

phosphorus and carbamate insecticides or if the identity of the AChE inhibitor is unknown and significant nicotinic symptoms are present.

30 KINETIC—DYNAMIC RELATIONSHIP IN A CASE OF ALDICARB POISONING

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Objective: To study the relationship between clinical symptoms, serum cholinesterases activity and plasma concentration of aldicarb in a case of carbamate insecticide poisoning. Case report: A 30-year-old woman was admitted for an acute poisoning after ingestion of 10 g aldicarb (a carbamate insecticide), 2.1 g sertraline and 15 mg alprazolam. Before admission she had developed coma (GCS = 4), bradycardia (40/min), miosis, salivation, diaphoresis, and muscle fasciculations. SpO_2 was 74% and the patient was intubated, ventilated, sedated and transferred to the intensive care unit. On admission, the examination showed: coma (GCS = 3), pulse = 60/min, BP = 140/70, temperature = 33.5°C, miosis, bronchial hypersecretion, diaphoresis, fasciculations and diarrhea. Treatment included mechanical ventilation, atropine (3 × 1 mg) and pralidoxime 1 g over 8 hours. Blood samples were drawn every 1 to 3 hours for analyses of serum cholinesterase and aldicarb. Aldicarb was analyzed in serum and urine by a HPLC/DAD method. On admission, serum cholinesterases activity was strongly decreased to 247 U/L (normal = 3500–8000) and remained below 506 U/L until the 36th hour. Serum aldicarb reached a peak value of 3.22 mg/L at the 3rd hour and, thereafter, decreased with a half-life of 5.75 hours. From the 36th hour symptoms improved rapidly and the patient was weaned from mechanical ventilation and extubated at the 44th hour. At the same time serum cholinesterase activity had rapidly increased and reached normal values at the 60th hour when the plasma aldicarb concentration was below 0.120 mg/L. Over 74 hours, 26.7 mg aldicarb were eliminated in urine. Conclusion: In this case of severe carbamate insecticide poisoning, there was a close relationship between the evolution of the aldicarb plasma concentrations, the symptoms and the serum cholinesterase activities. Treatment with pralidoxime, at the dose administered, had no effect on the symptoms and on the serum cholinesterase activity. Rapid recovery was related to the fast decrease of the plasma aldicarb concentration.

31 GLYPHOSATE—CONTEMPORARY CLINICAL FEATURES

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Background: Glyphosate was synthesized by a French chemist but its herbicidal activity lay undiscovered until the late 1960s when an American company serendipitously screened it among a bank of compounds. After 25 years of commercial availability, it is now one of the most widely used and studied herbicides in the world. Use continues to increase largely because of its suitability for ''no-till'' conservation planting of crops. It is also one of the non-selective herbicides for which genetically engineered crops have been developed, and this is expected to further increase its use. Glyphosate enjoys a favorable environmental safety profile which includes a mechanism of action specific to plants, relative lack of volatility, lack of residual soil activity and soil migration, and rapid biotic degradation. It appears to be non-carcinogenic (EPA category E), and is non-mutagenic and devoid of reproductive or developmental effects.It is formulated with other ingredients that must be considered in its toxicology. The classic concentrate formulation contains the isopropylamine salt of glyphosate (41% w/v), an ethoxylated tallow amine surfactant (15.4% w/v) and water. In the published literature there appears to be some confusion regarding glyphosate vs. the isopropylamine salt of glyphosate; glyphosate vs. Roundup herbicide; Roundup herbicide diluted for use vs. Roundup Ready-to-Use (which has other ingredients with medical implications) and other non-Roundup glyphosate products. Over 100 different brand names comprised of many formulations have been sold worldwide. Some contain the monoammonium or sodium sesqui-salt; some are dry formulations; some contain different surfactant systems or no surfactant at all. It is also sold in combination with other herbicides including various chlorophenoxy compounds, simazine, linuron, and picloram. Care must be taken to properly communicate and interpret any formulation or ingredient information to avoid perpetuating confusion. Features: Glyphosate kinetics and metabolic fate have been characterized in animals and human clinical data appear to follow the same general patterns. It is not well absorbed after oral or dermal exposure. It is not metabolized and is rapidly excreted unchanged in the urine with a half life of several hours. In fatal cases glyphosate blood levels have been reported to be as high as 6850 ppm and serum levels 1600 ppm. These measurements have not been characterized as useful clinically in assessing the severity of exposure or poisoning. Hemodialysis as well as resin hemoperfusion is effective in removing glyphosate from blood. Activated charcoal hemoperfusion does not remove glyphosate. However, pretreatment of rats with activated charcoal prior to a fatal oral dose of classic Roundup formulation prevents mortality.

This suggests that the primary toxic principle is adsorbed by activated charcoal and is indeed the surfactant. The kinetics and disposition of the surfactant are not known. Although it is described as nonionic, its tertiary nitrogen protonates at physiologic pH and it behaves more like a cationic surfactant. Clinical descriptions of benzalkonium chloride ingestion share striking similarities with those of the tallow amine-containing Roundup. Several large published series have characterized the range of symptoms produced by ingestion of the classic formulation. These are oral, laryngeal and GI tract irritation, erosions, and edema; vomiting and diarrhea; volume depletion hypotension followed by cardiovascular hypotension; hypoxia, and pulmonary edema. Secondary organ dysfunction may occur in the CNS, liver and kidneys. The surfactant is suspected to be the primary culprit, but the relative contribution of the surfactant and the glyphosate to the toxic syndrome remains controversial. Yamashita *et al.* confirmed the surfactant's role in causing hypotension through myocardial depression by in vivo intravenous studies in dogs. Their further work in vitro on isolated heart and coronary vessel preparations again confirmed the myocardial toxicity of the surfactant but also suggested that glyphosate, isopropylamine glyphosate and isopropylamine have their own cardiotoxic actions. Although these findings must be considered preliminary and have yet to be confirmed by other researchers, they are provocative and indicate that our current understanding of these issues is limited. Soon after the first large suicidal ingestion series were published, the amount of surfactant in the US Roundup formulation was halved. Thus, the literature probably overstates the toxic potential to humans there. Other options to the classic glyphosate formulation share this tenuous connection to the literature, which may eventually become largely irrelevant to contemporary clinical needs as the formulations continue to change and diversify. The introduction of new surfactant systems may be transparent to the consumer and medical community, yet experimental evidence suggests they may be quite relevant to human toxicology. Once diluted for use, glyphosate formulations offer little risk of adverse effect except minor eye, membrane or skin irritation. Allergic contact dermatitis is possible if a sensitizing preservative is contained in the particular formulation as is bronchospasm in sulfite-sensitive patients who use dry formulations.

32 HANDLING POISON CENTRE ENQUIRIES—A NEW US PERSPECTIVE

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In Fall 1996, the State of California contracted with the University of California School of Pharmacy to develop and implement a system for providing poison center services to the 32 million people of California. In January 1997, the California Poison Control System began operation. Four of the previous centers (San Francisco, San Diego, Sacramento, Fresno) were consolidated into the system and two centers ceased operations. An automatic call direction (ACD) telephone system was installed along with a wide area computer network linking the four sites electronically. Staffing was begun using multiple skill levels. A new category of staff, poison information providers, was introduced along with existing staff composed of registered nurses and pharmacists. Three toll free telephone numbers were placed for access to the system, one for the public, one for ambulance services and one for health care providers. The ACD telephone system is programmed to direct public calls to a poison information provider and if none is available to a nurse or pharmacist; ambulance service calls are directed to a nurse and if none is available to a pharmacist; and health professional calls are directed to pharmacists. Calls are first directed to one of the four sites based on geographic proximity. If staff at that site are all busy, calls are routed to one of the other sites. Poison information providers may independently handle calls that are either on an approved list of nontoxic substances or which fall within stringent protocols that have been developed. Provider calls are reviewed by a licensed staff member during each work shift. Cases that do not fit within the protocols or where the victim is symptomatic are immediately referred to a nurse or pharmacist. To promote consistency management guidelines have been developed which include circumstances requiring referral to a health care facility, laboratory monitoring parameters, follow-up call procedures as well as medical management of the substance involved in the exposure. Guidelines are posted on the CPCS Intraweb which is available to staff at all times. The guidelines contain hotlinks to the most recent version of the handbook, *Poisoning & Drug Overdose* written by staff and faculty of the CPCS and published by Appleton & Lange Publishing Company. Guidelines supplement the handbook which serves as the official protocols of the CPCS. Operations at each site are overseen by a pharmacist managing director, certified by the American Board of Applied Toxicology and a physician medical director certified in Medical Toxicology by the American Board of Medical Specialties. Management of the system is provided by an executive director.

33 HANDLING ENQUIRIES EFFECTIVELY—A EUROPEAN PERSPECTIVE

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Introduction: A regional poisons information centre in Europe serves either a single state, or only a part of a state. Most poisons information centres in Europe provide information to the public, health care professionals and emergency services on a 24-hour per day basis, every day of the year. Poisons information services in the UK and the Netherlands offer only access to health care professionals and emergency services. In these countries, the public are expected to consult or call their family doctor or a first aid department. In Europe, handling poison exposure emergency calls had to be done more efficiently for several reasons. Firstly, the workload of centres has increased over the years (e.g., more calls to handle, more different tasks in human risk assessment) while the budget for staff members was not in proportion to the demand. Secondly, the trend of closing smaller poisons centres in some European states has increased the workload for the remaining centres. Thirdly, intensified toxicovigilance activity followed by health education campaigns has increased the workload further. It was clear that enquiries needed to be handled more efficiently, without reducing the quality of the information supplied. Methods: In order to keep the time needed for dispatch calls as restricted and effective as possible, it is important to have well-trained staff members, who can be considered as specialists in poison information. In European poisons information centres, the educational background of the information suppliers is generally medical: nurses, physicians or pharmacists. Although when recruiting staff with this specific background, it is very difficult to find a 'fully-formed' poisons information specialist. Most new staff need a special training programme in clinical toxicology and skill in verbal communication. All centres have a medical doctor specialized in clinical toxicology or a qualified designee available, on call by telephone, at all times. In an emergency situation, all specialists in poisons information should be able to provide tailor-made information on the consequences of exposure, the kind of intoxication that can be expected, and the intervention measures needed to reduce the (harmful) health effects. In order to limit the expenses in several centres, the number of academically trained staff was restricted in favour of non-academic staff, e.g., nurses. The latter issue was one of the reasons for European centres to design a computerized data-base on potentially toxic compounds according to their local needs, and/or purchasing commercial data-bases to have ready access to current comprehensive texts covering both general and specific aspects of acute and chronic poisoning. In addition to poisons information service, the UK has an on-line database (TOXBASE) available, containing clinical toxicological information, which is directly accessible by health care professionals throughout the UK. Besides the importance of maintaining an efficient telephone system for handling direct incoming calls, the quality assurance and quality control of outgoing information is very important. This is one of the main reasons that justifies the existence of a poisons information centre. Most European centres have a formal or an informal internal quality assurance system. In Switzerland e.g., the Centre receives a written feedback report from the treating physicians. This clinical information is used for quality control, and also for better risk assessment with particular emphasis on dose-response relationships. Most centres collect patient data via follow-up letters to doctors that have contacted the poisons centre. Other centres collect their data through specially developed enquiries. Doctors who have contacted the poisons centre are asked to fill in these questionnaires. Conclusions: Although most poisons information centres in Europe are working on handling enquiries efficiently and to a high scientific standard, there are no European guidelines for these activities. Recently, the EAPCCT (European Association of Poisons Centres and Clinical Toxicologists) established a working group on "quality and accreditation of poisons centres." The working group has the task of producing draft guidelines on the above-mentioned issues, which will be discussed with the members of the EAPCCT.

34 QUALITY STANDARDS . . . WHO SHOULD SET THEM AND HOW CAN THEY BE DELIVERED?

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Webster defines quality as "a degree of excellence." Standard is defined as "something set up and established by authority as a rule for the measure of . . . quality." The identification and measurement of quality standards for poison centers is difficult and the standards must be defined, validated and quantified. Numerous papers have addressed the development of standards and measurement through discussions of the roles of poison centers,[1] identification of differences between centers,[2–4] description of poison center benchmarks,[5] and addressing strategies to measure quality in

poison centers.[6–9] The American Association of Poison Control Centers has defined criteria for the certification of poison centers that measure the ability of a poison center to adequately serve the residents of their region. The criteria address macroscopic aspects of poison center operations such as staff certification, quality improvement, data collection and analysis and education. While the document identifies specific criteria, it relegates the responsibility of implementation to the poison center—ultimately, the poison center should be responsible for establishing its own quality standards. For example, it may be appropriate for governmental agencies that provide financial support and for professional societies that promulgate standards to specify that a poison center needs a continuous quality improvement program. However, the particular process should be developed by the poison center itself because governing bodies lack specific knowledge about how to implement and optimize the process in an individual poison center. The product of a poison center is knowledge which is intangible and difficult to measure. Every effort should be made to insure that the knowledge imparted is accurate, adequate, documented and results in desirable patient outcomes. This can be monitored through daily peer review audits of patient records. Deviations in patient care can be identified rapidly and rectified, inadequate and inaccurate data can be corrected so that epidemiology and research data are correct and data for governmental and industrial clients reflect the high standards of the poison center. Quality generally signifies process in today's quality management-driven society. However, quality should emanate from the poison center's mission statement and represent a work-ethic that is embodied by everyone on the staff as a matter of principle, not as an artificial administrative mandate. A successful poison center will incorporate continuous quality improvement into its daily activities so that they become almost imperceptible ways to improve the poison center product through enhanced performance rather than intimidation. References: [1]Vale JA, Meredith TJ. Clinical toxicology in the 1990s: The development of clinical toxicology centers-A personal view. *J Toxicol Clin Toxicol* 1993;**31**:223–227. [2]Thompson DF, Trammel HL, Robertson NJ, Reigart JR. Evaluation of regional and nonregional poison centers. *N Engl J Med* 1983;**308**:191–194. [3]Geller RJ, Fisher JG, Leeper JD, Tooson JD, Ranganathan S. Poison centers in America: How well do they perform. *Vet Hum Toxicol* 1990;**32**:240–245. [4]King WD, Palmisano PA. Poison control centers: Can their value be measured? *South Med J* 1991;**84**:722–726. [5]Felberg L, Litovitz TL, Morgan J. State of the nation's poison centers: 1995 American Association of Poison Control Centers Survey of US poison centers. *Vet Hum Toxicol* 1996;**38**:445–453. [6]Dean BS, Guzzardi MA, Krenzelok EP. Performance management: An Essential program for poison centers. *Vet Hum Toxicol* 1987;**29**:169–171. [7]Dean BS, Jordan J, Mrvos R, Krenzelok EP. Quality assurance: How it can help a poison information center. *Vet Hum Toxicol* 1988;**30**:56–58. [8]Dean BS, Krenzelok EP. A ten-step quality assurance program for regional poison information centers. *Vet Hum Toxicol* 1992;**34**:445–447. [9]McGuigan MA. Quality management for poison centers. *J Toxicol Clin Toxicol* 1997;**35**:283–293.

35 DATA COLLECTION—HOW MUCH? HOW USEFUL?

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Poisons centres collect data, but are they collecting the "right" data and are they using it for the "right" purpose? The only reason for collecting data is so that it can be used to answer questions. Collecting data that are not used (or useful) is a waste of valuable resources. The subject of this paper is the "what," "why," and "how" of poisons centre data. Poisons centres generally collect two types of data: case or call data and process or activity data. The former is epidemiological data and is the type most commonly meant or understood when speaking of "poisons centre data." The latter type is the data which reflect the functioning of the internal operations of a poisons centre. Both of these types of data are most useful when considered in the broad context of "quality improvement." Poisons centres do not function in isolation—they provide health interventions or services to a given population such as the lay public or healthcare professionals. For this reason, a quality improvement program should include an overall evaluation of how a poisons centre functions in the social community. Since one of the primary functions of a poisons centre is to provide a service, data should be collected that will reflect how well that service is performed and how well it reduces the social burden of illness from poisonings. Underpinning this expanded construct of quality improvement are the epidemiological and the process data. This broader view of quality improvement and related data collection can be described in seven steps. The first step is to determine the current levels of morbidity and mortality from poisoning. Poisons centres epidemiological data provide some information but it is incomplete and its interpretation has been questioned. How much of this burden of illness is avoidable and how much is unavoidable will direct resource allocations. The second step is to identify the factors or causes contributing to the poisonings. The data describing the characteristics of young children who are unintentionally exposed to a poison are decades old and may not be relevant in today's

society. The third step is to evaluate how effective an intervention with potential for reducing the burden of poisonings is when applied in the community. Factors affecting community effectiveness of an intervention are efficacy, screening or diagnostic accuracy, health professional compliance, patient compliance, and coverage. The fourth step is to determine if the intervention is being provided efficiently, i.e. with an optional use of resources. This part involves the traditional internal quality improvement activities and economic evaluations of the interventions. The fifth step is to evaluate the feasibility of implementing or expanding an intervention. This step identifies possible limiting constraints including social, cultural, and political barriers in addition to appropriateness of the physical setting, personnel, and budgets. Part of this step includes the setting of realistic objective targets against which success will be measured. The sixth step is to monitor the impact of the intervention. Parameters reflecting the activity and progress of the intervention need to be readily identifiable and quantifiable. The seventh step, reassessment, is an evaluation of the changes in the burden of poisonings that can be related or attributed to the intervention. Poisons centres must collect data as part of a quality improvement progam; data that is collected after careful forethought is very useful. This paper described a broader than usual scope and scale of quality improvement by expanding the concepts from the internal operation of a poisons centre to the external community it serves. Regardless of the scope or scale of a quality improvement program, data collection is critical: data must be used to power the iterative approach to quality improvement. Reference: [1]Tugwell P, Bennett KJ, Sackett DL, Haynes RB. The measurement iterative loop: a framework for the critical appraisal need, benefit and costs of health interventions. *J Chronic Dis* 1985;**38**:339–351.

36 FOLLOW-UP OF ENQUIRIES—WHY BOTHER?

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Follow-up calls have been a stable part of operations in most poison centers in the US for over thirty years. This system has evolved and persisted in the US in part as a response to the caller mix experienced by most centers and by the needs to secure stable funding from public sources. Follow-up calls generally fall into two categories: calls made because of the necessity to maintain contact with a patient or treating facility in order to continue to provide appropriate treatment information (structured calls) and calls made for general data gathering, education, and public relations (non-structured calls). Structured calls for most poison centers follow pre-established protocols. Such calls would include calls made to a parent at home at designated times after syrup of ipecac is recommended to ascertain that the child has vomited and that the patient's condition remains satisfactory. Such routine calls are made following all home therapies or after referral of patients to emergency departments. Most centers also make routine protocol driven calls to hospitals to check on the condition of hospitalized patients. Examples of such protocols will be shown. The logic for such calls is based on some data showing the need for additional information after the initial call either because of significant and unanticipated changes in the patient's condition or because of errors or lack of compliance by the initial recipient of the information. Available data will be discussed. As poison centers, and their medical directors, are legally liable for the appropriateness of center recommendations, follow-up calls serve to minimize that liability. Calls also provide additional data relating to clinical course and outcome which are useful in managing future cases and often in clinical research. Non-structured follow-up calls are usually done on a time-available basis. They are done in part to reliably ascertain outcome on cases thought initially to represent non-toxic exposures. This data is part of the TESS data base of the AAPCC and is one data element used to determine a quality score for each center. Such calls also provide the opportunity to do some poison prevention education, particularly where young children were the initial case. They may also provide the opportunity to gather more data, including information about other potential cases for occupational and environmental exposures. It is the observation of most US poison centers that follow-up calls generate immense amounts of public good will and support for the center. This good will is often important as centers fight for adequate funding. The primary disadvantages of follow-up calls are cost and time commitment. Data from several centers have shown that follow-up calls may significantly outnumber incoming calls. Even though they are usually shorter, this still represents a considerable staff commitment and attendant cost.

37 EDUCATING THE ENQUIRERS

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Background: Since poison information is basically a form of risk communication and the common denominator for enquirer and information specialist is mutual trust, the emergency call situation can be used effectively to communicate

more information than the most urgently needed immediate advice. General public: Enquiries from the general public (46% of all exposition cases in Berlin poison center) no treatment advice is given without having been informed about any home remedy or measures taken prior to the phone call; this systematic approach stems from medicolegal reasons to recognize potentially life-threatening methods like table salt induced emesis by lay people but also to help people learn to cope with similar accidents in the future. Thus the poison center specialist reacts immediately and outlines the correct way of first aid measures. Since the effects of such educating measures are difficult to evaluate we have additionally used the concept of "anticipated guidance" in a 3 year case-control study including 24,000 parents of children in the risk group of age 1 year old, following this cohort through till the age of 4 years. We found that in possible household poisonings (2400 follow-up cases) the previously informed parents reacted more promptly (5 minutes) and more adequately (first call, then act: 90% versus 71.3% without prior information). These changes in behavior were sustained over the whole study period. Medical profession: Concerning calls from the medical profession our tailor made individual advice routinely takes, into account treatment measures already performed by the enquirer. Thus any discrepancy to the poison centers advice might form an ideal problem oriented learning (POL) for the enquirer. In these circumstances however problems of acceptance (doctor versus doctor; doctor versus nurse) hinder a systematic approach as does the urgent medical problem at hand and the restricted time for both enquirer and information specialist. Nevertheless do data from, for example, the Mainz Poison Center show a specific decline in use of gastric lavage in poisoned adult patients which can be traced directly to the Poison center's intervention rather than be explained by a general change of the policy in the communicating hospitals alone? We combine the individual contact approach with routine information packages sent to about 50 regional hospitals in the Berlin/Brandenburg area and to our 60 contractual hospitals throughout the country. Conclusion: A more systematic approach for training is urgently needed and it should combine the incidental educative measure during the risk communication procedure with a standardized approach of well-defined groups at risk (parents with toddlers) and groups in need of correct information (emergency dept., rescue teams etc) thus establishing a continuous medical education for the "potential" enquirer and underlining the role of poison centers in defining and promoting standards of treatment for poisoned patients.

38 THE DEVELOPMENT AND EFFECTIVENESS OF PROTOCOLS FOR TELEPHONE RESPONSE TO POISONINGS BY ALTERNATIVE PROVIDERS

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Objective: To describe the development and compare the effectiveness of protocols used in 3 models for the telephone management of low acuity poisonings from public callers. Methods: The models varied the background of staff responding to poisoning calls [Model I: non-licensed Emergency Medical Dispatchers (EMDs) from a 9-1-1 call center; Model II: Advice Nurses (RNs) from a health maintenance organization; Model III: non-licensed Poison Information Providers (PIPs) trained in a poison control center (PCC) and teamed with licensed pharmacist Specialists in Poison Information (SPIs)] and the scope of protocols [Model I: Algorithm with Quick Reference Card (QRC) listing 200 nontoxic products for managing asymptomatic pediatric ingestions; Model II: expanded QRC with added history taking and dose estimation; Model III: Expanded QRC using dose estimation for approximately 400 substances and topic-based protocols to identify low risk cases]. All three models utilized live PCC calls with one-on-one monitoring or indirect supervision through retrospective case review (Model III). The call length, number of calls managed and caller compliance and satisfaction were determined. Results: All models demonstrated the ability to effectively manage a subset of PCC calls. There was a trend of a higher proportion of calls managed correctly without transfer or consultation with a SPI and longer average time to manage the call as the protocols became less restrictive (Model I, most restrictive; Model III, least restrictive).

Model #	# calls fielded	# (%) of calls correctly managed	Average length of talk time (range)
I (EMDs)	745	40 (6%)	93 seconds (46–159)
II (RNs)	445	46 (12%)	172 (69–413)
III (PIPs)	753	279 (52%)	191.5 (51–595)

Callers were satisfied with the alternative providers, compliant with their recommendations and unaware of their professional backgrounds. None of the poisonings had unexpected effects or outcomes. Conclusion: These alternative models evaluated the feasibility of using protocols and EMDs, Advice Nurses and PIPs in the delivery of PCC services. Our results suggest that alternative providers can manage a small subset of poisoning cases using a structured protocol but ready access to a SPI for consultation and case referral is essential. The cost-effectiveness of these models is uncertain.

39 THIRD PARTY PAYER RESPONSE TO PCC COST-EFFECTIVENESS DATA

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Objective: A previously reported cost-effectiveness study by our state poison system suggested that third party payers are major benefactors from poison control services, despite an annual contribution of less than 0.8% to the operating budget. A larger scale follow up study was performed to further elucidate the payer mix of our callers and to evaluate whether awareness of such information augmented the corporate giving pattern of insurance companies. Methods: 20,000 consecutive callers were surveyed as to their health insurance status during a six month period. The annual cost savings to 28 insurance companies with the greatest call frequency was calculated by doubling the call frequency and multiplying by the cost-savings factor derived from our previous study, $131.75. This data was then provided to each company, along with a an appeal that 10% of their cost-savings be donated to support poison center services. Results: Only 8% of patients were uninsured or had unknown insurance status, 10% were insured by federally funded programs. Payer mix as a percentage of total calls was as follows: Blue Cross 19.2, Selectcare 2.76, Preferred Providers of Michigan 2.65, Health Alliance Plan 3.82, M-Care 1.20, Care Choices 1.1, Wellness Plan 1.0, Omnicare 0.98, Aetna .85, Health Plus of Michigan 0.67, Cigna 0.37, Total Health Care 0.33, John Deere 0.32, Detroit Medical Center Care 0.32, Physician's Health 0.22, American Med Security 0.21, American Community Mutual 0.16, Mesra 0.14, Champus 0.14, John Alden 0.20, HMO (unspecified) 0.12, Teamster 0.11, Great West Care 0.11, Preferred Health 0.11, Banker's Life 0.10, John Hancock 0.09, Employers Health 0.08, First Health 0.08, United Health 0.07, other constituting < 0.07, 62.5. Response to data presentation and direct appeal was received from six companies, five of which donated a total of $8,500, representing an increase of only $1,300 over previous years' unsolicited contributions from third party payers. Conclusions: Awareness of poison center-mediated direct cost savings to third party payers, as determined by large scale local survey information coupled with cost-effectiveness data did not significantly alter corporate donation patterns. Other methods of involving third party payers in the financial support of poison centers need to be explored, such as legislated annual fees, licensure fees, augmented capitation fees, or direct billing based on number of calls taken.

40 EPIDEMIOLOGY OF ACUTE POISONING: DISCREPANCIES BETWEEN POISON CENTER AND EMERGENCY DEPARTMENT DATA

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Background: Poison centers (PC) data are often used to describe the epidemiology of acute poisoning. However, several factors may influence the referral rate to PC and ultimately affect the epidemiological reliability of PC data. Objective: To evaluate differences between toxic exposures reported to a PC from the Emergency Department of an urban member hospital (ED) and the actual toxic exposures presenting to this ED. Methods: A retrospective analysis of 1-year calls to PC from the ED was made. Patient age and gender, agent(s), and circumstances and route of the exposure were recorded. ED medical records of the same period were reviewed to detect cases of acute poisoning, based on discharge diagnosis. Cases reported to PC were compared with not-reported cases; chi-square analysis was applied, when appropriate. Results: From a total of 56,421 ED visits, 628 acute poisonings were identified (1.1%). Pediatric poisonings ($\leq$ 14-y old) represented 9.1% (57/628) of cases; males were 61.1% (384/628). Alcohol (28.8%, 181/628), followed by medications (21.5%, 135/628), household products (14.0%, 88/628) and abuse substances (7.5%, 47/628) were more often involved. Accidental exposures accounted for 38.9% (244/628) of cases. In the period considered, PC received 141 calls from the ED. Males accounted for 41.8% (59/141) of cases. Medications (36.2%, 51/141), household products (22.0%, 31/141) and mushrooms (7.8%, 11/141) were more frequently involved. Accidental exposures represented 57.4% (81/141) of cases. Out of 141 cases reported to PC, 124 matched with ED medical records. The remaining 17 cases concerned patients calling the ED for advice without being there or cases in whom PC excluded toxic etiology. Overall, PC was called for 19.7% (124/628) of cases of acute poisoning seen in ED. PC was more likely to be called

for female than for male patients (30.0% vs. 13.2%, $p < 0.01$), and for cases of poisoning by ingestion rather than for inhalation, injection or eye/skin contact (23.1% vs. 6.8%, $p < 0.01$). PC was never called for carbon monoxide poisoning (0/38) nor for alcohol intoxication (0/181), and drug abuse was rarely reported (3/47, 6.4%). Conclusion: In this study, PC data do not reflect the epidemiology of acute poisoning as seen in the ED, because of a referral bias. In countries where a large amount of PC calls come from EDs, the analysis of PC utilization by EDs and the introduction of correction factors in PC data might be a meaningful manner to obtain a more realistic profile of toxic diseases.

41 HEALTH EFFECTS OF HAZARDOUS MATERIALS EXPOSURES: A PROSPECTIVE STUDY IN WASHINGTON STATE

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Objective: The goal of this study was to identify variables predictive of adverse outcomes in humans exposed to hazardous materials. Methods: Hazardous materials incidents were identified at the time of exposure by telephone calls from medical personnel, firefighters, or laypersons to the Washington Poison Center. Scene information was collected at that time. Exposed individuals were contacted to administer a telephone questionnaire within 8–30 days after the incident. Psychological scores were assessed using the Brief Symptoms Inventory. Regression analyses were conducted to identify predictors of adverse outcomes. Results: Fifty-one incidents were reported between December 1997 and November 1998. Contact information was available for 236 people, and 150 (64%) completed the survey. Eighty-two (55%) of the subjects were female, 17 (11%) were children, and 42 (28%) were minorities or did not select a racial category. One hundred thirty-seven (91%) breathed in fumes and 20 (13%) spilled the chemical on skin or clothing. Ninety-two (61%) were exposed for <1 hour, 25 (17%) for 1–2 hours, and 20 (13%) for > 2 hours. Ninety-five (63%) of people were transported to a medical facility. Thirteen (9%) left work or school for more than two days due to the exposure. Forty-six (31%) reported at least one persistent symptom at the time of survey. The most frequently reported persistent symptoms included fatigue and mucous membrane or respiratory irritation. Thirty (24%) had elevated psychological scores. The most commonly elevated psychological sub-scores were somatization (51%), hostility (30%), and anxiety (23%). Regression analyses were done for time loss, persistent physiological symptoms, and psychological scores. The number of persistent symptoms were associated with longer duration of exposure, exposure while not at work, and hospital transport ($R^2 = 0.230$). Time loss (>2 days) was associated with prior asthma and increased alcohol consumption ($R^2 = 0.127$). Higher psychological scores were associated with prior psychological counseling, spills on skin or clothing, significance of exposure not described to the patient, and longer duration of exposure ($R^2 = 0.144$). Conclusion: Hazardous materials incidents significantly impacted individuals with actual or perceived exposures. Incident factors (such as duration of exposure), medical/treatment factors (such as prior asthma and description of exposure significance) and other individual characteristics (such as prior counseling and drinking history) were associated with persistent symptoms, time loss, or psychological score. Following additional data collection and analysis, medical treatment and transport guidelines will be developed in an effort to optimize health care following hazardous materials exposures.

42 EFFECTIVENESS OF SHORT-TERM HOSPITAL OBSERVATION IN MANAGING CHILDHOOD POISONING

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Background: Minor emergencies can be safely managed by a short hospital stay for clinical observation, diagnostic procedures and/or treatment, avoiding hospital admission. This could be useful also for childhood poisoning. Objective: To evaluate effectiveness of short-time observation in managing childhood poisoning personal experience has been analyzed. Methods: Children referred to our Emergency Room (ER) because of toxic exposure are registered on an ongoing basis in a specific database. Decision making on hospital admission, short-time observation or discharge is based on guide-lines. For the present study the 1992–97 database has been analyzed. Possible influence of patient's age, manner of exposure, symptoms at ER presentation and clinical severity has been evaluated, as were changes over time. Results: Of the 478 patients under 16 years of age registered in 1992–97, 38.1% were admitted, 35.6% were observed, 26.6% were discharged. Changes in the ratio between hospital admission and short-term observation according to age, manner of exposure and symptoms at ER presentation are reported in the table (discharge from ER is not shown).

	Age (years)		Manner of exposure			Symptoms at ER	
	0–4	5–15	accidental	deliberate	passive	no	yes
N° of cases	335	143	349	67	58	303*	175
Observation %	38.5	27.8	39.6	31.3	17.5	40.9	32.6
Admission %	34.6	45.8	26.1	67.2	73.7	21.5	41.7

*176/303 were early treated in ER

Short-term observation was more frequently carried out in younger children because at this age exposure is almost exclusively accidental and hospital referral occurs early. Therefore treatment can avoid clinical consequences. In other instances clinical assessment and/or diagnostic procedures can exclude the diagnosis of poisoning. In older children the need of hospital admission is often related to deliberate or passive poisoning from carbon monoxide and other environmental agents. Clinical severity also influenced decision making. In mild and moderate poisoning observation was carried out in the 27.1% as compared to 65.1% of admissions. All severe poisonings were admitted as were the 4 cases of child abuse. In 1997 as compared to 1992 observation increased to 54.9% of the cases from 24.9%, and admission decreased from 41.0% to 25.4% of the patients. Conclusion: Short-term observation proved to be mainly effective in managing poisoning under the age of 5, from accidental exposure, and with minor or no symptoms at ER presentation. These represent most cases of childhood poisoning. In some of them safe discharge from ER can be uncertain. A short stay for clinical control, diagnostic procedures and/or treatment can reduce the need of hospital admission for these children.

43 PSYCHIATRIC AND SOMATIC DISEASE IN PATIENTS WITH SUPPOSED MULTIPLE CHEMICAL SENSITIVITY OR ENVIRONMENTAL ILLNESS

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Background: Spreading from the USA, the controversial phenomenon of MCS (multiple chemical sensitivity) or "environmental illness" increasingly arouses attention in European countries. Many people feel bothered by toxic chemicals in the environment. The affected patients consider themselves sensitive to low doses of environmental chemicals. After contact with these agents they experience adverse somatic reactions. However, the existence of MCS as an illness is doubted by many scientists. Several studies showed that a large proportion of patients with MCS or environmental illness have psychiatric diseases. Objective: The aim of this study was to examine patients coming to a University based outpatients' department for environmental medicine because of supposed intoxication with environmental chemicals and/or chemical sensitivity. The central question was whether they suffered from other, non-environmental diseases, i.e., somatic or psychiatric illness, that could account for their symptoms. Materials and methods: 120 consecutive patients, 82 women and 38 men, consulting our environmental medicine outpatients' department within 10 months underwent a standardized diagnostic procedure. A precise history was taken, and a physical examination with routine laboratory testing was performed with every patient. Biomonitoring for potentially toxic chemicals was applied where appropriate. After that all patients underwent a psychiatric diagnostic procedure with the structured clinical interview according to DSM-IV (SCID) and a number of additional diagnostic instruments predominantly referring to personality traits (Münchner Persönlichkeitstest (MPT-Sb), Fragebogen zur Erfassung dispositionaler Selbstaufmerksamkeit (SAM), Screening für somatoforme Störungen (SOMS-2)). Results: 83.3% (n = 100) of the examined patients had at least one psychiatric diagnosis. In 49 patients (40.8%) the symptoms could be fully explained by a psychiatric disease, in 24 patients (20%) by a somatic disease. 26 patients (21.7%) had symptoms that could be explained by the simultaneous existence of a somatic and a psychiatric illness. In only two patients the symptoms were regarded as effects of a toxic substance. In one case, a psychiatric disease, a somatic one and a toxic effect together were considered causal. In 16 patients (13.3%) no somatic or psychiatric disease nor an intoxication were regarded as cause of the symptoms. Conclusion: This study confirms previous findings that psychiatric disease can be found in a large proportion of patients with supposed environmental illness or MCS. Toxic chemicals seem not to play a causal role in the majority of cases. Obviously, definite psychiatric or somatic diseases are frequently attributed to environmental chemicals by mistake.

44 VENLAFAXINE IN OVERDOSE—EXPERIENCE OF THE NATIONAL POISONS INFORMATION SERVICE (LONDON CENTRE)

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Objective: Venlafaxine (Efexor®) is a new antidepressant which acts as a selective serotonin and noradrenaline reuptake inhibitor. Since its launch in the UK in 1995 the National Poisons Information Service (London) has been prospectively reviewing all overdose enquiries involving venlafaxine. Methods: The computerized database of the National Poisons Information Service (London) was searched for all cases relating to venlafaxine for the study period January 1995 to September 1998 inclusive. Where possible, follow-up information regarding the clinical outcome was obtained by means of a postal questionnaire. Results: For the study period, the total number of enquiries involving venlafaxine, both alone or in mixed overdose was 2954. Of these, follow-up information was obtained in 632 patients (21.4%). 626 cases involved adults, the age range being 13–87 years. The range of stated doses taken was 187.5 mg to 10.5 g. The male to female ratio was 1:1.71. In the majority of cases, the clinical course was benign, even when large doses had been ingested. 120 patients (19%) remained asymptomatic. In symptomatic patients, 253 (50%) were drowsy and 251 (49.6%) tachycardic. Six (0.96%) patients were deeply unconscious, but coingestants may have contributed to the clinical effects seen. Two cases of serious cardiotoxicity were reported. The first developed left bundle branch block and had runs of ventricular tachycardia and Torsade de pointes, after ingesting an unknown amount of venlafaxine and 60 chlorpromazine of unknown strength. In the second patient, ventricular tachycardia occurred after 10.5 g of venlafaxine along with 50 mg thioridazine and unknown sleeping tablets. Both patients made a full recovery. Convulsions occurred in 30 cases (4.8%), with stated doses ranging from 375 mg to 10.5 g. The majority of convulsions (83.3%) occurred with amounts >1.5 g. In 46.7% of these 30 cases, venlafaxine was the sole reported agent. All patients recovered uneventfully. The six remaining patients were under the age of five. A 3-year-old became hyperactive and had dilated pupils after reportedly ingesting 187.5 mg. He was discharged after 24 hours. The other five cases remained asymptomatic, with stated doses ranging from 37.5 mg to 300 mg. Conclusion: This is the largest series of venlafaxine overdose cases so far reported. It appears to be of relatively low toxicity when taken in overdose and this is consistent with previous reports in the literature. The Medical Toxicology Unit has established an assay for venlafaxine. Further work comparing clinical effects with blood concentrations may identify the small group of patients that appear to be at greater risk of toxicity.

45 ARE INTOXICATIONS INFLICTED UPON OTHERS ALWAYS CRIMINAL?

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Introduction: Intoxications inflicted voluntarily upon others are rare. While intoxications inflicted upon others are not always intended to do harm, the possibility of serious injury or death makes these attempts detestable, whatever the will of the perpetrator. Methods: We reviewed medical records in an attempt to locate cases of poisonings intentionally induced by persons other than the patient. Among 35,000 patients treated in our unit from 1967 to 1995, we identified only 32 such cases. While the search was nonexhaustive, we believe the numbers are representative of the impact of third party poisonings seen in our intensive care unit. We then classified these cases according to their intent. Result: The cases are summarized in the Table:

Categories	Number of cases	Deaths	Products implicated
Chemical submission	10	0	Benzodiazepines, opiates, phenothiazines, amphetamines
Altruistic suicide	7	0	Psychotropes Smoke inhalation (fire)
Compassionate homicide	5	0	Psychotropes Cyanide
Professional "practical jokes"	5	0	Trichloroethylene, cantharidin, furosemide, butyrophenones
Conjugal conflicts	3	0	Sodium chlorate, arsenic, bromide
Punitive dissuasion	1	1	Paraquat
Chemically-battered children	1	0	Benzodiazepines

Discussion: These poisonings represent the will of man to control his fellow man for a multitude of purposes. In chemical submission, it may be to obtain services (financial, sexual, others). These cases have been observed with increased frequency in recent years. In altruistic suicide, it is most often a depressed mother committing suicide who does not wish to leave her children behind. Compassionate homicide is seen among caregivers of the severely handicapped and those suffering from severe illness. In the work environment, the purpose may be to dominate or ridicule, "in good fun." In spousal conflicts, it may be to control the sexual or other behaviour of a partner. Poisoning may be committed to "teach a lesson" or "get even." Finally, in the case of poisoned children, it may result from lack of patience with a hyperactive or noisy child. In all these cases the risk exists for serious harm, whether intended or not. Conclusion: Intentional poisonings inflicted upon others are rare, but certain of them may be increasing in numbers. While the intent of the perpetrator is not always criminal, such poisonings may result in severe outcomes or death.

46 MECHANISM OF PROTHROMBIN TIME PROLONGATION IN PARACETAMOL (ACETAMINOPHEN) POISONING WITHOUT HEPATOTOXICITY

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Background: Anecdotally, paracetamol has occasionally been noted to prolong the prothrombin time (PT) in overdoses not complicated by hepatotoxicity. This may be an important observation in two respects. First, a prolonged PT has been used as an indicator of the severity of hepatotoxicity and suggested as an indication for treatment and further monitoring. Defining the range of PT that is normal in this setting and does not mandate prolonged monitoring is therefore necessary. Secondly, paracetamol has been recommended as a safe drug to use with warfarin. However, studies of the effects of regular maximal doses of paracetamol in patients stabilized on warfarin suggest that a small but definite increase in prothrombin time may occur. The mechanism for this increase has not been determined. We speculated that the effect may be a direct (pharmacodynamic) effect on coagulation factor production and may also be seen in overdose. Methods: Thus the aim of our study was, in patients with a non-hepatotoxic paracetamol overdose, to describe the range of prothrombin times seen, the time course of the abnormality and to measure the effect on selected coagulation factor production. Results: A retrospective review of PT measured on 199 occasions in 139 admissions with paracetamol overdose without hepatotoxicity was performed. In a separate prospective study, Factor VII, VIIIc and IX levels were measured in 37 patients and seven controls who had ingested psychotropic drugs. The PT showed a time-dependent prolongation. Factor VII fell with a similar time course to the rise in PT. There was a small but statistically significant fall in factor IX and no effect on factor VIIIc. The effect was less common under 10 hours post ingestion but the PT was greater than 14 seconds in two thirds of results after this time. The longest PT was 24 seconds at 14 hours post overdose. A PT $\geq$ 20 seconds was seen with overdoses as low as nine grams and with "non toxic" paracetamol levels. There was no correlation between the effect and either the dose ingested or the nomogram-based risk. Vitamin K was used in a small number of patients without effect. The controls had no significant differences from the reference range. Warfarin reversibly inhibits the final activation step in the synthesis of Vitamin K dependent clotting factors (II, VII, IX, X) leading to a reduction in functionally active factors and an accumulation of inactive precursors. Paracetamol reduces functional levels of two Vitamin K dependent clotting factors (VII and IX) but not antigenic levels by inhibiting the same synthetic step. We speculate that the mechanism is different to that of warfarin. Paracetamol probably directly inhibits Vitamin K carboxylase rather than inhibiting conversion of Vitamin K to its active form (the action of warfarin). This is because the time course of action of paracetamol is significantly faster (10 hours) than that of warfarin (24 hours), and given the half life of Factor VII, the earliest a reduction should be able to be detected is approximately 10 hours after cessation of production of the protein. Conclusion: An isolated, small rise in PT is common after paracetamol overdose and does not necessarily indicate hepatotoxicity.

47 AN 11 YEARS SURVEY OF POISONINGS ADMITTED TO AN EMERGENCY AND INTENSIVE CARE UNIT. WHAT HAS CHANGED IN THE MANAGEMENT?

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Objective: To analyze the changes in the epidemiology and the management of poisonings admitted to an emergency and intensive care unit over a period of 11 years. Methods: Using a computer data base, we analyzed the epidemiologic data of all patients admitted from 1987 to 1997 for acute poisoning. Data included: age, sex, type and cause of poisoning, treatments, duration of hospital-stay and outcome. Results: 10335 patients were admitted during this period for poisoning. Per year the number of patients ranged between 776 and 1058. During the period the percentage of patients under 20 years old has decreased from 20 to 12% in contrast with the group of patients between 20 and 40 years old (55% vs 66%). 92% of the poisonings were voluntary and 84% were due to the ingestion of pharmaceutical drugs, mostly psychotropic drugs (72%) and especially benzodiazepines (59%). Ethanol was associated in 30% of cases. Over the period there were no particular changes in the frequency of the main drug categories (benzodiazepine, barbiturate, carbamate, neuroleptics, antidepressants) except an increase of paracetamol and serotonin reuptake inhibitors poisonings. The number of acute drug addictions has decreased from 15% in 1995 to 8% in 1997. The major changes over this period concerned the management: gastric lavage was performed in 70% of the cases in 1987, in 43% in 1991 and only in 0.5% of the cases in 1997; the administration of activated charcoal has decreased from 14% in 1991 to 4% in 1997; the antidotal treatments (*N*-acetylcysteine, flumazenil, naloxone) have decreased from 16% in 1991 to 9% in 1997. The number of patients intubated and requiring mechanical ventilation was 11% in 1987 and 4% in 1997. The percentage of patients staying in hospital less than 24 hours has remained stable (89 to 91%) since 1990. 64 patients died (0.61% of the cases). The causes were pharmaceutical drugs in 42 cases, industrial and agricultural products in 9 cases, heroine overdose in 12 cases and mushroom in 1 case. None of these deaths was related to the changes in the management. Conclusion: Most poisonings recover with supportive treatment. Changes in the therapeutic strategy, especially the dramatic decrease of gastrointestinal decontamination, were not associated with an increase in mortality and morbidity.

48 CARDIOTOXICITY IN VALPROIC ACID POISONING

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Objective: Valproic acid (VPA) is a branched chain fatty acid with anticonvulsant properties thought to be mediated by altered central nervous system GABA metabolism and neuronal ion channel function. We recently reported a patient with VPA poisoning who exhibited marked prolongation of the QT interval.[1] QT prolongation to >500–550 msec is a risk factor for the development of torsade de pointes. The aims of the present study were to determine whether QT prolongation is likely to be VPA-related, and to investigate the effect of VPA on the rapidly activating delayed rectifier (I_{Kr}) potassium current, which is blocked by most drugs causing torsade de pointes. Methods: We retrospectively analyzed consecutive cases of VPA poisoning at our institutions (Nashville, Paris) between 1989 and 1998. We assessed heart-rate-corrected QT intervals (QTc according to Bazett's formula) at the acute stage (high VPA concentrations) and at baseline (low VPA concentrations). Cases without sufficient documentation of plasma drug concentrations and/or ECG changes, and cases with co-ingestion of substances known to affect the QT interval were excluded. I_{Kr} in the absence and presence of VPA was recorded in atrial tumor myocytes (AT-1 cells, n = 4) using the whole-cell configuration of the patch clamp technique according to a standard protocol.[2] Results: Sixteen cases were included in the study. Peak total plasma VPA concentrations ranged from 184 to 1640 μg/mL (median 410 μg/mL). Low total plasma VPA concentrations ranged from 22 to 156 μg/mL (median 56 μg/mL). Twelve of 16 patients exhibited a longer QTc during the acute stage than at baseline. Acute QTc values were greater by 62 ± 73 $msec^{0.5}$ (mean ± S.D.) than at baseline ($p < 0.01$). Nine of 16 cases had acute QTc values >450 $msec^{0.5}$ (6 cases >500 $msec^{0.5}$). VPA (50 μmol/L; 7.2 μg/mL) completely abolished I_{Kr} *in vitro*. Conclusion: Significant prolongation of the QT interval occurs commonly in VPA poisoning. The inhibitory effect of VPA on I_{Kr} in AT-1 cells was marked at low therapeutic concentration. This result suggests that VPA-related QT prolongation may be mediated by diminished potassium currents in cardiomyocytes. This is consistent with known alterations in cardiac potassium currents in acquired and congenital long QT syndromes.

References: [1]Kupferschmidt H, Seger D, Dawling S, Murray L, Meredith T. *J Toxicol Clin Toxicol* 1989;**36**:471. [2]Yang T, Wathen MS, Felipe A, Tamkum MM, Snyders DJ, Roden DM. *Circ Res* 1994;**75**:870–878. *Note*: VPA conversion: 1 μg/mL = 6.93 μmol/L.

49 INGESTION OF BUTTON BATTERIES—MANAGEMENT

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Objective: The ingestion of button batteries by small children is a frequent emergency problem in pediatric medicine. The actual management of this situation is controversial. While some authors recommend initial radiological evaluation in all children (Litovitz *et al.* 1992; Rumack *et al.* 1992), other clinical toxicologists suggest a radiological evaluation only in symptomatic children (Marcus *et al.* 1993). To improve the evidence for the most economic procedure, we evaluated further the frequency of late gastrointestinal complications after button battery ingestions. Methods: All cases of children with button battery ingestions registered at the Swiss Toxicological Information Centre (STIC) between 1985–1998 were analyzed with regard to initial symptoms and late gastrointestinal complications. Results: During the investigated time period the STIC was involved in a total of 1095 pediatric cases with button battery ingestion. 339 cases (31%) cases required medical evaluation, whereas the other 756 (69%) children could stay at home without any further complications. Detailed medical reports from treating physicians and hospitals were available in 236 cases. Among these medically evaluated cases, 220 (93%) children remained without any initial symptoms. The batteries were excreted in the feces and none of the children had any late gastrointestinal complications. Sixteen children (7%) had mild initial symptoms such as eating difficulties, nausea, dysphagia, vomiting, abdominal cramps, diarrhea and/or black stools. Among these symptomatic patients only one child with ingestion of a lithium disc battery (diameter 20 mm) had a severe outcome. The battery was radiographically localized in the esophagus from which it had to be removed endoscopically. Nevertheless, the transient impaction of the battery in the esophagus caused esophageal perforation and mediastinitis. Some weeks later an esophageal stricture developed, so far without any need for dilatations. The 1.5-year-old boy continues to have problems with swallowing of solid food, but otherwise his growth and development are normal. Conclusions: Our data provide further evidence that severe complications after button battery ingestions are in general very rare events. More specifically, none of our initially asymptomatic patients developed late gastrointestinal complications, indicating that asymptomatic patients do not require extensive medical evaluation and treatment. Thus, our data support the concept that radiological evaluation after button battery ingestion is only indicated in symptomatic patients. Because of the very rare complications radiologic evaluation of asymptomatic patients appears not to be cost effective and cannot be recommended as a general advice by poison information centers.

50 SMOKING "WATER": PHENCYCLIDINE (PCP) AND FORMALDEHYDE ABUSE IN EMERGENCY DEPARTMENT (ED) PATIENTS

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Objective: Phencyclidine abuse frequently involves the concurrent use of other psychoactive substances. The combination of PCP with formaldehyde (using formalin) has been infrequently reported. It is unknown whether the chemical reaction of formaldehyde with phencyclidine produces a substance with different effects or toxicity. The objective of this case series is to describe ED patients who presented after smoking "water," a term used to describe the combination of PCP and formaldehyde. Methods: All cases of PCP toxicity presenting to an urban teaching hospital adult ED between 7/89 and 7/96 were identified by daily review of ED records using key terms. The use of "water" was identified by patient history of use or the presence of a characteristic odor in patients who had PCP present in urine. Case Series: Of 514 PCP cases during the study period 193 were documented as "water." 88% presented between 7/93 and 7/96. The 193 cases involved 178 different patients who were 27 $\pm$ 8 years of age, 79% male and 96% black. The "non-water" cases involved 311 visits by 285 different patients who were 27 $\pm$ 7 yr. of age, 86% male, and 96% black. Smoking was the route of use in all cases except one IV injection. Other drugs (cocaine, THC) were present in 28% and ethanol in 46% of cases. Urine drug screening was performed in 99 cases with 3 cases negative for PCP. The most common presenting complaints were injury (18%), PCP use (16%), CNS depression (16%), and bizarre behavior including nudism (15%). The majority of cases (53%) were alert and oriented upon arrival, with 28% disoriented/confused and 18% with CNS depression (6 unresponsive). The most frequent abnormal behavior was aggression (32%), 5 patients were hallucinating and 6 were mute. Nystagmus was present in 23%, blood pressure $>$ 140 and/or 90 mmHg in 50%, and heart rate $>$ 100 bpm in 37% of cases. Discussion and Conclusions: Compared to the 1000 PCP cases described by McCarron and associates (*Ann Emerg Med* 1981;**10**:237–242) "water" generally has similar effects and toxicity.

Patients presented to the ED for many different reasons. Violent and/or bizarre behavior were the most common abnormal findings; seizures, loss of consciousness, cardiopulmonary arrest, and chest pain/shortness of breath were uncommon. The abuse of PCP and formaldehyde does not appear to result in findings different from that expected with PCP in adult emergency department patients.

51 THE AMSTERDAM EXPERIENCE: CANNABIS PSYCHOSIS IN NAIVE DRUG USERS

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Background: Acute psychosis following a single exposure to cannabis is very uncommon in individuals who are naïve (first-time) users and who have no previous psychiatric history. We report two further cases of acute psychosis following first time recreational use of cannabis in individuals who went to Amsterdam for social reasons and who had no previous psychiatric history. Case 1: A 28-year-old Asian male dentist presented after ingestion of "Cannabis Cake" in Amsterdam. He became fearful, tearful and panicky and experienced visual hallucinations. Although these features began shortly after exposure, he was not brought to hospital for six days. On examination the patient's temperature was 37.5°C. He appeared fully conscious but was regularly incontinent of urine. He did not answer questions directly, but muttered indecipherably, as if responding to hallucinatory experiences. He was restless and agitated, and frequently adopted poses which appeared to be of religious significance. A drug screen performed eight days after exposure was negative for cannabis and other psychoactive or illicit drugs, save those administered as therapy. Despite six days of intensive treatment with haloperidol, his mental state continued to fluctuate, with periods of agitation and total sexual disinhibition. On day 7 he was transferred to a psychiatric hospital and remained an inpatient for a further 27 days. He was treated with risperidone for four months. Eight months after the initial exposure he was able to return to work. Case 2: A 17-year-old Asian female was admitted four days after smoking cannabis whilst in Amsterdam. She expressed paranoid ideas shortly after exposure and described auditory hallucinations. As an act of deliberate self-harm she ingested 6 g of paracetamol and was admitted to hospital in Amsterdam, where a diagnosis of "paranoid reaction, possibly to the use of soft drugs" was made and she was detained overnight in hospital. On return to the UK she still experienced paranoid ideation and took a further paracetamol overdose (20 g); the plasma paracetamol concentration was 272 mg/L four hours post-ingestion and she was treated with intravenous *N*-acetylcysteine. She continued to express paranoid ideas, believing her friends were persecuting her. She was commenced on trifluoperazine and made a full recovery after several weeks. Conclusion: First-time use of cannabis can precipitate an acute psychotic episode persisting for several months in individuals with no previous psychiatric history.

52 TREATMENT OF HYDROFLUORIC ACID BURNS WITH INTRA-ARTERIAL ADMINISTRATION OF CALCIUM GLUCONATE

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Objective: Treatment of cutaneous burns by hydrofluoric acid (HFA) is based on the detoxification of fluoride ion by a binding agent, usually calcium, in order to promote the formation of insoluble calcium salts. Calcium is mostly administered by topical application but its efficacy may be limited in severe poisonings. Intra-arterial (IA) administration of calcium gluconate (CaGl) has been proposed and several reports have confirmed the efficacy. We report 4 cases of HFA burns of the hands treated with this technique. Case series: *Case 1*: 28-year-old man admitted 6 hours after dermal exposure to HFA. On admission: intensive pain and 2nd degree burns of 3 fingers of the left hand with subungueal necrosis. No relief of pain with topical application of CaGl gel. Treatment with IA infusion of CaGl, 6.6 g over 33 hours. Relief of pain within 2 hours. Complete recovery. *Case*: 23-year-old man admitted 24 hours after dermal exposure to HFA. edema and 2nd degree burn of the right hand with necrosis of the extremity of the thumb and intensive pain not improved with topical CaGl gel. IA infusion of CaGl, 12 g over 48 hours. Immediate relief of pain. Complete recovery. *Case 3*: 71-year-old man admitted 26 hours after dermal exposure to HFA. On admission: 2nd degree burn of the left thumb with subungueal necrosis and intensive pain. IA infusion of CaGl, 3 g over 10 hours. Relief of pain within 30 min. Complete recovery. *Case 4*: 27-year-old man admitted 7 hours after dermal exposure to HDA. On admission: 2nd–3rd degree burns of the right hand (palm and fingers), and 2nd degree burn of the left thumb, intensive pain. IA (right radial artery) infusion of CaGl, 12 g over 48 hours. Relief of the pain in the right hand within 30 min,

whereas the pain on the left thumb persisted despite topical treatment with CaGl gel. Complete recovery. Conclusion: IA infusion of CaGl is an efficient treatment for dermal burns of the extremities due to HFA and which do not respond to topical CaGl gel. The efficacy is confirmed by the rapid relief of the pain and IA infusion should be continued until pain does not recur.

53 BOTANICAL VILLAINS . . . PERCEIVED AND ACTUAL. AN EVIDENCE-BASED EXAMINATION

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Introduction: Plant exposures constitute the fourth most common type of inquiry reported by poison information centers in the United States.[1] The words "poisonous plants" engender anxiety in both the lay public and healthcare professionals. A shroud of mysticism and folklore often overshadow knowledge, reason and common sense following exposure to a botanical. Parents become anxious and upon discovering a possible exposure to a plant, they may take their child to an emergency department for evaluation. Since there is a void in health professional education on this topic, caution prevails and primary care practitioners err on the side of safety when a plant has been ingested. The toxicology and medical literature have relatively few citations that provide clear direction in the management of plant exposures. Anecdotes that describe fatal outcomes from plant ingestions have been perpetuated for decades.[2] In some cases reputable toxicology references immortalize myth and embellish fact. Unlike many aspects of contemporary clinical toxicology, there is a gap between the reference literature and the evidence. Methods: Utilizing twelve years of data from the American Association of Poison Control Centers Toxic Exposure Surveillance System, 1,147,156 plant exposures were analyzed to identify selected gaps between perception and reality and to profile the symptoms and outcomes associated with some of the most common plant exposures and some perceived to be associated with significant morbidity and mortality. Results: The most common plant exposures, by species, are tabulated according to those reported most commonly to a poison center, the most commonly self-referred and those most commonly referred for emergency care by a poison center:

Rank	Most common	Most common self-referred	Most common PC-referred
1	Unknown	Unknown	Unknown
2	Philodendron	Toxicodendron	Toxicodendron
3	Dieffenbachia	Datura	Solanum
4	Capsicum	Dieffenbachia	Nerium
5	Euphorbia	Philodendron	Phytolacca
6	Ilex	Solanum	Dieffenbachia
7	Crassula	Phytolacca	Capsicum
8	Toxicodendron	Capsicum	Berries
9	Phytolacca	Nerium	Taxus
10	Solanum	Ilex	Datura

Poison centers had an inordinately high referral rate for exposures that had favorable outcomes. There were a minimal number of patients who suffered a life-threatening outcome and only 18 fatalities were reported. Seven of the fatalities involved either Cicuta or Conium species. The literature presents a more grave prognosis with many plant exposures. With regard to patient outcome, there was significant disparity between the reported symptoms and those proposed in the literature (e.g., Dieffenbachia, Taxus). However, the anticholinergic toxidrome, as described in the literature, following Datura exposure was consistent with the actual exposure reports. Contrary to standard treatment recommendations, gastrointestinal decontamination had no demonstrable effect on patient outcome. Conclusions: Many of the alleged botanical scoundrels are not as toxic as they are purported to be in the literature. There is substantial discordance between the reference literature and reality. References: [1]Litovitz TL, Klein-Schwartz W, Dyer KS, Shannon M, Lee S, Powers M. 1997 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance

System. *Am J Emerg Med* 1998;**16**:443–497. [2]Krenzelok EP, Jacobsen TD. Plantlore Folklore. *J Toxicol Clin Toxicol* 1998;**36**:751.

54 A RETROSPECTIVE REVIEW OF THE USE OF ACTIVATED CHARCOAL AND PHYSOSTIGMINE IN THE TREATMENT OF JIMSON WEED POISONING

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Objective: Physostigmine effectively antagonizes the signs and symptoms of Jimson Weed (Datura stramonium) poisoning. Unfortunately, case reports document seizures and bradyarrhythmias when physostigmine has been administered to treat some drug-induced anticholinergic syndromes. This study was undertaken to review the safety and benefit of both physostigmine and activated charcoal in the treatment of Jimson Weed poisoning. Methods: A retrospective chart review including 1990 through 1998 was performed on all patients diagnosed with Jimson Weed toxicity by the toxicology admitting service at a university teaching hospital. Physostigmine was administered in 1–2 mg boluses not exceeding 0.5 mg/min. Doses could be repeated after 15 minute intervals. A length of stay (LOS) in hours was determined for each patient from the time of presentation until medical clearance. A two-tailed *t*-test was used to compare those patients who received activated charcoal and/or physostigmine to those who did not receive these treatments. For those patients receiving physostigmine the change in heart rate and blood pressure were recorded. Results: During this nine-year period 29 patients were treated for Jimson Weed poisoning. Twenty patients received physostigmine, while 21 patients were given activated charcoal. The mean LOS (hours ± SD) for patients receiving AC was 30 ± 15, while those not given activated charcoal was 69 ± 74 ($p = 0.14$). Only two patients had LOS greater than 70 hours, both these patients did not receive activated charcoal (LOS 113 and 238 hours). The mean LOS for patients receiving physostigmine was 46 ± 51, while those not given physostigmine was 29 ± 16 ($p = 0.51$). After receiving physostigmine 8 patients were able to drink the activated charcoal. There were no adverse effects (bradycardia, seizures or hypotension) reported following physostigmine administration. The mean heart rate after physostigmine was 92 ± 6 compared to 108 ± 5 before its administration. Conclusions: Physostigmine administration can safely and effectively reverse the delirium and agitation of Jimson Weed poisoning. Activated charcoal diminished the LOS for patients who received it, although this was not statistically significant in this small series. The use of physostigmine facilitated activated charcoal administration in some patients.

55 VIPERS WITH NEUROTOXIC VENOM IN SOUTHEASTERN FRANCE: EFFECTIVENESS OF THE POLYVALENT ANTIVENOM VIPERFAV* FOR THE TREATMENT OF ENVENOMED PATIENTS

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Background: In 1991, 2 viper envenomations collected by the Marseilles Poison Centre were characterized by the development of neurotoxic signs (ptosis, drowsiness, dyspnea). Both cases were published in 1994,[1] and for one of them, the responsible snake was captured alive. The electrophoresis of the venom of this *Vipera aspis aspis* specimen showed that the venom was different from other *V.a.a.* venom. We asked then 2 questions: 1) May an envenomed child present in respiratory distress? 2) Are we sure that the antivenom is able to neutralize the new neurotoxic venom? Case series: Since 1994, 6 new cases were observed in the same area (north of Nizza), concerning 4 persons and 2 dogs. With the dogs, our fear was confirmed: they both had the weight of a 9-year-old child, and they presented a complete paralysis of the 4 paws and respiratory distress. The symptoms decreased spontaneously in few days. The 4 patients received infusions of Viperfav* antivenom. This polyvalent immunotherapy made with the venom of three European adders (*V.a.a., V.berus* and *V.ammodytes*) was efficient: the neurological signs decreased a few hours after one or two infusions. We can presume that Viperfav* contain antibodies against the neurotoxin responsible of the clinical feature. Genetic and immunological research: A molecular cloning and sequencing of the neurotoxin (a Phospholipase A2, PLA2) of the captured snake was realized. The total RNA was isolated from the venomous gland of this adder, and the nucleotide sequence of the 2 subunits was determined. The acidic subunit has exactly the same sequence than the neurotoxin acidic subunit of another adder, *V.a.zinnikeri*. The basic subunit differs only by one amino acid from vipoxin which is a PLA2 of *V.ammodytes*. The new neurotoxin seems to be an hybrid of 2 other adders PLA2, and is neutralized by anti-ammodytoxin antibodies. In contrast, antibodies against *V.berus* or classic *V.a.a.* venom are not efficient.

Viperfav* cured our patients because it is a polyvalent antivenom containing antibodies against the toxins of a snake which does not live in France!!! These data were confirmed by the quantification of the venom concentrations in patients' blood using a sandwich ELISA technique: high levels of venom were found for 3 human patients before treatment, and venom was undetectable after one or two Viperfav* infusions. Conclusion: A characteristic of the natural toxins is to evolve. Our experience shows that a new toxicity in an animal population is able to appear with consequences for human health. References: [1]de Haro, *et al. Rev Prat MG* 1994;**265**:20–23.

56 RECURRENCE OF LOCAL SYMPTOMS OF CROTALID ENVENOMATION IN OVINE FAB ANTIVENOM TREATED PATIENTS

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Objective: To document the recurrence of initially controlled local symptoms in crotalid envenomations treated with ovine, Fab antivenom and the current experience in treating such recurrences. Methods: Patients were enrolled in the first phase of a multi-center trial of affinity purified, mixed monospecific crotalid antivenom, ovine Fab for injection (Fab-AV). Patients received up to 8 vials, maximum, of Fab-AV for control of local and coagulopathic venom effects. Local symptoms were assessed using predefined procedures at baseline, every 30 minutes from the start of Fab-AV infusion to 6 hours, every 2 hours between 6 and 12 hours, every 12 hours between 12 and 48 hours and as needed. Local symptoms were defined as a documented increase in circumferential limb measurements or proximal progression of the leading edge of tissue edema. Control of local symptoms was defined as a documented cessation of proximal progression and cessation of increasing circumferential measurements. Local recurrence was defined as documented increasing local symptoms requiring additional antivenom following initial control. Results: Of 11 patients, all obtained initial control of local symptoms with Fab-AV. Three patients (27%) developed local recurrence, (mean time to first recurrence = 16.3 hours, range 12–19 hours). All three had one recurrence each. Two patients' recurrences were each controlled with one additional dose of Fab-AV. The third patient was withdrawn from the study and given Antivenin Crotalidae Polyvalent (ACP, Wyeth) because he had already received the maximum of eight vials of Fab-AV to obtain initial control. Local recurrence in this patient was controlled with 15 vials of ACP. Discussion: Local recurrence of symptoms following initial control was documented in our study of patients treated with ovine, Fab antivenom. The cause is uncertain, but Fab-AV has a relatively short half-life. The implication is that unneutralized, locally active venom remains at the bite site following initial control and that local symptoms recur when protective serum concentrations of Fab-AV are lost. Additional antivenom given during the first 24 hours was effective in achieving control of recurrent local symptoms. Conclusions: Local recurrence of symptoms after initial control occurred in 27% of crotalid envenomated patients treated with ovine, Fab antivenom. Re-dosing of antivenom in the first 24 hours was effective in achieving control of recurrent local symptoms.

57 THE NEUROTOXICITY OF CANNABIS

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Background: Cannabis is the most widely used illicit drug in many developed countries. It is produced from the female plant of *Cannabis sativa*, and can produce acute and chronic effects on the central nervous system (CNS) in man. The principal active substance is delta-9-tetrahydrocannabinol (THC) which is thought to act on a cannabinoid receptor in the brain. An arachidonic acid derivative (anandamide) has been identified as a possible endogenous ligand, although the physiological function of the receptors and any potential ligands remains unclear. Nevertheless, receptors are widely distributed in the CNS particularly in the cerebral cortex, hippocampus, striatum, and cerebellum. Review: *Acute effects*: Cannabis is normally used to achieve a "high" which is characterized by changes in mood, perception and motivation different from the "stimulant high" and the "opiate high." This effect is dose-dependent, but may last up to 2 hours after smoking marijuana. Cannabis may produce a dose-dependent effect on cognitive and behavioral performance, particularly for tasks that require sustained attention. Effects on psychomotor function appear to be approximately additive with those of other CNS sedatives, including alcohol, which is often taken concomitantly. These effects may significantly affect driving ability. Impairment of co-ordination and tracking behavior has been reported to persist for

several hours beyond the perception of the "high." Large doses may produce confusion, panic, hallucinations and delusions, which normally respond to cannabis withdrawal. Some surveys indicate that more than half of marijuana users may experience at least one anxiety experience. These effects are more commonly seen with higher doses and with oral rather than smoked marijuana, since smoking allows the user to titrate the dose according to the wanted rather than unwanted effects. *Chronic effects*: Long-term use of high doses of cannabis does not appear to produce the effects on cognitive function, memory and attention to the degree seen with the long-term use of alcohol in excess. Nevertheless, it may produce impairment of attention, memory and thought processes to a smaller but clinically important extent. The degree of reversibility of these effects is unknown. One of the most controversial effects claimed to be caused by marijuana is the so-called "amotivational syndrome." which describes those who opt out of social activities and show little interest in school, work, or other socially accepted behavior. However, the evidence for the existence (and persistence) of this of this condition is weak. It has been suggested that chronic cannabis use can exacerbate the symptoms of schizophrenia, but there is little evidence that it precipitates the condition in those who were not already predisposed to develop this disease. A cannabis dependence syndrome has also been described, with reports of tolerance to repeated doses and withdrawal effects on sudden abstinence. It is estimated that 10% of cannabis users become dependent on the drug at some time, a frequency similar to that for alcohol dependence. Reference: [1]Hall W, Solowij N. Adverse effects of cannabis. *BMJ* 1998;**352**:1611–1616.

58 DRUG TRANSPORT: FROM THE CELL TO THE POISONED PATIENT

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Many drugs and other xenobiotics are amphipathic polar compounds with one or several positively and/or negatively charged side chains. They cannot easily penetrate across cell membrane barriers unless their transmembrane movement is facilitated by distinct transport proteins. In recent years up to 23 different solute carrier (SLC) *gene*-families have been cloned and functionally characterized including many drug transporting polypeptides. The official "human gene nomenclature database" distinguishes several primary active, i.e. ATP-dependent ABC-transporter families and numerous secondary/tertiary active *SLC*-families of organic anion (SLC21) and organic cation (SLC22) transporters. While some of these carriers are specific for certain endogenous compounds (e.g., phospholipids, glucose and amino acids), others exhibit a polyspecific substrate pattern that also includes many drugs and other xenobiotics. *First,* many epithelial organs (e.g., intestine, liver, brain, kidney) express so called "organic anion transporting polypeptides" (rat: Oatp1, Oatp2, Oatp3 and OAT-K1; human: OATP) that can function as multispecific sodium-independent drug transporters. These members of the *Oatp*-gene family of membrane transporters are involved in the intestinal uptake, hepatobiliary excretion and transport across the blood brain barrier of xenobiotics such as cardiac glycosides, ACE-inhibitors, quinine/quinidine and the mycotoxin ochratoxin A. *Second*, the organic anion transporters of the *OAT*-gene family and the *OCT*-types of organic cation transporters accept more water soluble substrates (e.g., p-aminohippurate, (α-ketoglutarate, choline, guanidine) that are preferentially excreted by the kidney. *And third*, members of the ABC-transporter superfamily such as MDR1 and MRP2 are involved in the active excretion of cationic drugs (e.g., vincristin, colchizine, verapamil) and of anionic drug conjugates (e.g., glutathioneconjugates), respectively, into bile and/or urine. The multiple organ distribution and the polyspecific nature of these drug transporters can have considerable consequences for toxicokinetics and the severity/duration of intoxication in poisoned patients. *Example 1.* The combined ingestion of digoxin and verapamil increases the cerebral accumulation and toxicity of digoxin because of its decreased transport out of the brain through verapamil induced inhibition of MDR1 at the blood brain barrier. In addition, digoxin excretion into feces and urine is inhibited by blockage of MDR1 in the intestine and the kidney, respectively. *Example 2.* Ingestion of high doses of cyclosporine and/or the oral hypoglycemic drug glibenclamide can cause cholestatic liver disease through inhibition of the hepatocanalicular bile acid export pump Bsep(rat)/BSEP(human). *Example 3.* The preferential nephrotoxicity of the mycotoxin ochratoxin A can be explained by its tubular reabsorption via Oatp1 that is expressed at the apical membrane of renal proximal tubular cells. Other high affinity Oatp1 substrates can inhibit the renal tubular reabsorption of ochratoxin A and thus potentially reduce the nephrotoxicity of ochratoxin A. Conclusions: The molecular identification and functional characterization of an increasing number of xenobiotic solute transporters is important to further increase our understanding and prediction of the disease severity as well as the treatment options in poisoned patients.

59 DERMAL CONTAMINATION

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Background: Dermal contact with chemical agents is a frequent route of systemic exposure to toxic agents. While dermal absorption may have different time constants than other routes of exposure, the integument also imparts discrete metabolic pathways. When dermal contamination occurs, it is universally accepted that decontamination of toxic materials is required. However, decontamination is not always effected, and there is no evidence-based consensus as to the method of dermal decontamination to be employed. Review: This paper reviews the unique parameters of dermal absorption and the methods of decontamination of the integument. The advantages of general methods of decontamination versus agent specific neutralizing agents are contrasted. In general, immediate water irrigation is indicated; however, the optimal flow rate, duration, and pressure of irrigation has not been determined. Early washing with dilute acid solutions may minimize injuries due to alkali contact.[1] However, this intervention addresses only the local effect of the alkali. Phenol injuries to the skin have a more serious ramification on systemic absorption and the development of phenol toxicity. Methods to increase the removal of phenol from the skin have included oils, polyethylene glycol, and other materials.[2] However, improvement on patient outcome has not been demonstrated. Conclusion: As there is no standard model for chemical contamination of the integument, and no standard endpoints for the systemic effect of chemicals by skin absorption, progress in this area is difficult. Recommendations for dermal decontamination must distinguish between amelioration of dermal injury, curtailment of systemic absorption, and an improvement in patient outcome. References: [1]Yano K, Hata Y, Matsuka K, Ito O, Matsuda H. Experimental study on alkaline skin injuries-periodic changes in subcutaneous tissue pH and the effects exerted by washing. *Burns* 1993;**19**:320–323. [2]Brown VKH, Box VL, Simpson BJ. Decontamination procedures for skin exposed to phenolic substances. *Arch Environ Health* 1975; **30**:1–6.

60 THE HYPOTENSIVE POISONED PATIENT

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Cardiovascular disturbances are a major cause of severity and mortality in poisonings. The overall mortality of poisonings is less than 1% but may reach 10 to 20% in poisonings by cardiotropic drugs. Hypotension may be due to several mechanisms. Moreover, other factors not related to the poison, such as underlying cardiovascular diseases, infectious complications, previous treatments, may favour the occurrence of hypotension. Therefore, the determination of the precise cause and mechanism is crucial in order to optimize the treatment and correct the tissue oxygen debt and the subsequent lactic acidosis. Mechanisms of hypotension: Direct cardiovascular toxicity may result from an effect on ion channels or on the sympathetic system. Sodium channel blockers (class I antiarrythmics, chloroquine, tricyclic antidepressants) by their membrane stabilizing effect decrease the cardiac automaticity, contractility and the conduction. Calcium channel blockers decrease the cardiac contractility and induce arterial vasodilation. Digitalis by inhibiting the Na-K ATPase decrease the conduction. A direct effect on the sympathetic system may be due to cholinergic drugs (acetylcholine, organophosphate insecticides), beta-blockers, betamimetic drugs (theophylline, xanthines) or alpha-lytic drugs. All these mechanisms may induce hypotension as a consequence of severe bradycardia or tachycardia, or of a decrease of the inotropism or of the after-load. Hypotension may also result from other mechanisms not related to a direct cardiovascular toxicity of the poison but to complications such as hypovolemia, respiratory failure, hypothermia, infections, decrease of oxygen transport, metabolic disturbances and especially dyskalemia. Several mechanisms are often associated such as in class I antiarrythmics, calcium channel blockers, colchicine, theophylline poisonings. Diagnosis: The major parameters are the values of blood pressure (BP) and heart rate. The value of BP must be compared to the normal previous BP in the patient and should include the systolic, diastolic and mean BP. Special attention should be given to symptoms indicating tissue hypoperfusion: cyanosis of the extremities, disturbances of consciousness, decrease of diuresis. Basic monitoring includes BP, ECG, hourly diuresis, chest X ray, arterial blood gases, lactates, electrolytes, pulse oximetry. In some cases other cardiac monitoring techniques may be necessary in order to conduct the treatment: Swan Ganz catheterism, invasive BP, cardiac echo-doppler. Usually analytical data are not useful for the treatment. Management: All patients with hypotension should be admitted in an emergency or intensive care unit. First line treatment includes vascular filling with crystalloids or colloids associated if needed with dopamine in order to maintain an adequate cerebral and coronary perfusion, oxygenotherapy and if necessary mechanical ventilation. Initial

vascular filling should not exceed 1000 mL in order to avoid pulmonary edema. Aggravating factors such as hyperkalemia, acidosis should be corrected. Afterwards, the treatment will depend on the exact mechanism of hypotension: correction of dysrhythmias; vascular filling in the case of hypovolemia and decreased vascular filling pressures; inotropic agents, dobutamine, adrenaline in the case of cardiogenic shock with increased vascular filling pressures; alphamimetic catecholamines, and especially norepinephrine, if hypotension is due to arterial vasodilation. Other treatments are indicated for specific poisons: hypertonic sodium salts for poisonings by membrane stabilizing drugs with intraventricular block; glucagon for betablocker poisonings; beta-blockers for theophylline poisoning. Sometimes very large doses of catecholamines are needed in order to reverse hypotension or shock. Conclusion: Treatment of hypotension in the poisoned patient depends on the cause and on the mechanisms of cardiovascular toxicity. Usually the critical period lasts no longer than 48 hours. The relative high mortality due to cardiovascular toxicity should be decreased by an early and careful management.

61 THE POISONED PATIENT WITH DYSRHYTHMIAS

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Introduction: Cardiac dysrhythmias are seen in about 10 per cent of poisoned patients. Aetiology: These arrhythmias may be caused by ingestion of cardiotoxic agents, any underlying cardiac disease, or, metabolic disturbances. Although cardiotoxicity may result from any poisoning depending on the dose, dysrhythmias are typically the complication of patients suffering from an overdose of tricyclic antidepressants, neuroleptics (thioridazine), sympathomimetic agents, digitalis, beta-blockers or other antiarrhythmic agents. Tricyclic antidepressant poisoning may be complicated by ventricular fibrillation or bradyarrhythmias with a broadened QRS-complex on the ECG. All antiarrhythmics also may have a proarrhythmic effect which may complicate overdose. Torsade de pointes is a type of ventricular tachycardia characterized by polymorphic QRS complexes alternating in amplitude and cycle length, giving the appearance of oscillations around the baseline. By definition this rhythm is associated with QT-prolongation. Underlying coronary heart disease may cause dysrhythmias, especially in older patients, if sympathomimetic drugs are taken or if hypotension develops. If oxygen transport is compromised, e.g., in patients with carboxyhemoglobinemia or methemoglobinemia, myocardial ischemia and dysrhythmias may develop even in younger patients. Metabolic disturbances such as pronounced alterations in the acid-base status or electrolyte abnormalities, may also cause dysrhythmias in the poisoned patient. Examples are metabolic acidosis and hyperkalemia in any poisoning precipitating acute renal failure, and hypokalemia in theophylline poisoning. Management: The golden rule when approaching poisoned patients with dysrhythmias is "above all else, do not harm." In these circumstances most antiarrhythmic agents are contraindicated. Instead, the mechanism(s) causing the arrhythmia should be explored. If the etiology is clear one should aim at specific therapy if available, e.g., Fab-antidotes in digitalis poisoning. In most circumstances, however, treatment is symptomatic only and aimed at restoring vital body functions and to correct metabolic disturbances. In torsade de pointes ventricular tachycardia, magnesium sulphate, cardioversion and overdrive pacing should be considered.

62 THE CONFUSED INTOXICATED PATIENT

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Disturbances of central nervous system (CNS) functions are a prominent feature in many conditions associated with acute poisoning. In some cases, this effect is evident because the patient is comatose. However, in many other circumstances encephalopathy associated with the poisoning only results in less marked changes in the level of consciousness (stupor, lethargy), disorientation, confusion, delirium or behavioral alterations, including violence. Several mechanisms may be involved in this impairment of CNS function. In many cases, the changes are directly related to a toxic effect on the neuronal activity in the cerebral cortex and/or the brain stem reticular activating system. Most of these compounds are able to modulate or mimic the action of neurotransmitters by binding to cellular receptors (sedatives or opiates, for example) or have more diffuse cellular actions (such as ethanol or solvents). These effects are not easily evaluated for several reasons: the absence of a clear relationship between blood levels and CNS response for the vast majority of the substances, the large interindividual variation of tolerance and the unavailability of rapid accurate determinations of blood concentrations in many cases. These effects are functional in their nature and are usually fully reversible as the toxins are cleared from the body. Some substances may however induce or promote seizures and may result in organic

damage if the condition remains unrecognized and is left untreated (anticholinergic or sympathomimetic syndromes, for example). Chronic abuse may sometimes result in the development of permanent psycho-organic changes associated with brain lesions. Indirect mechanisms are also commonly involved and should be systematically searched for in patients with impairment of CNS function: indeed, they are more likely to induce long-term cerebral damage. These mechanisms include cellular hypoxia, hypoglycemia, hydroelectrolytic and acid-base disturbances or ischemia. Finally, complications of some poisonings may be associated with the late development of encephalopathy (hepatic encephalopathy associated with hepatic damage, intermediate syndrome in poisonings with some pesticides, delayed neurological deterioration in carbon monoxide intoxication) even when the causative toxic agent is no longer detectable in the patient's tissues. Alternative or associated causes of CNS impairment should always be excluded, especially head trauma, cerebrovascular damage, CNS infections or withdrawal syndromes which are not infrequent in patients with acute poisoning or a history of drug or alcohol abuse. These conditions usually require specific management. Early recognition of CNS dysfunction associated with acute poisonings is of the utmost importance. Careful evaluation of the patient and analysis of all the potential underlying mechanisms are required to ensure the accuracy of the clinical diagnosis and to prevent further deleterious evolution or permanent neurological damage.

63 THE COMATOSE POISONED PATIENT

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Introduction: The appropriate approach to acute poisoning is still a matter for discussion and a source of uncertainty among emergency physicians (EPs) and general practitioners (GPs). The common dilemma is how to prioritize management and establish what the most effective treatment should be. Antidotes are still considered the mainstay of treatment and the question often asked by doctors of Poison Centre (PC) operators is "which antidote should I use in this situation?" Gastrointestinal decontamination (GI) is another source of uncertainty and mistakes. Most EPs and GPs are not familiar with the EAPCCT/AACT Position Statements; gastric lavage is still considered a routine procedure as are forced diuresis and cathartics. The comatose poisoned patient presents a challenging clinical problem; EPs and GPs need to be clear about how to prioritize and avoid errors. There can be little doubt that physical examination and supportive care are the priorities when approaching the comatose patient. To assess and to support vital functions is the principal requirement regardless of the cause of coma. In assessing the patient one must ask whether breathing is spontaneous and effective and whether circulatory parameters are within the normal range? It is of primary importance to assess, and support if necessary, the respiratory and cardiovascular systems. Fortunately, guidelines on cardiopulmonary resuscitation are available world-wide and quite often correctly used by EPs. In this context, it is unimportant to stress "how to resuscitate," but it is important to remember that poisoned patients must be managed initially using all the general rules of critical care medicine. Management: Nevertheless it is possible to highlight some special points in the management of the comatose poisoned patient. First of all, it is vital that rescuers are not exposed to any toxic hazard. If the casualty is contaminated with a poisonous substance, gloves, an apron and boots must be worn, and contaminated clothing removed as soon as possible. Because intoxicated casualties may have a history of drug abuse, there may be a risk of transmission of blood borne viral infections such as hepatitis B and HIV. As far as resuscitation techniques are concerned, direct mouth-to-mouth ventilation in the presence of toxic substances such as cyanide, hydrogen sulfide, corrosives and organophosphates must be avoided. The patient must be ventilated by using a face-mask or bag-valve mask assembly. There are exceptions to the use of oxygen in high concentration, for example in paraquat ingestion where pulmonary injury may be exacerbated by oxygen. There is an increased risk of pulmonary aspiration after poisoning (especially when a neurodepressant substance has been taken), and early intubation with cricoid pressure is therefore recommended. If the casualty is comatose, tracheal intubation is mandatory before gastric lavage. Intubation may be difficult, requiring an experienced anesthetist: this is particularly true when thermal lung injury or airway burns are present (they usually accompany the irritant and systemic effects of the products of combustion). In poisoned patients myocardial depression and arrhythmias may be present. Fluid overload must be avoided and acid-base disturbances corrected. Antiarrhythmic drugs have a very limited role, but inotropes such as adrenaline and dobutamine may be indicated. Electromechanical dissociation (EMD) can result from the ingestion of drugs with a negative inotropic action but carries a better prognosis than "primary" EMD (purely cardiac cause). Blood glucose and electrolyte concentrations must be checked (particularly potassium) as well as the core temperature. All these parameters may reflect the severity of poisoning. Conclusion: Intensive supportive therapy is of primary importance; specific antidotes are available in only

a few cases. As far as prognosis is concerned, managing a poisoned comatose patient may require a long period of time, particularly in young casualties. For example, CPR efforts must be continued much longer than in non-poisoned casualties. This is true also because many toxic substances can cause hypothermia. Moreover, some poisons may be metabolized or excreted during extended life support measures. Finally, although respiratory and myocardial depression are common, the heart is usually healthy. Some of these considerations could be considered obvious by toxicologists; others could be obvious to anesthetists and intensivists. To treat a poisoned comatose patient requires the skills of both. It is perhaps not too obvious to stress that a good toxicologist is a good emergency physician too.

64 THE INTOXICATED PATIENT WITH SEIZURES

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Introduction: In the context of poisoning, seizures can occur under the following circumstances. 1. As a direct result of the effects of the toxin on the brain, e.g., central stimulants such as amphetamines and cocaine. 2. During withdrawal from e.g., alcohol, benzodiazepine or opiates following admission to hospital, the seizure not necessarily being due to the ingested toxin. 3. Convulsions due to metabolic consequences of poisoning, which might include hypoxia, hypocalcemia, hypoglycemia, hyponatremia and organ failure, including renal and liver failure. 4. Seizures secondary to reduced brain perfusion, particularly secondary to arrhythmias or severe hypotension. 5. Convulsions secondary to treatments used in the management of poisoning, for example use of flumazenil or naloxone in benzodiazepine- or opiate-dependent patients. The consequences of convulsions in patients with overdose vary from the innocuous, such as is often seen in patients taking mefenamic acid, to the catastrophic, in which patients suffer irreversible brain damage from repeated fits and secondary brain hypoxic damage. Convulsions result in hypoxia and increase acidosis, they therefore increase the risk of arrhythmias in patients who have ingested arrythmogenic drugs. Prolonged fitting may produce muscle damage with a rise in creatine kinase activity and, in severe cases, rhabdomyolysis. Hyperpyrexial states may result. In the acute assessment of patients it is important to differentiate seizures from other conditions, in particular acute dystonia. The ''ABC'' principles of management should be applied rigorously. Management: From the above it will be clear that the management of the patient with convulsions will vary depending on the primary cause. In addition, in some clinical scenarios appropriate intervention may reduce the risk of fitting, for example, use of prophylactic benzodiazepines in the management of alcohol withdrawal. In the patient who has no other predisposing factors that need correcting the appropriate management of convulsions is in general the use of intravenous anticonvulsants, the drug of choice in most Units being the long-acting benzodiazepine, diazepam. Diazepam is associated with an increased risk of respiratory depression, but in other respects is generally without significant complication when used in overdose management. Older anticonvulsants, such as phenytoin and phenobarbitone, are less commonly used. These agents are more toxic, alter drug metabolizing enzyme activity by enzyme induction, which in some situations is potentially hazardous, and have far narrower safety margins than is the case with benzodiazepines. In addition, there is evidence suggesting that phenytoin is less effective in fits secondary to cocaine than are benzodiazepines. The management of the patient who does not respond to first line treatment with benzodiazepines becomes increasingly difficult. To maintain respiration it may be necessary to paralyze and ventilate such patients, but then the important clinical features of seizure activity are lost and it is essential to use a cerebral function monitor to document EEG activity and treat this activity accordingly. Again, infusions of benzodiazepines, either short-acting such as midazolam or long-acting may be appropriate. In this setting barbiturate infusions may also be required to control convulsive activity. A patient with status epilepticus is a medical emergency and his or her care may be clinically extremely challenging. Seizure activity itself may be an important feature indicating the severity of poisoning. Good examples would include central effects of salicylate in children or of tricyclic antidepressants in adults. Managing the metabolic consequences of these seizures may be as important as the control of the seizures themselves. Aggressive treatment of acidosis in tricyclic poisoning or cocaine poisoning, and correction of acid-base balance in salicylate poisoning, are important measures.

65 THE INTOXICATED PATIENT WITH HYPERTHERMIA

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Background: Hyperthermia is an uncommon medical emergency. However, pharmacologically induced hyperthermia is increasing in frequency, mainly due to illicit drug misuse and the introduction of novel pharmaceutical agents. The drugs involved include atropine, cocaine, amphetamines (including MDMA), antipsychotic agents, anesthetic agents,

monoamine oxidase inhibitors, selective serotonin reuptake inhibitors and L-dopa. Most of these may be aggravated by agitation, exertion and environmental factors. Mechanisms: Several distinct drug related syndromes can be identified which involve excessive heat production. The main ones are: sympathomimetic, serotonergic, anticholinergic and L-dopa withdrawal. Neuroleptic malignant syndrome and malignant hyperthermia are specific hyperthermic syndromes which must always be borne in mind. In hyperthermia heat production exceeds heat loss. Ultimately the body's thermoregulatory mechanisms are overwhelmed by excessive heat production or impaired heat dissipation, and this can lead to further heat production since high temperatures cause a reduction in the calcium requirement of excitation-contraction coupling in skeletal muscle. Hypotensive collapse, seizures, rhabdomyolysis and disseminated intravascular coagulation are all potential outcomes. Hypothalamic disturbance due to central hypoxia, cerebrovascular accident and hyperthermic cerebral damage can also lead to sustained hyperthermia. Assessment: The clinical problem has to be assessed and treated as an emergency. The first priority is to measure the core temperature. Measurement of axillary temperature alone is misleading and can lead to dangerous complacency. The cause of the hyperthermia must be identified, since different chemicals produce hyperthermia through widely differing means. Management: Depending on the cause, actions can be taken to reduce body temperature and limit any hyperthermic damage. Several management strategies can be employed. These are: to facilitate thermoregulation by providing adequate fluid replacement, by paralysis to overcome heat production due to centrally induced muscle contraction and by specific therapeutic measures such as physostigmine for anticholinergic poisoning. External cooling may be useful in certain circumstances but could be counterproductive as peripheral vasoconstriction may reduce heat loss from the body. Dantrolene, a calcium antagonist which raises the calcium requirement for excitation-contraction coupling can limit heat production originating from muscle. It is effective in malignant hyperthermia and in any severe or uncontrolled hyperthermic state.

66 THE POISONED PATIENT WITH RESPIRATORY COMPLICATIONS

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Introduction: There are diverse reasons for developing respiratory failure after exposure to toxic substances. Generally, there are two main causes of respiratory insufficiency leading to arterial hypoxemia. Firstly, arterial hypoxemia can be induced by alveolar hypoventilation. Secondly, arterial hypoxemia can be provoked by interstitial and alveolar edema; then an insufficient O_2 diffusion from the alveoli to the capillaries and CO_2 diffusion from the capillaries to the alveoli can be observed, frequently in combination with ventilation-perfusion mismatch. However, the diffusion of CO_2 occurs more easily than the diffusion of O_2. Both causes of arterial hypoxemia can also be observed in combination. Mechanisms: Alveolar hypoventilation induced by intoxications can be caused via e.g. central nervous system depression, paralysis of the respiratory muscles, glottis edema, and uncoupling of oxidative phosphorylation. Diffusion disturbances, eventually in combination with ventilation-perfusion mismatch, caused by intoxications can be observed after e.g. aspiration of toxic compounds or inhalation of toxic gases. The severity of the symptoms after inhalational exposure depends on the concentration of the intoxicating substance, the duration of exposure, toxic potency of the substance, water solubility, minute ventilation, and the individual susceptibility of the victim. Clinically, two types of responses due to acute inhalation intoxications causing lung involvement can be discerned. In type I, the clinical symptoms start in the upper airways. The severity of the intoxication is generally manifest shortly after cessation of exposure. In type II, the clinical symptoms are usually absent during the first hours following exposure. After several hours acute respiratory distress syndrome (ARDS) may become manifest. Management: For risk assessment, it is essential to be informed about the nature of the substance involved and the type of clinical symptoms it may cause. This is relevant because if, for example in the case of type I inhalatory exposure, no symptoms are manifest when the patient consults the physician, it is unlikely that symptoms will appear later. Thus no treatment or observation is needed. In e.g. type II inhalatory intoxication, however, judgment is often impossible at the time when the patient visits the physician, because the full extent of the intoxication may only become manifest after several hours. The patient should therefore be kept under observation until more information is obtained regarding the severity of exposure or until clinical effects can no longer reasonably be expected. Beside highlighting the causes of respiratory failure induced by toxic substances, the diagnostic procedures and treatment will be discussed.

67 ROLE OF VOLATILE ORGANIC COMPOUNDS IN EARLY DEATH DUE TO SMOKE INHALATION

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The toxicity of fire gases is most often attributed to the presence of carbon monoxyde and cyanide. However, both laboratory combustion studies and limited human blood analyses have demonstrated the presence of a large number of other volatile organic compounds (VOCs). Their importance in contributing to smoke inhalation death remains unclear. This prospective study was conducted in order to assess the frequency and the quantity of such VOCs and the relationship to early mortality in human subjects. Materials and Methods: The study group consisted of non-fatal and fatal fire victims whose blood was sampled at the fire scene by fire department physicians. The control group consisted of living patients admitted to the hospital for acute drug poisoning and patients found dead at the scene from non-fire related causes. Blood cyanide was measured by a colorimetric method, blood carbon monoxide was measured by infra-red analysis. Blood VOCs were measured by purge and trap gas chromatography. Results: Twenty-six fire fatalities were enrolled, as well as 28 living fire victims; 55 non-fire dead, and 25 acute poisoned patients served as controls. Thirty-three VOCs were measured in the blood of fire victims and controls. Blood concentrations of eight VOCs did not differ significantly between fire victims and controls, namely: 2-butanone, 2,3-butanedione, 2,3-pentanedione, furan, isoprene, m-xylene, cyclohexanone, and ether. Ten additional products were found to be characteristically augmented in fire victims but not associated with a fatal outcome, namely: acetone, methanol, acroleine, 2-propanol, acetonitrile, chloroform, styrene, carbon tetrachloride, 2-methyl 1,3-dioxolan. Fifteen VOCs were associated with death in fire victims. These included: ethyl acetate, acrylonitrile, propionitrile, tetrahydrofuran, toluene, benzene, o- and p-xylene, ethylbenzene, nitromethane, tichlorofluoromethane, indene, trichloroethylene, 2-pentanone, and acetaldehyde. Among this group, three products (benzene, nitromethane, and ethyl acetate) are distinguished by their frequency of appearance, their blood concentrations, and their correlation with blood carbon monoxide concentrations. This study underscored the important role of aromatic hydrocarbons including benzene, toluene, ethylbenzene, and also o- and p-xylenes in fire death, illustrating the importance of pyrolysis as opposed to simple combustion. Certain molecules such as trichlorofluoromethane were observed less frequently but with blood concentrations rendering their presence toxic. Conclusion: These data illustrated that smoke inhalation leads to a potentially fatal intoxication, the cause of which is not limited to the actions of carbon monoxide and cyanide but also to volatile organic compounds.

68 COMBUSTION TOXICOLOGY IN A POSTCRASH AIRCRAFT FIRE

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Introduction: In July 1996 a Hercules aircraft with 4 crew members and 37 members of a military brass band of the Royal Dutch Airforce crashed while performing a landing at a military airport. There were no physical injuries or casualties due to the crash itself, but immediately after the crash a flash fire broke out. It took approximately 40 minutes from the moment of the crash till the rescue of the first two victims, who were both still alive. During the next hour all victims were taken out of the remains of the aircraft. Initially ten people were rescued alive, however eventually only seven people survived. During the evaluation of the entire rescue operation several questions arose, some of which were addressed to the National Poisons Control Centre. These questions concerned the following items: "Would a quicker rescue operation have resulted in less casualties and better treatment possibilities for the survivors?" and "Did the victims suffer?" Methods: In order to answer these questions the Inspectorate of Health Care established a working group consisting of two medical inspectors for health care, an internist-toxicologist from the National Poisons Control Centre, a specialist (surgeon) in the pathophysiology of burns and a lung specialist. All data available, including data on the materials of the aircraft, statements from the survivors, firemen and medical personnel, patient-data and data from post-mortem examinations were evaluated. Results: By combining these data with general knowledge of combustion toxicology a reconstruction of what had most likely happened inside the aircraft after the crash and following fire was made. Based on the development of the fire, the knowledge of the materials of the aircraft and the statements from the survivors, it was assessed that the toxic smoke released consisted of narcotic substances and asphyxiants such as carbon monoxide and hydrogen cyanide, as well as irritating substances. Post-mortem analysis confirmed the presence of carboxyhemoglobin (highest COHb 33%) and cyanide (highest blood cyanide concentration 1.3 mg/L) in the victims.

Exposure to the combination of these substances and most likely a concomitant low oxygen level in the breathing air caused loss of consciousness in all victims within several minutes after the onset of the fire. As exposure to toxic gases went on, the number of casualties rose. Conclusions: In this aircraft crash and fire the exposure to heat and the combustion toxicants released caused incapacitation and death through various hypoxia-inducing mechanisms. As the effects of toxicants depend upon the accumulated doses it is likely that the number of casualties would have been less if the duration of the exposure had been much shorter. The rapid loss of consciousness of the victims most likely shortened their period of suffering.

69 THE ROLE OF HEALTHY VOLUNTEER STUDIES IN TOXICOLOGY

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Introduction: The number of pharmaceutical and non-pharmaceutical chemicals in use involves a large variety of products. At present, premarket risk data associated with non-pharmaceutical products is derived primarily from animal studies and, to a lesser extent, from *in vitro* studies. When using the results of animal and *in vitro* studies there is always the difficulty of interpretation. For the majority of non-pharmaceuticals, so far, there are limited data on human metabolism and toxicity. Consumer products should be safe and it is obvious that human risk assessment should be performed before they are marketed. Essential human data needed for human risk assessment can be generated by volunteer studies. Volunteer studies: For a number of reasons it is expected that the demand for human volunteer studies in the framework of human risk assessment will increase in the near future. Firstly, because some recently marketed new products are designed explicitly to induce effects in human body functions (functional foods), for instance, the bacterial-culture-enriched dairy products (claimed to beneficially change the gastrointestinal flora). Secondly, because new legislation and guidelines for the production and marketing of non-pharmaceutical products will be more restrictive concerning safety aspects. Thirdly, because of the strong international trend to decrease the number of animals used for studies. In line with this trend, ethical review boards already review protocols for animal studies more intensively. As a result, human volunteer studies will be considered increasingly an appropriate alternative. Fourthly, consumers are more up-to-date, better informed and more demanding than in the past. Patients consult their physicians more and more about the health aspects of consumer products. Volunteer studies are especially needed to study the biokinetics and metabolism of a compound. Comparison of these data with those of laboratory animals can increase the accuracy in extrapolating results from animals to man. Furthermore, the results of volunteer studies can be used to fill in the gaps of knowledge which cannot be solved with *in-vitro* or animal studies in order to develop adequate physiologically based biokinetic or biodynamic models for human risk assessment. Conclusion: The increasing complexity of human risk assessment requires more interdisciplinary co-operation than ever before to help bridge the gap between results found from *in vitro* and animal studies and those from human studies so that the risks for humans can be better predicted.

70 ARE SOOT DEPOSITS AND NEUROLOGICAL DISTURBANCES PREDICTIVE OF CYANIDE POISONING IN FIRE VICTIMS?

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Objectives: Smoke inhalation is a leading cause of cyanide poisoning. However, the indications for cyanide antidote administration in fire victims are not well defined. The aim of this study was to determine the diagnostic value of two clinical signs in predicting cyanide poisoning: soot deposits in the airway and neurological impairment. Methods: We prospectively studied victims of residential fires in the Paris area who were examined by ambulance physicians at the scene of the fire. Blood specimens were collected in dry heparin by the first medical squad to reach the scene, after the start of isobaric oxygen therapy, but before the administration of hydroxocobalamin. Pre-printed case sheets were used for the collection of the history and initial symptoms. Soot deposits in the mouth and/or the sputum were noted on admission. Neurological disturbances included mental confusion, seizures, transient loss of consciousness and coma. Blood carbon monoxide and cyanide concentrations were measured using infrared analysis and colorimetric assay respectively. Cyanide intoxication was defined by the presence of a blood cyanide concentration greater than or equal to 40 μmol/L. Results: Soot deposits in the upper airway were recorded in 408 fire victims and neurological disturbances

in 138 casualties with soot deposits. In the fire victims without soot deposits the mean blood CO and HCN concentrations were 0.42 ± 0.82 mmol/L and 2.93 ± 6.29 μmol/L respectively. In the fire victims with soot deposits, the mean blood CO and HCN concentrations were 1.9 ± 2.0 mmol/L and 38.5 ± 57.7 μmol/L respectively. The sensitivity of the presence of soot deposits for cyanide poisoning was 98%; the specificity was 56%, the positive predictive value 28%, and the negative predictive value was 99%. In the context of smoke inhalation with soot deposits, the sensitivity of the presence of neurological disturbances for cyanide poisoning was 98%; the specificity was 49%, the positive predictive value was 44%, and the negative predictive value was 98% (Table 1).

	Blood HCN ≥ 40 μmol/L	**Blood HCN < 40 μmol/L**
Neurological disturbance+	39	50
Neurological disturbance−	1	48

Conclusion: In fire victims, soot deposits and neurological disturbances are sensitive but non-specific signs with regard to cyanide poisoning. Neurological disturbances may also result from other asphyxiant gases such as carbon monoxide or organic volatile compounds. In contrast, the lack of neurological disturbances in victims with soot deposits obviates the need for consideration of the administration of a cyanide antidote.

71 CYTOTOXICITY OF ETHYLENE GLYCOL METABOLITES IN CULTURED HUMAN PROXIMAL TUBULE CELLS

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Objective: A major characteristic of ethylene glycol poisoning is the development of acute renal failure due to proximal tubular necrosis. The mechanism for the nephrotoxicity has been suggested to be calcium oxalate precipitation within the renal tubule, although there have been no studies directly linking oxalate precipitation with tubular necrosis. Cytotoxicity could also result from renal accumulation of ethylene glycol metabolites, primarily glycolate or oxalate. The present studies were designed to assess the effects of ethylene glycol metabolites on the viability of normal human proximal tubule (HPT) cells, which in culture exhibit transport and other functional characteristics of the proximal tubule in vivo. Methods: HPT cells were isolated by enzymic digestion of human kidney cortical tissue (judged normal by diagnostic pathologist and cleared for use as pre-existing specimen). Cells were grown in tissue culture plates to confluent monolayers in a serum-free medium containing added essential growth factors. Cells were treated with glycolate (0–25 mM), oxalate (0–5 mM) or glyoxylate (0–5 mM) in buffers of pH 6.5, 7.0 or 7.4 for 0–6 h at 37°C. The resulting cytoxicity was measured by rinsing treated cells and incubating with ethidium homodimer. Cell lysis allows uptake of this dye and binding to DNA, releasing a fluorescent product. Degree of cytotoxicity correlates with increased fluorescence. Accumulation of oxalate and glycolate by HPT cells in these incubations was determined chromatographically. Results: Oxalate, in a dose-related manner, induced significant increases in ethidium homodimer fluorescence, indicating lysis of the HPT cells in culture. The effects of oxalate occurred maximally by 4 h and were not altered by the incubation pH. Neither glycolate nor glyoxylate produced any significant cytotoxicity at the indicated concentrations, even at the lowest pH. In the META trial of fomepizole treatment of ethylene glycol poisoning, plasma glycolate levels ranged up to 25 mM. Plasma oxalate levels were not detectable (< 0.5 mM), although urinary oxalate concentrations reached 5 mM. Conclusion: These data suggest that the renal necrosis related to ethylene glycol poisoning is most likely due to cytotoxic effects from the accumulation of oxalate in the proximal tubule. The excessive levels of glycolate in these poisonings do not appear to affect normal human kidney cells.

72 AMITRIPTYLINE INHIBITION OF EXCITATION-CONTRACTION COUPLING IN CARDIAC MYOCYTES IS PARTIALLY REVERSED BY ALKALOSIS

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Objective: Overdose with amitriptyline can result in a variety of cardiovascular side effects, including cardiogenic shock. Conflicting clinical results have been presented regarding the relative importance of pH change and sodium loading in the reversal of the cardiotoxicity of tricyclic antidepressants. In this study, we evaluated the effect of amitrip-

tyline on the excitation-contraction coupling in isolated cardiac myocytes and the relative role of alkalosis and sodium ions in the reversal of the depressant effect of amitrityline on Ca^{2+} transients and cell contraction. Methods: Isolated rat cardiomyocytes were loaded with the fluorescent Ca^{2+} indicator fura-2. A high-speed technique using a charge coupled device was used to measure simultaneously the changes of cytosolic-free Ca^{2+} concentration ($[Ca^{2+}]_i$) and cell shortening under electrical stimulation. Results: Amitriptyline at doses of 100 to 600 ng/mL caused a dose-dependent reduction in $[Ca^{2+})]_i$ transient amplitude and cell contraction, that were reversible after washout ($p < 0.01$, both). Thus, amitriptyline (200 ng/mL) reduced $[Ca^{2+}]_i$ transients and cell shortening by 38 ± 8% and 43 ± 7%, respectively, compared to control ($p < 0.001$, both). At greater doses (up to 20,000 ng/mL), amitriptyline abolished the electrically-induced $[Ca^{2+}]_i$ transients and contraction, which recovered after washout. We observed that sodium loading (increase in 20 mM Na^+), and mainly alkalinization of the buffer (from pH 7.3 to pH 7.6 with NaOH, Ca^{2+} corrected) partially reversed the depressant effect on the excitation-contraction response of the cardiomyocytes, provided the cell was not totally inhibited by amitriptyline.

	Control	AM(Na^+ 130 mM)	AM(Na^+ 150 mM)	Washout
$[Ca^{2+}]_i$ transient (nM)	270 ± 54	146 ± 17	195 ± 33	292 ± 44
Contraction (%)	10.2 ± 0.9	5.5 ± 1.6	6.2 ± 1.6	10.2 ± 1.2
	Control	AM (pH 7.3)	AM (pH 7.6)	Washout
$[Ca^{2+}]_i$ transient (nM)	314 ± 37	183 ± 44	273 ± 49	320 ± 67
Contraction (%)	11.7 ± 1.2	6.7 ± 1.4	8.8 ± 1.4	12.3 ± 1.4

AM: amitriptyline 200 ng/mL. N = 8 for each condition. Data expressed as mean ± SEM. Comparisons to the previous condition showed $p < 0.05$ in all cases (paired *t*-tests). Conclusion: Amitriptyline has a depressant effect on single cardiac myocytes by interfering the excitation-contraction coupling. This inhibitory effect of amitriptyline on $[Ca^{2+}]_i$ transients and contraction is partially reversed by alkalosis and to a lesser extent by sodium ions. Supported by grants FIS 96/0388 and 98/0330.

73 LITTLE EFFECT OF HAEMODIALYSIS AND CAVHDF ON THE ELIMINATION OF ARSENIC COMPARED TO DMPS TREATMENT

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Objective: The aim of the study was to compare the effect of haemodialysis and CAVHDF with the urinary excretion of arsenic under DMPS-treatment in a case of accidental arsenic poisoning. Case report: A 24-year-old student of chemistry took home from the laboratory a glass in which a residue of arsenic powder was left. When he felt thirsty at night he filled up the glass with water and drank it. Fifteen minutes later he started vomiting. He was sent to our department 16 hours after the ingestion. He was hemodialyzed 22 hours and 36 hours after the ingestion for 5 hours each time. Between the two hemodialyses a continuous arterio-venous hemodiafiltration was performed. On the first and the second day he was treated with 1.2 g of DMPS intravenously. Methods: Serial serum and urinary arsenic levels were determined by atomabsorption spectrometry after oxidation to AS^{5+}. During hemodialysis and CAVDHF arsenic levels were determined in the blood of influx and efflux of the dialyzator, the central venous blood and the dialysate/ultrafiltrate. Results: The starting level of arsenic was 245.8 µg/L in serum (normal < 2 µg/L). Seven days after the intoxication the serum level was 2.3 µg/L. In the urine the patient excreted during the first 17 hours 6.475 mg. The next day the patient excreted 74.18 mg arsenic in the urine. During the first 87 hours after admission 89.67 mg of arsenic was recovered in the urine. While the first hemodialysis was performed, 0.168 mg of arsenic were removed. In the dialysate of the CAVHDF 0.061 mg of arsenic were found. The next dialysis treatment removed 0.12 mg arsenic. The half-life of the serum arsenic level was 8 hours at the first day and 15 hours at the second day. Hemodialysis and CAVHDF did not alter the arsenic kinetics significantly. Discussion: The patient recovered without any other signs of arsenic poisoning besides the gastrointestinal symptoms. His kidney function was not impaired at any time. Different from other own observations when arsenic poisoning led to kidney failure, in this case the extracorporal elimination measures were ineffective. Although no urinary levels were measured before DMPS treatment was commenced, the

treatment with DMPS seemed to be very effective. Conclusion: In arsenic poisoning without kidney failure DMPS treatment is a hundred times more effective than all secondary elimination measures together.

74 PROLONGED HALF LIFE OF CHILDHOOD BLOOD LEAD AFTER TERMINATION OF ENVIRONMENTAL EXPOSURE

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Objective: Determine the quantitative and qualitative (natural isotope composition) changes of blood lead (B Pb) of infants and children during recovery from increased B Pb due to home remodeling. Methods: Prospective, longitudinal observational study for 2–4 years of 22 children 2–3 years old and 20 mother-infant pairs beginning the first trimester. Monthly duplicate diet (F Pb), hand wipe (HW Pb) and urine (U Pb); quarterly B Pb and floordust (FD Pb), carpet dust (CD Pb), window sill (S Pb) and door mat (DM Pb). All samples collected under clean conditions and analyzed by a Finnigan MAT 261 thermal ionization-mass spectrometer (TI/MS) with ^{205}Pb spike for total Pb and isotopic ratio $^{206}Pb/^{207}Pb$. Results: Six children had increases in Pb B from neonatal concentrations < 4 μg/dL to 7–12 μg/dL related to remodeling projects: 3 were exposed to short term, professional projects before 12 months of age; 3 were exposed to lengthy projects carried out by the parents over many months. $^{206}Pb/^{207}Pb$ of blood and urine were virtually identical and reflected the primary contribution of HW Pb. HW Pb, in turn, was significantly correlated with FD Pb and CD Pb. FD Pb was essentially undetectable in the isotopic ratio of blood. The dust load ranges were 11–404 μg/m^2 FD Pb, 1.0–217 μg/m^2 CD Pb, 178–9670 μg/m^2 S Pb. HW Pb declined after termination of remodeling but showed wide within-individual variability after age 12 months. The apparent $t^1/_2$ of Pb B after short term exposure was 8–11 months; the $t^1/_2$ after prolonged exposure was 20–38 months. The Pb B isotopic ratios of these 6 children and of others with early, unique sources of environmental exposure showed even more prolonged persistence of isotopic lead typical of the remodeling source, reflecting continued recycling from bone to blood for 4 years or more. Conclusions: The prolonged $t^1/_2$ of B Pb after termination of an environmental exposure should be anticipated in the evaluation of the responses to chelation and environmental remediation. Household, neighborhood and soil remediation projects should be designed to compare the blood lead of the next generation of children growing up in the modified environment with that of the historical controls. Longitudinal pre- and post-abatement studies of a target population should be extended to 2–4 years postabatement to determine the full effect. Supported by National Institute of Health Grant #ES04762.

75 NATURAL REDUCTION OF BLOOD LEAD IN NON-CHELATED CHILDREN

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Objective: To determine the time for a reduction in blood lead to less than 10 mcg/dL once the child is enrolled in an active case management program. Background: A commonly asked question from pediatricians is "how long do I need to continue following a patient's lead levels?" One paper describes a "natural reduction in blood lead after chelation therapy" on a population followed in the 1970s. There is otherwise little information to guide the pediatrician on proper follow up of lead levels. Methods: Data from 1,148 lead poisoned children who have been followed from early 1990 to August 1998 were examined retrospectively. All lead levels are measured in mcg/dL. Patients that were excluded from the analysis included those who received chelation therapy, whose blood lead elevations were based on capillary samples alone, and whose blood lead levels have not fallen below the action level defined as < 10. Capillary samples were deleted. Finally, children with a gap of more than 15 months between the last level above 10 and the first level below 10 were deleted, assuming a lapse in follow up. The time between peak elevation of lead levels and achievement of a level less than 10 was calculated. Data were grouped based on peak of elevation, age at peak, and season of peak. All data were analyzed using SAS. Results: The analysis included 579 patients whose lead level dropped below 10. 95% of the children were black and the average peak lead was 16. 84%, 73%, and 68% of children who peaked at ages 12–23 months, 24–35 months, and 36 months or older dropped to less than 10. More than half the children who have not dropped to < 10 were older than 35 months when they peaked. The average peak lead level for each age group was 17, 15, and 15.5. Children were more likely to peak in the summer. There was no difference in rate of decline according to season ($p = 0.19$). Children with levels between 22–25, 18–21, 14–17, and 10–13 took 23.6, 17.1, 13.0, and 8.8 months respectively to decline to less than 10. This linear relationship is as follows: Months to achieve a blood lead less than $10 = .876 \times$ peak value -0.567; $p < 0.0001$. Conclusion: The average time for blood

levels to decline was linear, and the higher the peak of elevation, the longer it took for levels to return to < 10. Peak lead is the strongest determinant for rate in decline compared to age or season at peak.

76 PRENATAL LEAD EXPOSURE IN A HIGHLY POLLUTED AREA IN KAZAKHSTAN: EFFECT ON MENTAL DEVELOPMENT

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Objective: To study the extent of prenatal lead exposure and its effect on neurobehavioral development in newborns residing near a large lead plant in comparison with a control group. Methods: Mothers of 156 newborns residing <3 km from a large lead plant in Shimkent (Group A) were interviewed, and their newborns were examined. Similarly, 175 control newborns residing 3–10 km from the plant were examined (Group B). Maternal blood samples (prenatal) and umbilical cord blood (neonatal) samples were collected at delivery and assayed for lead levels, zinc protoporphyrin (ZPP), aminolevulinic acid dehydratase (ALAd) activity, and hemoglobin. Neurobehavioral development was assessed at 6 months using the Bayley Mental Development Index Score. Results: Blood lead levels (BLL) in Group A were higher than in Group B (5.34 ± 3.7 μg/dL and 4.54 ± 2.5 μg/dL respectively, p = 0.013). Umbilical BLL were also higher in Group A than in Group B (4.99 ± 3.6 μg/dL and 3.74 ± 2.3 μg/dL respectively, p = 0.0001). Maternal and umbilical cord BLL decreased with distance from the plant. By contrast, hemoglobin levels in umbilical cord blood increased with distance. There was a significant correlation between BLL in mother-newborn pairs in Groups A (r = 0.83) and B (r = 0.56). There were no differences in the mean ZPP and ALAd between the groups. However in newborns with higher BLL (>11 μg/dL) ALAd activity was lower, and inversely related to BLL. At 6 months of age, Mental Developmental Index of infants in Group A were slightly lower than controls (p = 0.09), However, the Mental Developmental Index of infants with cord BLL > 20 μg/dL was significantly lower than those with cord BLL <20 μg/dL (p = 0.00024). Conclusions: 1. Our survey of an endemic area for lead pollution in Kazakhstan revealed significant intrauterine lead exposure which was inversely related to distance from the source. 2. Inhibition of ALAd activity by lead occurs also in newborns, with a threshold at 11 μg/dL, and can be used as a sensitive and practical marker of low level lead exposure. 3. Prenatal lead exposure impairs neurobehavioral development.

77 ACTIVATED CHARCOAL IS NEEDED RARELY IN CHILDREN BUT CAN BE ADMINISTERED SAFELY BY THE LAY PUBLIC

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Objective: It is accepted generally that activated charcoal (AC) is the method of choice for GI decontamination after many potentially toxic ingestions in children and adults. Should parents of small children have AC at home? Methods: In a prospective case-control-study we developed an "Emergency-Packet" (EP), containing 30 mL of simethicone, two portions each 5 g of AC and instructions for proper use. The telephone number of the Berlin Poison Center (BPC) was printed on the outside of the cardboard box. Using the established age-related pediatric counselling system, 24,000 EPs were distributed during counselling over a 12-month period to Berlin children of the age-group 10–12 months, they being the intervention group. The control group comprised all Berlin children of the age 10–47 months who did not receive an EP. During the same 12-months period from July 1995 to June 1996 data sheets on all calls to BPC were checked. Structured telephone interviews were carried out by the first author including all Berlin parents having children 10–47 months old who had called the BPC after an unintentional ingestion and agreed to being interviewed. Results: Evaluating 858 interviews, administration of AC at home was recommended in 55 cases (6.4% of all). In 33 cases (60%) AC was available at home, in 22 cases (40%) it was not. 19 cases were part of the intervention group, 35 of the control group, 1 case was not classified. Time to AC administration post ingestion was a mean of 14 min (SD 11.6) in the intervention group and 48 min (SD 43.5) in the control group. In 28 cases there have been no problems with the administration of AC, whereas 15 cases revealed the following difficulties: 1) child refused to take AC (5 cases), 2) child took only a part of the recommended dose (9 cases), 3) incorrect dose as a result of misunderstanding (1 case). 12 parents did not cooperate due to different reasons. No complications have been reported. Conclusion: AC in unintentional childhood ingestions can be safely administered by lay public, but is needed relatively rarely (6.4%)

and successfully administered in only 65%. If EP is available, administration of AC is much faster than without this method of anticipatory guidance.

78 SERIOUS POISONING ACCIDENTS IN CHILDREN UNDER 6 YEARS OF AGE

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Objective: To investigate how common serious accidents were in children less than 6 years old treated for poisoning in a large pediatric hospital, which substances were involved, what kind of treatment was needed and what was the outcome. Our aim was also to identify risk factors for prevention. Methods: Retrospective review of case records. All children under the age of 6 years treated during a 5 year period (1.1.1989–31.12.1993) for serious poisoning were included. Serious poisoning was defined as life-threatening symptoms requiring intubation and ventilation, major cardiovascular symptoms, convulsions, loss of consciousness, renal or hepatic insufficiency, G-I perforation or clear risk of it. Children who had a documented/verified ingestion of a toxic amount of a hazardous substance or residual disability after the poisoning were also included. Results: During the study period 317 children were treated for acute poisoning, with 37 (12%) of the episodes classified as serious. Serious poisoning was most common in the age group of 1–2 years. Pharmaceuticals were most often ingested (n = 28), but also technochemical products (n = 4; machine dishwasher detergents, drain cleaner, industrial cleaner), and others (n = 5; alkaline button battery, adder bite, Amanita regalis mushroom) were involved. The pharmaceuticals were: neuroleptics (n = 8), iron supplements (n = 7), benzodiazepines (n = 4), cardiovascular agents and diuretics (n = 3), antihistamines (n = 4), and others (n = 3). The ingested pharmaceuticals were most often prescribed to parents (in 56%), and as often to grandparents (in 13%) as to children (in 13%). On arrival 26 children (70%) had some symptoms: 6 were unconscious at or soon after arrival, 15 (40%) had impaired consciousness, 4 needed intubation, 4 were treated for convulsions, 11 received treatment with an antidote and 7 OGD-endoscopy. They were hospitalized for a total number of 193 days, 174 (90%) in a normal ward. Total number of days in intensive-care was 19 (10%), with a range of 1–7 days (median 2.5). None of the patients died or had permanent sequelae. Conclusions: Prognosis of serious poisoning accidents in children under 6 years of age is generally excellent. Ingestion of pharmaceuticals, especially of psychopharmacological agents or iron supplements, was the most common cause. Families with psychiatric problems were identified to be at risk, especially if they have a "pill eating culture." These families at risk could possibly be reached via education targeted to psychiatric personnel, with an aim to reduce the accessibility of hazardous substances in homes of young children.

79 CHILD SAFETY CAPS IN NEW ZEALAND—A GAME OF CHANCE?

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Background: Childhood poisoning remains a significant child health problem, being second only to falls as the reason for unintentional child injury resulting in hospital admissions in New Zealand. In 1994, the Public Health Commission recommended that a target of a 10% reduction annually in hospitalizations by the year 2000 be achieved. A key strategy identified was the introduction of Child Resistant Packaging (CRP) for medicines and toxic substances. Objective: For decades health professionals and community groups in New Zealand have sought safer packaging of medicines and toxic substances, with limited success. This paper describes the many chance events that influenced the outcomes of recent efforts to implement a CRP strategy. Results: In the early 1990s a Task Force on CRP identified both the barriers to, and methods for, implementing a CRP strategy. Widespread consultation and lobbying by this Taskforce achieved agreement from government, industry and health professionals for action. This was suddenly halted following unexpected changes in government and public health policies. In late 1994, government support resulted in a working party established by the Northern Regional Health Authority. It identified 12 medicine classes (the "Dirty Dozen") which because of their childhood poisoning frequency and/or toxicity required Child Safety Caps (CSCs) for dispensed solid and liquid dose forms. In 1995, following slow progress, the Project was transferred to Midland Health, which focused on four key areas: payment to pharmacists, sourcing appropriate CSCs; legislation changes, and promoting the Project. A Standard for CRP was developed but never applied. Further changes of government and public health policies again impeded progress of the Project and related CRP activities. In January 1997, on advice from PHARMAC (which manages the public funding of medicines) the Regional Health Authorities decided to fund CSCs only for oral *liquid* Dirty Dozen medicines listed in the Pharmac Medicines Schedule. In November 1997 the Project was finally implemented, albeit

on a much limited scale. In July 1998 the long-awaited (although voluntary) Code of Practice for Child Resistant Packaging of Toxic Substances was launched. Legislation amendments to make the use of CRP mandatory for medicines and toxic substances have remained enmeshed within the long-running and complex Trans Tasman Harmonization of therapeutic and hazardous substances legislation between Australia and New Zealand. Conclusion: It is now unlikely that the original Health Targets for Poisoning can be met. Making the packaging of medicines and toxic substances safer for children in New Zealand relies more on chance than on well planned policies.

80 MASSIVE POLYDRUG INGESTION IN AN INFANT

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Objective: Pediatric overdose, especially in infants, is uncommon and may be difficult to diagnose/manage due to the limited recommendations in the literature. We present a case of massive polypharmaceutical ingestion in a 2-month-old illustrating management dilemmas encountered in this population. Case report: A 2-month-old previously healthy male infant, brought to the emergency department by his father, was reported to be unresponsive and crying inconsolably. The infant was left unattended with his 2½-year-old sibling for approximately 6 hours. On arrival, the infant appeared toxic. Triage vital signs: rectal temperature 39.1°C, pulse 224 bpm, respirations 44/min, blood pressure 102 mm Hg palpable and capillary refill approximately 3 seconds. Physical exam: high-pitched cry, unresponsive to verbal or visual stimuli but localized to painful stimuli, no evidence trauma and normal bowel sounds. Pupils were reactive at 7 mm. Skin was warm and dry, without lesions. The remainder of the exam was appropriate for age. Initial resuscitation efforts included IV bolus of 0.9% saline at 20 mL/kg, 100% oxygen administration and evaluation on cardiac monitor revealed a narrow-complex tachycardia. Accucheck was 88 mg/dL. A household first aid kit was found at the scene. Missing medications from the kit included acetaminophen, calcium carbonate, dextromethorphan, ibuprofen and pseudoephedrine. Due to the possibility of overdose, both children were evaluated; the older child remained asymptomatic. Chest/abdominal X-ray of the infant revealed multiple large radio-opaque pills in the stomach. Saline lavage via 14 F nasogastric tube revealed few pill fragments. Activated charcoal (10 g) was administered. Laboratory evaluation including CBC, electrolytes, acetaminophen, salicylate, urinalysis and ECG was normal except: HCO_3^- 13.6 mEq/L, anion gap 22 and acetaminophen level 201 μg/mL. A gastroenterologist was consulted. Endoscopy revealed approximately 30 pill fragments in the stomach but multiple attempts with an endoscopy retrieved only 18 fragments due to technical difficulties (visual and mechanical obstruction secondary to charcoal). *N*-acetylcysteine was administered per standard protocol. Infant was discharged on day 2 without complication. One-year follow-up has detected no further sequelae. Conclusion: In conclusion, massive overdose in the infant is a rare event. Available literature does not provide adequate scientific data to establish a standard decontamination protocol for pediatric patients. Gastric lavage is probably not helpful and may actually increase the risk for complications. Endoscopy may be useful in massive pediatric ingestion if immediately available. Delaying activated charcoal may be indicated. If endoscopy is not readily available, aggressive decontamination with activated charcoal and whole bowel irrigation may be the treatment of choice. Controlled studies for evaluating gastrointestinal decontamination in the pediatric population are needed to prove the efficacy of these theoretically therapeutic interventions.

81 THE INCIDENCE OF CONTROLLED DRUGS AND OTHER ABUSED SUBSTANCES IN PAEDIATRIC CASES: AN INVESTIGATION USING ANALYTICAL TOXICOLOGY DATA

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Objectives: The Medical Toxicology Unit Laboratory analyses samples from several hundred cases each year where poisoning is suspected in children (<15 years) and a significant number involve controlled drugs and other abused substances. The data have been analyzed for 1996 to determine the incidence of individual substances and their prevalence in different age groups. Methods: The analytical case files for all cases of child poisoning referred in 1996 were examined for data on the drugs/substances present and the age of the patient. Results: A total of 916 cases of child poisoning were dealt with in 1996 and 610 cases were tested for the presence of amphetamines, cocaine, cannabis, opiates, methadone and benzodiazepines as part of a full or partial drug screen. The incidence of detection in descending order was benzodiazepines (17.7%), opiates (10.6%), methadone (5.1%), cannabis (3.8%) and amphetamines (1.6%). Butane was found in 5 cases where a specific request was made to carry out analyses for volatile solvents. Alcohol tests were carried out on 460 cases and 41 (9%) were positive. In the 10–15 years age group alcohol, solvents and cannabis were the most common findings. The incidence of amphetamine use in this group was very low and no cases of "Ecstasy" use were found. Amphetamines and cocaine were present almost exclusively in neonates of mothers

using these drugs. Methadone occurred predominantly in the 1–5 year age group and was usually associated with severe toxicity. Conclusion: The incidence of controlled drugs and other abused substances in child poisoning is high and there is a relationship between the type of substance involved and the age group of the child.

82 POISONING IN THE ELDERLY IN SCOTLAND—A PERSPECTIVE FROM A POISONS INFORMATION CENTRE

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Objective: To look at the relative frequency and reasons for poisoning enquiries from Scotland concerning those aged 70 or over and compare them with calls about the 20–69 age group. Methods: All records for Scottish telephone enquiries to the Scottish Poisons Information Bureau concerning both groups for the period 1989–1998 were retrieved from our relational databases, analyzed for age, sex, type of product, clinical course and reason for poisoning and the two groups compared. Results: During the 10-year period 1227 enquiries were received from Scotland concerning 1230 patients aged 70 years or over (2.1%). These were compared with 17785 enquiries concerning those aged 20–69 (30.9%). 63% of calls about the elderly concerned women compared with 49% in the 20–69 group, probably reflecting the proportion of women in the older age group in the general population (67.5%). 69% of exposures were accidental (29% in the 20–69 age group). The study showed a lower percentage of pharmaceuticals (58% in the over 70s against 80% in the lower age group) and higher percentages of household products (14% against 5%) and especially of toiletries (13% against 1%). The most common cause of enquiries about the elderly was ingestion of denture cleaners, accounting for 109 calls (9%), followed by digoxin, paracetamol, temazepam and calamine lotion. Among pharmaceuticals CNS drugs were most commonly followed by cardiovascular drugs. In some cases other products were mistaken for pharmaceuticals. Poisoning with more than one substance was more common in the 20–69 age group with an average of 1.4 substances/enquiry compared with 1.2 in the over 70s. Alcohol was reportedly taken with the overdose in only 1.9% of cases in the older group but 9.4% of the 20–69 age group. Despite the fact that pharmacokinetics and dynamics are altered in the elderly a relatively small percentage of cases were reported to show features of poisoning (40% in the elderly compared with 54% in the younger group). Conclusion: This study contrasts with the perceptions of poisoning in the elderly from in-patient studies where serious poisonings and completed suicides are common. Most exposures reported to a poisons centre are accidental, often involve household products or toiletries and do not result in serious toxicity. There has been publicity about poisoning in children resulting in advice for carers and the introduction of child-resistant containers. Although the incidence of poisoning in the elderly is much lower they also deserve advice and attention to packaging. Clearer labeling in larger letters might go some way to help reduce poisonings.

83 TOXI—A MULTIFUNCTIONAL SYSTEM FOR POISONS INFORMATION AND CLINICAL TOXICOLOGICAL DATA EVALUATION

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Objective: To present the experience of the STIC in computerized data collection and evaluation and to show the practical usefulness of the newly developed TOXI system in clinical toxicological situations. Methods: TOXI was realized in two steps: First, a relational database was designed to obtain detailed information on products (ATC) and clinical case characterizations (EAPCCT guidelines with a few modifications). For optimal user-friendliness, synoptical viewing of four full pages on large monitors, as well as unrestricted free-text searching is provided. The second specified core feature is the definition of quality control, i.e. quality assurance of outgoing information by senior residents and the structured evaluations concerning the evolution of the poisoning cases. In addition, the TOXI system requires poisoning severity scoring based on EAPCCT guidelines (none, minor, moderate, severe or fatal) and a causality assessment (definite, likely, possible, conditional, doubtful or unrelated) of all registered cases. Results: The physicians on duty at the STIC actually have immediate access to more than 120,000 case reports and 10,000 structured and evaluated feedback reports. Additionally, they can use 40,000 product data and 40,000 literature excerpts. Their everyday work is quality-controlled and based on the written feedback report obtained from the treating physicians. These clinical judgments are an essential quality-controlled basis for better risk assessment with particular emphasis on dose-response relationships. The usefulness of the TOXI system is illustrated by two examples: First, the two-year experience with structured data regarding intoxications with non-steroidal anti-inflammatory drugs demonstrated severe intoxications exclusively for mefenamic acid with a minimal dose for induction of convulsions of 3.5 g. Second, the analysis of 131

monointoxications with selective serotonin reuptake inhibitors (SSRI) (citalopram 50 cases, fluvoxamine 34, fluoxetine 23, paroxetine 15, sertraline 9) demonstrated moderate and severe cases in 14% for citalopram, 9% for fluoxetine, 6% for fluvoxamine and 0% for paroxetine and sertraline. Conclusions: These results and our experience with the TOXI system demonstrate a marked improvement in the efficiency and reliability of quality-controlled collection and evaluation of clinical toxicological data. Most importantly, the TOXI system permits the rapid screening for dose-dependent and differential toxicities of newly introduced drugs and other chemical products. Hence, the TOXI system should be of considerable help in a more efficient and more adequate identification of the toxicological risk of new chemical agents introduced into the market and thus further contribute to overall drug and chemical safety and to reliable risk assessment in human pharmacology and toxicology.

84 ASSESSMENT OF THE UTILIZATION OF EMERGENCY MEDICINE RESIDENTS AS TOXICOLOGY CONSULTANTS FOR THE POISON CENTER

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Objective: In the US, most poison centers offer the health care professional (HCP) caller the option of speaking to a physician toxicologist consultant. These consultants are either board certified or board eligible toxicologists. In Connecticut and Massachusetts, a training program exists whereby emergency medicine residents (EMRs) are utilized as toxicology consultants, with the back-up of the physician toxicologist on-call. We assessed HCP satisfaction with this toxicology consulting service. Methods: From December 8, 1998 through January 4, 1999, all HCPs who spoke to an EMR were contacted by telephone and a 12 question survey was implemented. Results: 22 cases were identified in which the EMR was consulted. 3 cases were eliminated because of potential bias since the EMRs were trained onsight at these facilities. 19 HCPs were contacted for their opinion of the service. 4 HCPs did not respond to initial or 3 follow-up calls. Respondents to the survey included 5 emergency medicine attending physicians, 1 internal medicine attending physician, 1 family practice attending physician, 1 MD/RPh board certified in internal medicine and pediatrics, 1 undeclared physician, 3 internal medicine residents, 1 dental resident, 1 physician's assistant and 1 intensive care nurse. Results of the 15 completed surveys showed the following: 13/15 felt that the response time of the EMR was very quick and 14/15 felt that the advice given was relevant to the poisoning case. 13/15 followed the advice given by the EMR. 10/15 felt that his/her knowledge base was expanded by the consult with the EMR. 13/15 felt that the EMR answered all of his/her questions. 11/15 felt they could access the consultant easily if needed again. 10/15 had used the service before, and all 15 stated they would use the service again. When asked to rate the service on a scale of 1–5 with 5 being extremely valuable, 12 HCPs rated it with a 5, 1 gave it a 4.5 and 2 rated it as a 4, for an average of 4.8. When asked for any other comments or suggestions for improvement, 7 had no comments, 3 had suggestions, and the remaining 5 had praise for the service. Conclusion: Utilization of emergency medicine residents as toxicology consultants in the poison center, with the back-up of attending toxicologists, meets with high satisfaction and is well-received by those using the service.

85 ACCURACY OF CARBON MONOXIDE (CO) MEASUREMENT IN EXPIRED AIR FOR THE DIAGNOSIS OF CO POISONING

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Objective: Suspected carbon monoxide poisoning requires laboratory confirmation for carboxyhemoglobin (HbCO) determination which usually leads to hospitalization. Moreover, the delay between cessation of CO exposure and HbCO measurement is often so long that any interpretation is precluded. Measurement of CO level in expired air has been used in occupational settings for fire fighters and in smoking cessation programs. The aim of our study was to evaluate the accuracy of such a method for the diagnosis of CO poisoning. Methods: Every patient suspected of CO poisoning and admitted to the Hyperbaric Oxygen Unit (HBO) in a 3 month period (January–March 1998) was enrolled if conscious and self-ventilating. CO levels were measured in expired air by a device (TX-II, Oldham, France) using an electrochemical determination method. Patients were instructed to expire in order to obtain an end expiratory plateau. End tidal CO level (CO_{ET}) was taken as the alveolar CO level. HbCO was determined at the same time using a CO-oxymeter (OSM3, Radiometer, Denmark). Measurements were done at hospital admission and, when a HBO session was needed, immediately after. Results: 79 patients were enrolled (age 39 $\pm$ 6 years). Only 13 complained of headache, nausea or dizziness,

15 had objective neurologic abnormalities, 50 had lost consciousness during CO exposure. On admission, these 3 groups did not differ in CO_{ET} or HbCO levels. There was a significant linear relation: HbCO (%) = 0.12 CO_{ET}; r = 0.91; $p < 10^{-3}$. After the HBO session (69 determinations), a significant linear relation still existed but was weaker: HbCO (%) = 0.09 CO_{ET}; r = 0.54; $p < 10^{-3}$ showing that oxygen breathing is an important factor to take into account for interpretation. If the HbCO level to diagnose CO poisoning is set at 6%, a 50 ppm CO_{ET} level has a 91% accuracy. Conclusion: Determination of CO_{ET} concentration is a simple reliable non invasive method for CO poisoning diagnosis confirmation. Its interest for on-site use remains to be evaluated.

86 PULMONARY FIBROSIS ASSOCIATED WITH CHRONIC INHALATION OF JET FUEL

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Objective: We report a biopsy-proven case of interstitial pulmonary fibrosis in an individual chronically exposed to aviation fuel vapors and aerosol. Although animal studies suggest the possibility of this reaction and pulmonary fibrosis has been reported in association with exposure to some petroleum distillates, this reaction has never been reported with exposure to jet propellants (JP-4 and JP-8). Case Report: A 46-year-old man presented with 9 months of exertional dyspnea and cough. Physical exam was notable for fine crackles at both bases. There was no clubbing, jugular venous distention, or cyanosis. Pulmonary function tests revealed evidence of a restrictive defect with altered gas exchange. Following an intercurrent infection, a lung biopsy demonstrated chronic interstitial pneumonitis and fibrosis, with honeycombing. The patient was removed from exposure, treated with prednisone and cyclophosphamide with stable pulmonary disability over the subsequent year. A review of his medical history was unremarkable for connective tissue diseases, medications or drug use; the biopsy did not demonstrate any malignant cells, amyloid deposits, or ferruginous bodies. The symptoms preceded his acute infection. His occupational history was notable for 21 years of fuel distribution system work. In this capacity, the patient obtained and analyzed up to 500 fuel samples a month, handling 3 million gallons of aviation fuel annually. All work was done in an inadequately ventilated area without respiratory or eye protection. In addition, there were multiple documented spills with spray of fuel onto the patient's face. The patient experienced headaches, nausea, and nonspecific dizziness during work, which required "fresh air" breaks. No ambient measurements of the jet fuel components or biologic monitoring of the worker were performed. Various rat models of jet fuel vapor or aerosol exposure have demonstrated alteration in pulmonary epithelial integrity as well as interstitial edema. Fibroblast aggregation and collagen deposition have been demonstrated in a rat model following 12 weeks of gasoline vapor inhalation. A human case/control study of occupational kerosene exposure has demonstrated an increase in pulmonary fibrosis among exposed workers. Several studies of workers exposed to jet fuel have described subjective respiratory complaints, and both subjective and objective neurologic dysfunction, but no mention has been made of pulmonary fibrosis. Conclusion: This worker developed acute, transient neurologic symptoms and biopsy-proven pulmonary interstitial fibrosis. The exposure history, lack of alternative causes, the experimental evidence and biologic gradient provided by animal studies, and the analogy of other kerosene product exposure in humans, supports a causal link between the chronic occupational inhalation exposure to jet fuel and pulmonary interstitial fibrosis.

87 ASSESSMENT OF ERYTHROCYTE CHOLINESTERASE ACTIVITY IN VICTIMS OF SMOKE INHALATION

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Objective: The nature of the toxic gases that cause death from smoke inhalation is incompletely understood, and the mechanisms leading to incapacitation remain to be determined. Thermal degradation products of various compounds, including phosphorous-based fire retardants, are suspected to be capable of impairing human cholinesterase activity. The aim of this study was to measure the erythrocyte cholinesterase activity in victims of smoke inhalation. Methods: We prospectively measured the erythrocyte cholinesterase activity in blood samples obtained at the scene of residential fires from 49 fire victims. We compared the results with those in 45 persons with acute drug poisoning. Results: There was a significantly greater number of women in the control group (p = 0.02). The median age of the fire victims was not significantly different from the control group. Twelve fire victims had burns. Seven fire victims were found dead

at the scene of the fire. The median (25^{th}–75^{th} percentiles) erythrocyte cholinesterase activity in the 49 fire victims, 1968 IU/L (1660–2276), was significantly lower than in the 45 control subjects 2460 IU/mL (1968–2890), ($p = 0.0004$). There was no significant difference of the red blood cell counts or plasma protein levels between the two groups, while the hematocrit was significantly greater in the fire victims than in the drug-poisoned patients. There was a significant correlation between blood cyanide and carbon monoxide concentrations in the fire victims ($r = 0.494$, $p = 0.002$). There was no correlation between erythrocyte cholinesterase activity and either blood cyanide ($r = 0.11$, $p = 0.44$) or blood carbon monoxide concentrations ($r = 0.04$, $p = 0.78$). Conclusions: The determination of (pre-exposure) cholinesterase activity is of great importance in view of the wide range of activity in normal, unexposed populations. A major limitation of our study is that we did not measure repeated cholinesterase activity over time, which is the best alternative when pre-exposure activity is unknown. This study showed that there is a significantly lower level of erythrocyte cholinesterase activity in victims of residential fires, when compared with hospitalized poisoned patients. The erythrocyte cholinesterase activity correlates neither with cyanide nor carbon monoxide blood concentrations. We believe that toxic gases, as yet undetermined, may be responsible for this impairment. We suggest that acute combustion toxicity tests should be designed to detect any anticholinesterase activity of smoke.

88 TOXICITY AND ANALYSIS OF GLYCOL ETHERS

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Objective: Glycol ethers, mostly derivatives of ethylene glycol and diethylene glycol, are constituents of brake fluids and are used as odorless solvents in many professional and household products with increasing frequency (e.g., cleaners and glues). Therefore, ingestion of glycol containing products and exposure via other routes are observed frequently. Only few data are available concerning the toxicity of glycol ethers as compared to data for ethylene glycol and diethylene glycol. In animal studies, the toxicity of derivatives is comparable or higher than that of free dihydroxy compounds. Some molecular species show individual toxic effects. The rate of alcohol dehydrogenase-mediated oxidation leading to toxic metabolites differs and has not been sufficiently studied for all substances. The indication for alcohol dehydrogenase inhibition therapy by ethanol or fomepizole has not been clearly defined in many clinical cases. Analysis of glycol ethers will help to differentiate between subtoxic and toxic absorbed doses. Methods: Acetone-deproteinated serum samples or (dilutions of) technical products were injected directly into a gas chromatographic system with a Nukol® column (Supelco, 15 m × 0.53 mm fused silica, oven 60°–150°C). Signals from flame ionization detection were primarily interpreted by retention times. With doubtful case history the identification of the glycol compounds was reconfirmed by gas chromatography coupled to mass spectrometry. Calibration was done with external standards. Results: 13 different glycols and glycol ethers were detectable at serum levels of 0.05 g/L or below. Screening analysis was performed within 30 min, quantitative results were available within 60 minutes. The method was tested in 2 cases with confirmed ingestion of glycol ether containing products: Case 1: Ingestion of an unknown dose of brake fluid by a 19-month-old boy. No symptoms. Analysis of product: mainly triethylene glycol monomethyl ether and triethylene glycol mono-*n*-butyl ether, serum: triethylene glycol monobutyl ether < 0.05 g/L. No antidote therapy. Case 2: Ingestion of 50 mL of all purpose cleaner containing ethylene glycol mono-*n*-butyl ether and 0.2% sodium hydroxide by a 53-year-old male patient. Symptom: burning throat. Analysis of product: 10% ethylene glycol mono-*n*-butyl ether, serum: no glycols detected. No antidote therapy. Conclusion: The glycol analysis described here can differentiate between ingestion of non-toxic and toxic amounts of 13 different glycol compounds quickly, easily and accurately. Furthermore glycol analysis will help to clarify the dose-dependence of toxic effects in humans.

89 UNINTENTIONAL OPIATE RELATED US MORTALITY TRENDS 1979–1996

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Introduction: Poisoning is the third leading cause of injury mortality in the USA and opiates are now the agent responsible for the largest number of poisoning deaths. Objective: To describe unintentional opiate-related death rate trends in USA overall and within subgroups. Methods: Trends in US National Center for Health Statistics' (NCHS) compressed mortality data were analyzed via the Center for Disease Control's (CDC) Wonder computer program. Unintentional opiate-related deaths were identified from the underlying cause of death (UCOD) field containing both ICD9 N & E codes. Trends in sex, race and age groups; 52 states and 4 national regions were determined and plotted. Unintentional

opiate-related death rates per 100,000 population were reported. Results: From 1979 to 1996, 20,666 unintentional opiate-related deaths were identified with the following distribution: 85.4% E850.0 (Accidental Poisoning, Heroin), 5.5% E850.1 (Accidental Poisoning, Methadone), 4.6% E850.2 (Accidental Poisoning, Other Opiates), 2.8% N305.5 (Nondependent Abuse of Opioids), 1.6% N304.0 (Opioid Dependence), 0.2% E935.0 (Adverse Effects of Heroin) and 0.1% E304.7 (Dependence on Opioid Combinations). Opiates were responsible for 9.5% of all unintentional deaths in the USA in 1979 compared to 23% in 1996. Codes specific for heroin identified >85% of all cases. The unintentional opiate-related death rate in males was 4x than females and 80% overall. Blacks had higher rates (0.69) than Whites or the "Other" racial group but accounted for only 18% overall. The 25–34 year old and 35–44 year old age groups had the highest overall rates (0.93 and 1.24) and accounted for 33.2% and 37.5% of unintentional opiate-related deaths, respectively. From 1979 to 1996, the US unintentional opiate-related death rate increased 329% overall, 380% in males, 374% in whites and 809% in the 35–44 year old group. The five states with the highest overall unintentional opiate-related death rates were California (1.5), New Mexico (1.3), Oregon (1.1), Arizona (0.9), Washington (0.8) and the Western region had the highest overall rate (1.2). Conclusions: The USA is in the midst of another epidemic in unintentional opiate-related deaths. The highest unintentional opiate-related death rates occurred in the black racial group, male sex, 35–44 year old age group and the western region of states. Unless vigorous and effective countermeasures are taken, unintentional opiate-related death will continue to be a major cause of poisoning mortality. Recent marked increases in purity and decreases in price of heroin in the USA have probably not fully impacted upon these unintentional opiate-related death rates and may lead to even higher rates in the coming years.

90 DELAY IN TREATMENT OF PARACETAMOL OVERDOSE

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Objective: Paracetamol overdose is a frequent cause of casualty attendance and hospital admission in Ireland and Britain. It is also one of the most common causes of fulminant hepatic failure in these islands. *N*-acetylcysteine is a specific antidote and can prevent liver damage if given in time. However it is a time dependent antidote and efficacy declines rapidly if treatment is delayed. The most common reason for treatment failure is late administration. Late presentation is outside medical control whereas delays in treatment after arrival in a casualty department are potentially preventable. The aim of this study was to determine whether there are significant delays in treatment after patients arrive in a casualty department. Methods: The study was conducted in two large casualty departments located in university teaching hospitals in Dublin. Data was collected on all patients admitted to hospital with paracetamol overdose for a 2 year period. Only patients presenting initially to the hospitals concerned were evaluated and transfers from other hospitals were excluded. This was a retrospective study. Data was collected from casualty records, hospital admission notes and nursing records. Results: Over the 2 year period there were 177 admissions with paracetamol overdose. Sixty-three percent of patients were female and the mean age was 26.5 years. The vast majority (156) presented directly to casualty and 18 were referred from another medical source, e.g., GP, pharmacist etc. Approximately one third had taken an overdose previously. The mean paracetamol dose was 18.3 g and a third had taken other drugs. Approximately 30% had consumed alcohol in addition to paracetamol. The mean time from overdose to presentation at casualty was 7 hours. Eleven patients presented after 24 hours. The mean time from casualty presentation to administration of *N*-acetylcysteine was 109 minutes. Treatment was delayed by more than 4 hours in 10% of patients. In patients presenting more than 4 hours after overdose *N*-acetylcysteine was given at a mean time of 83 minutes. The majority of patients had no adverse sequelae but 4 required ventilation, one hemofiltration and one died. The patient who died presented at 35 hours. Average length of stay for the 2 hospitals was 2.5–3 days. Conclusion: *N*-acetylcysteine is given in a timely manner in the majority of patients with paracetamol overdose. However delays in treatment do occur and may be important in the small minority of patients who develop significant liver injury.

91 IRON POISONING REQUIRING LIVER TRANSPLANTATION

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Objective: We present a case of iron overdose requiring liver transplantation. Case report: A 17-year-old female ingested a maximum of 69 iron tablets containing 36 mg Fe^{++}/tablet (total dose approximately 30 mg/kg elemental iron). Addi-

tionally she ingested 4 g of ibuprofen, 40 tablets of a cold preparation (each tablet containing 10 mg noscapine hydrochloride, 30 mg caffeine, 150 mg phenazonesalicylate, 200 mg salicylamide and 200 mg ascorbic acid) and a bottle of wine. When admitted to a local hospital 3 hours after the ingestion, she presented with abdominal pain, vomiting, hematemesis, metabolic acidosis, hyperglycemia, hypokalemia and a serum iron level of 1076 micromol/L. Serum acetylsalicylic acid level was negative. Her hemodynamic condition was initially stable. Abdominal x-ray revealed no signs of iron tablets. Treatment was initiated with gastric lavage, activated charcoal, sodium bicarbonate infusion and electrolyte infusion. Deferoxamine infusion 35 mg/h was given until s-Fe normalized after 14 h. Whole bowel irrigation could not be performed because she was constantly vomiting. Viral and other causes for the liver failure were excluded. On day 3, she became lethargic and the laboratory tests revealed severe liver cell damage and a developing liver necrosis (INR >4, ALAT 5990 U/L). During the next days, the patient became gradually more unconscious and developed grade III encephalopathy and hepatorenal syndrome treated by hemofiltration. On day 7, she underwent a successful emergency liver transplantation. At the 6 months follow-up the patient was well and had excellent liver function. The most common genetic marker of hemochromatosis, the point mutation (Cys282Tyr) of the HLH-H gene was negative. Discussion: The amount of iron involved in this case is generally considered too small to produce such a high serum iron concentration and a severe poisoning. To achieve these concentrations, the amount of iron ingested should have been 10-fold (690 tablets). However, 69 tablets was the maximum amount in the household. Ascorbic acid (present in the cold remedy) is known to enhance the absorption of iron by about 100%, but not 10-fold. Even if the liver damage could have been due to hypersensitivity to the medicines ingested, it would not explain the unusual dose/concentration ratio, so abnormal absorption of iron is postulated. Conclusion: The most probable explanation for the severe course in this case is hemochromatosis, in which the iron absorption is usually increased about 10-fold. Hemochromatosis is one of the most common genetic diseases. Typical symptoms usually begin in the middle age, are vague and the disease is underdiagnosed, especially in females.

92 A CASE OF CIBENZOLINE OVERDOSE

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Case report: A 38-year-old woman ingested in a suicide attempt 3250 mg cibenzoline together with 685 mg flurazepam and 25 mg lorazepam. When she was found 10 hours later by the first medical rescuers (Day 1, 10:00 a.m.), she was comatose (Glasgow Coma Scale 5/15), with intermediate but reactive pupils. The heart rate was only 42/min, the arterial systolic pressure 75 mm Hg and the pulse oxygen saturation was 72%. The patient was intubated and 500 mL olloids were infused. Wide QRS complexes were seen on the ECG monitoring during the transfer to the hospital. On arrival, the arterial systolic pressure was still 75 mm Hg, and the heart rate had increased to 120/min. The first ECG disclosed sinus rhythm (120/min), with wide (>200 msec) QRS complexes and prolonged QT interval (400 msec instead of a theoretical value of 290 msec). The first arterial blood gas analysis revealed significant metabolic acidosis, with arterial pH 7.24 and arterial blood lactate concentration 5.1 mmol/L (normal value < 2 mmol/L). The patient received 100 mL molar sodium lactate, without any significant change on the ECG and dopamine infusion (333 µg/min) was then started. The patient was referred to the Intensive Care Unit for further treatment. Arterial blood pressure (118/73 mm Hg) increased after an additional infusion of 200 mL sodium lactate. At this time, the ECG analysis showed: PR interval 200 msec, QRS duration 140 msec, QT/QTc 480/330 msec. Again, 100 mL sodium lactate was given and QRS duration was 100 msec about 7 hours following admission. A Swan-Ganz catheter had been inserted and a first hemodynamic calculation was done at the end of sodium lactate infusion (Day 1, 3:00 p.m.), while the patient was receiving 166 µg/min dopamine. Cardiac output was only 3.11 L/min, cardiac index 1.79 L/min/m^2, pulmonary capillary wedge pressure 13 mm Hg, systemic vascular resistances 2005 dyne.sec.cm^{-5} and left ventricular stroke work index 25.8 g.m/m^2. Dopamine infusion was increased to 500 µg/min but could be weaned 5 hours later (cardiac index 4.02 L/min/m^2). Low doses of isoprenaline (0.83 µg/min) were infused for 42 hours in order to maintain the heart rate above 90/min. No further complications were observed. Discussion: Cibenzoline is a class Ic antiarrhythmic agent (with also class III and IV activity). Cibenzoline lengthens AH and HV intervals. Prolongation of the PR and QRS intervals with slight prolongation of the QTc interval are possible electrocardiographic findings. Overdose with cibenzoline may lead to intraventricular block and cardiogenic shock. It seems that sodium lactate is partially effective and that, as in the present case, large doses have to be used.

93 CHANGES IN INDICATIONS FOR VALPROIC ACID THERAPY HAVE LED TO INCREASED FREQUENCY OF VALPROIC ACID POISONING

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Objective: Valproic acid (VPA) is a branched-chain fatty acid introduced in the 1970s to treat epileptic seizures. Indications for its use were extended in the 1990s to non-epileptic conditions including migraine prophylaxis and mood disorders. This led to an increase in the number of individuals treated with the drug. More importantly, the group of individuals to whom its use was extended included those who, theoretically, are at greater risk of taking an overdose. The aim of our study was to assess changes in frequency of VPA poisoning over the last 10 years and to determine the indications for VPA treatment in those individuals who overdosed with the drug. Methods: We undertook a retrospective chart review of all cases of VPA poisoning seen at Vanderbilt University Medical Center (VUMC) between 1989 and 1998. We determined whether the patients were treated with VPA prior to their overdose and, if so, for what indication. Data obtained were contrasted with figures recorded for VPA poisoning in AAPCC TESS Annual Reports (1986–1997). Results: Between 1989 and 1998, 37 patients with VPA poisoning were seen at VUMC. Only six presented between 1986 and 1995. Subsequently, the number of cases of VPA poisoning increased markedly (1996: 5; 1997: 10; 1998: 16). Of the 37 VUMC cases, 76% (28) were being treated with VPA for non-epileptic conditions, mainly bipolar disorders; 19% (7) of patients were being treated with VPA for seizure disorders; and only 5% (2) were not being treated with VPA. TESS data indicate an almost exponential increase in VPA exposures between 1986 (n = 402) and 1997 (n = 8085). The total number of exposures registered during the same period only doubled (1.1 million in 1986; 2.2 million in 1997). Intentional and adult exposures rose disproportionately. In striking contrast, the frequency of lithium poisoning has decreased steadily since 1994. Conclusion: The marked rise in the frequency of VPA poisoning is probably secondary to its changed indications for use. The introduction of VPA therapy into a population with a high risk of self-harm appears to have led to an increased number of suicide attempts with this substance. This conclusion is supported by the fact that the countrywide number of intentional overdoses and of adult cases increased disproportionately, and that the majority of VUMC cases with VPA poisoning were patients with newer indications for treatment with VPA (mood disorders). The observed national trend is associated with a decrease in frequency of lithium poisoning.

94 METHEMOGLOBINEMIA FOLLOWING DAPSONE OVERDOSE

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Objective: To describe three cases of methemoglobinemia following dapsone overdose reported to the National Poisons Information Centre (NPIC), Dublin. Case series: The NPIC received enquiries about only five cases of dapsone overdose between 1993 and 1997. Methemoglobinemia developed in four of these (80%) and in one additional case in 1998. Three of these cases are described. *Case 1.* A 25-year-old woman was admitted 9.5 hours after ingesting 6 g dapsone and 30 mg zopiclone. She appeared cyanotic but had no neurological signs or changes in level of consciousness. The methemoglobin concentration ([metHb]) was 41%. Two hours later her oxygen saturation was noted to be 65% on 100% O_2 and she was given methylene blue 2 mg/kg. Oxygen saturation increased to 85% and the [metHb] fell to 5%, 5.5 hours after admission. Oxygen saturation was maintained between 84–90% on 40% O_2. Six hours later the [metHb] rose to 18% and a further 1 mg/kg methylene blue was administered. The patient also received 50 g activated charcoal four-hourly. There were no further measurements of [metHb]. *Case 2.* A 27-year-old woman with a history of depression, asthma and alcoholism was admitted less than two hours after ingesting 1.4 g dapsone with 2.8 g metoprolol, 150 mg diazepam and unknown amounts of paracetamol and alcohol. On admission she was conscious and vital signs were stable. Bilateral rhonchi were audible, she complained of dyspnea and appeared cyanotic peripherally. She was intubated and ventilated. Aminophylline, hydrocortisone, salbutamol, and ipratropium were administered by nebulizer for bronchospasm. Oxygen saturation measured by pulse oximetry was 85% but arterial blood gases on 100% O_2 were pH 7.264, pCO_2 6.44, pO_2 45.19, BE −3.9, SaO_2 99.7%. The [metHb] was 19% and she was given 50 mg methylene blue. Subsequently pO_2 fell to 27.43, SaO_2 99.4% and she developed peripheral cyanosis. The [metHb] was 17.3% and a further 50 mg methylene blue was administered. The patient was extubated the following morning when the [metHb] was 8%. The [metHb] fell further to 2.4% prior to discharge. *Case 3.* A 16-year-old man attended Emergency Department 40 hours after ingestion of 5 g flucloxacillin and 40 unidentified tablets. He had appeared pale and cyanotic since the previous day and had suffered hallucinations during the night. He appeared very cyanotic on admission and complained

of abdominal pain and constipation. The [metHb] was 35%. A diagnosis of dapsone poisoning was made based on the clinical presentation and the availability of dapsone in his home. He was treated with methylene blue and discharged after 5 days. Conclusion: Methemoglobinemia is a common occurrence following dapsone overdose. It may be delayed in onset and persist for several days.

95 ACUTE DAPSONE EXPOSURE AND METHEMOGLOBINEMIA: A PEDIATRIC CASE SERIES

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Background: Dapsone, a widely used antileprotic and anti-inflammatory drug, can cause methemoglobinemia and hemolytic anemia at therapeutic doses and above. Although several cases of acute dapsone poisoning have been reported, there have been few case series studies in children. We describe the outcome of 17 children admitted to our hospital from January 1988 to December 1996, with acute exposure to dapsone complicated by a methemoglobin concentration greater than 20% of the total hemoglobin. Patients and Methods: Seventeen patients (aged 1–13 years, median 3 years), were admitted 1–72 h after the ingestion of 100–1200 mg (median 350 mg, 10 patients) or an unknown amount of dapsone (7 patients). The methemoglobin blood concentrations upon admission ranged from 23.5%–49.7% (median 37.8%) and the main clinical features were cyanosis (17), tachycardia (17), vomiting (11) and tachypnea (8). All of the children received multiple doses of activated charcoal (MDAC) orally or via nasogastric tube (1 g/kg, 4–6 times/day, 3–16 doses with a median of 8 doses). Twelve of the 14 patients with methemoglobin levels greater than 30% were also treated with a single dose of methylene blue (MB 1–2%, 1–2 mg/kg) infused IV over 5 minutes. Results: There was a progressive decrease in the methemoglobin levels after the beginning of both treatments (MDAC, MDAC+MB), and only one dose of MB was necessary. There were no significant statistical differences between the results of the two treatments ($p = 0.49$, non-linear regression adjustment of repeated measures of the methemoglobin, and the Wilcoxon test). Conclusions: Repetitive doses of activated charcoal given when methemoglobin levels were greater than 20% was found to be a safe and efficient treatment for pediatric patients after acute dapsone exposure.

96 NON VOLUNTARY INGESTION OF CANNABIS. AN UNUSUAL CAUSE OF A COLLECTIVE POISONING

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Objective: Cannabis is mostly smoked and its use is usually a group activity. Cannabis is occasionally ingested and some accidental poisonings have mostly been reported in children. Case series: Four persons working at the same company were admitted to the emergency unit for troubles which had appeared 30 to 60 minutes after eating a chocolate mousse at a party given at their workplace by a colleague. Ten other work mates had also developed minor troubles in the same conditions. On admission clinical features included drowsiness, dizziness, blurring of vision, abdominal pain, visual and auditory hallucinations, ataxia, dilated pupils, mouth dryness and tachycardia. A poisoning by a substance inducing an anticholinergic syndrome was first suspected. Symptoms resolved in all patients within 5 hours. A toxicological screening was negative except for cannabis and its metabolites analyzed in plasma and urine by gas mass spectrometry. Plasma concentrations ranged between 1 and 2.5 μg/L for delta-9-tetrahydro-cannabinol (THC), between 1.7 and 2.5 μg/L for 11-hydroxy-THC, between 13 and 30 μg/L for 11-nor-9-carboxy-THC. Urine concentrations of 11-nor-9-carboxy-THC were 10 to 235 μg/L. The analysis of the chocolate mousse showed a concentration of THC of 50 μg/g. The investigation revealed that the colleague who organized the party wanted to give some "special taste" to the chocolate mousse. Conclusion: Cannabis poisoning may be suspected in the case of a non-voluntary collective poisoning with an anticholinergic syndrome and should be confirmed by the analysis in plasma and urine of cannabinol and its metabolites.

97 NATIONWIDE REGISTRATION OF INCIDENTS WITH ECSTASY IN THE NETHERLANDS

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Introduction: This study was performed to identify the content of Ecstasy (XTC) tablets, because from previous studies

it became clear that XTC tablets not only contain MDMA, but include a number of compounds. Before attributing effects to XTC, i.e. MDMA, it is necessary to know the composition of the "XTC" tablets and to evaluate concomitant drug abuse. This study is a registration of the extent, severity and circumstances of exposure of acute "XTC" intoxications for which hospitalization was considered necessary. Methods: From August 1997 until July 1998 every hospital in the Netherlands was asked to contact the National Poisons Control Centre (NPCC) immediately after a patient suspected of "XTC" use was admitted. The treating physician was asked to take blood and urine samples for analysis. A clinical investigator of the NPCC made a bed-side visit to obtain informed consent and to evaluate the exposure. The clinical phenomena as well as blood and urine samples of patients suspected of having used "XTC" were analyzed. This drug screening made it possible to relate the symptoms to the substances that were really used by each patient. Sometimes spare tablets were available and also sent to the laboratory for drugs screening. Results: Fifty Patients were included in the study, 36 men and 14 women, mean age 24. Most patients mentioned having used one or more substances besides "XTC." Eighty per cent had a mild clinical picture with symptoms like agitation, restlessness, mydriasis, nausea, sweating and tachycardia. Twenty per cent had serious symptoms: hypo- or hypertension, convulsions or coma. One patient died. The blood and urine analyses confirmed that most patients used several drugs (such as cocaine, gamma-hydroxy-butyric-acid (GHB), cannabis or alcohol) besides "XTC." Moreover, by comparing the blood and urine results with the reported intake, it became obvious that the composition of the tablets sold as "XTC" varied widely. In this study 17 different substances were found such as: MDA, MDMA, amphetamine, 2-CB, MDDM, 2-CT-2 and ephedrine. Clinical severity was not different between the mono MDMA and MDEA intoxications and the rest of the study population, with the exception of GHB. Conclusions: The population of "XTC" users seen in this study is actually a population of poly-drug users. Moreover "XTC" tablets contain many different substances. In this group of poly-drug users an important point of concern is the fact that after the intake of "XTC" tablets together with other substances of abuse it is unpredictable which kind of effect can be expected.

98 ACCIDENTS CAUSED BY *PHONEUTRIA* (ARMED SPIDER)

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Background: The Brazilian Ministry of Health has reported about 2,850 accidents per year caused by venomous spiders, mainly by *Loxosceles spp* (57%) and *Phoneutria spp* (42%). Regarding this high frequency, few studies have reported clinical aspects and the outcome of the accidents caused by armed spiders. Patients and Methods: From January 1984 to December 1996, 422 patients (ages 9 months–99 years, median 29 years) were admitted after being stung by spiders which were brought and identified as *Phoneutria spp*. Most of the stings occurred on the body extremities (feet 40.9%, hands 34.3%), inside houses (54.5%), during the day (76.5%), and during the months of March and April (29.2%). The severity of envenoming was classified according to the recommendations of the Brazilian Ministry of Health. On admission to hospital, most of the patients presented with only local complaints, mainly pain (92.1%) and edema (33.1%) and were classified as presenting mild (89.8%), moderate (8.5%) and severe (0.5%) envenoming. Only a few patients (1.2%) did not present signs of envenoming. Severe accidents were confirmed in only two children (9 months, 3 years). Both developed acute pulmonary edema, and the older died 6 h after the accident. Moderate envenoming was significantly more frequent in patients older than 70 years than those aged 10–70 years old ($p < 0.05$, chi-square). Procedures to relieve local pain were performed frequently (local anesthesia 45.7%, oral analgesics 32.7%). Only 2.3% of the patients (two cases classified as severe and eight as moderate, eight of them in children) were treated with undiluted antiarachnid antivenom (5–10 vials, 1 vial = 5 mL, Fab'_2, I. Butantan, São Paulo- Brazil), infused IV over 5–20 minutes. No antivenom early reactions were observed. Conclusions: We conclude that severe accidents caused by *Phoneutria spp* spiders are uncommon. However, children and older patients should be considered as risk groups after being stung by these spiders.

99 MUSCARINIC SYNDROME AFTER MUSHROOM INGESTION (GENUS *INOCYBE* AND *CLITOCYBE*), EXPERIENCE OF THE MARSEILLES POISON CENTRE

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Objective: Mushroom poisonings are frequent in southern France where wild fungi have a great place in the provençal recipes. Muscarinic syndromes are observed after ingestion of small species with gills (some *Inocybe* or *Clitocybe*

species which contain muscarine). In order to evaluate the importance of these poisonings, the authors researched the muscarinic mushroom syndromes collected by the Marseilles Poison Centre between 1973 and 1998. Case series: 248 incidents were studied, involving 483 patients (41 children, 1 to 8 patients by case). Muscarinic syndrome is common during some years (20 cases in 1991) and rarer in other years (no case in 1978), because the responsible species need mild weather to grow. It is possible to observe cases during the whole year, but 87% of the poisonings were collected during the fall (50% in October). Patients frequently misidentified edible fungi with a similar aspect like *Tricholoma terreum* (29% of the mistakes), *Tricholoma geogii* and *Marasme oreades* (22% for both species called in French "mousserons"). For 23% of the cases, the patients ingested *Inocybe* when they thought they ate mushrooms with a very different aspect (*Boletus sp.*, *Lactarius sp.*); showing they were not able to recognize toxic species. For the last 26%, the patients ate wild mushrooms without any identification! The average delay between the meal and the beginning of the symptoms was about 2 hours. The first signs were digestive troubles (vomiting for 70% of the patients, diarrhea 62%), quickly followed by cholinergic symptoms (perspiration 96%, hypersalivation 36%, myosis 25%, shivering 22%, bradycardia 20%). All patients needed medical management, and 58% of them went to hospital where 24% received atropine and 21% activated charcoal. Two cases were characterized by the severity of the clinical features: Case 1: a 58-year-old man with a previous history of gastrectomy presented in cardio-respiratory arrest due to bronchorrhea and bronchospasm; Case 2: a 70-year-old woman treated with digoxin presented in vascular shock with hypotension and bradycardia. Both patients were managed in the intensive care unit. The 483 patients recovered, and the average duration of the signs was 13 hours for the whole series (2 to 180 hours), and did not change if atropine or activated charcoal were used; but these treatments must be employed to improve the comfort of the suffering patients. Conclusion: As muscarinic mushroom poisonings are less dangerous than amatoxin poisonings, this frequent kind of intoxication is not often described in the literature. The Marseilles Poison Centre series shows that the severity and the cost of such a pathology must not be underestimated.

100 LETHAL POISONING AFTER INGESTION OF A TEA PREPARED FROM THE ANGEL'S TRUMPET (DATURA SUAVEOLENS)

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Objective: Angel's trumpet (*Datura suaveolens*) is a plant that grows naturally in South and Middle America, but is also found as an ornamental plant in the United States and in Europe. It contains the tropane alkaloids atropine, scopolamine and hyoscyamine. The use of Angel's trumpet as a hallucinogen goes back to the precolumbian time. In the last few years, however, reports of its abuse as a hallucinogen have increased in the United States as well as in Europe. Here we report cases with Angel's trumpet poisoning reported to the STIC since 1993, including a group poisoning with a lethal outcome in the city of Zurich during the summer of 1998. Case series: The STIC had registered an increasing number of cases with Angel's trumpet abuse since 1993 (1993, 6 cases; 1994, 9 cases; 1995, 19 cases; 1996, 26 cases; 1997, 29 cases; 1998, 67 cases). Until 1998 no severe anticholinergic intoxications occurred. However, on July 23, 1998, a group of eight adolescents consumed a "magic drink" prepared from the Angel's trumpet. Subsequently all 8 patients became agitated and developed tachycardia. Three patients experienced severe hallucinations. One 20-year-old woman, who was under substitution therapy with methadone, was found comatose 1–2 hours after Angel's trumpet intoxication. She developed tonic-clonic seizures that were treated with midazolam. All patients had to be hospitalized and received primary care treatment including physostigmine application in two cases. While 7 patients completely recovered from their anticholinergic poisoning within 24 hours, the 20-year-old woman developed rapidly central hyperthermia of 42.9°C. The pulse rate increased to above 200/min and the blood pressure decreased to 70/30 mm Hg. Finally, the patient developed ventricular tachycardia and fibrillation. Despite massive external cooling, fluid and electrolyte replacements, administration of physostigmine and vasopressors and cardiodefibrillation the woman finally died approximately 4 hours after ingestion of the Angel's trumpet extract. Conclusions: The data demonstrate that intoxications with "magic drinks" prepared from extracts of the Angel's trumpet are an increasing clinical toxicological problem in Switzerland. Most importantly, severe Angel's trumpet poisoning resulted in a lethal anticholinergic intoxication in one patient. The exact cause of death remains unknown. It is possible that the patient ingested other drugs (to be determined) and/or experienced an idiosyncratic hypersensitivity against the natural tropane alkaloids of the Angel's trumpet.

101 ECBALIUM ELATERIUM—MEDICINE OR POISON?

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Backround: *Ecbalium elaterium* is a plant endemic to the Mediterranean basin. Its cucumber-shaped fruit has been used in folk medicine since antiquity. Cathartic, analgesic and mainly anti-inflammatory activities have been attributed to the fruit juice. Biochemical analysis of the plant extracts revealed mixtures of alkaloids containing triterpenes and elaterins. The active anti-inflammatory principle is believed to be cucurbitacin B, a triterpene derivative. We observed 5 patients who were exposed to the juice; four of these patients required treatment for acute symptoms of poisoning. Case histories: Out of the 5 patients in our series, four received the juice in its natural form, either intranasally or by ingestion, allegedly for the treatment of sinusitis or liver cirrhosis. This caused irritation of the buccal and respiratory mucosa accompanied by sore throat, drooling, dysphagia, edema and dyspnea of varying degrees of severity that appeared within minutes of exposure. The patients' condition deteriorated over the next several hours. Following treatment with antihistamines, corticosteroids, $beta_2$ agonists and oxygen, all four recovered without complications within 24 hours of the exposure. The fifth patient, aged 20 months, was unintentionally exposed to the juice dermally and remained asymptomatic. Conclusion: In folk medicine *Ecbalium elaterium* juice is commonly used in the diluted form. Nasal aspiration, inhalation and ingestion of the undiluted juice, as in our patients, may result in symptoms leading to upper airway obstruction. Close observation and supportive treatment are warranted. Our small series supports the statement that 'medicinal' plants can be toxic if improperly used and that herbal preparations should be subjected to the same scrutiny and rigorous testing as any other material intended for clinical use.

102 GRAPEFRUIT SEED EXTRACT—CASE REPORTS

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Objective: In Sweden there are at least three products—drops or capsules—containing grapefruit seed extract. They are sold as ''natural products'' in health stores, by mail-order or via the Internet (Citroseed, Citrosept and BioCitrine). The manufacturers claim that these products can be used to strengthen the immune system and therefore these products should by definition be pharmaceutical preparations. None of the manufacturers has registered their products at the Medical Products Agency in Sweden. In four cases, reported to the Swedish Poisons Information Centre, serious side effects developed. Case reports: Four cases of mucous membrane lesions in mouth or esophagus were reported to the Swedish Poisons Information Centre during 1998. Two women took one capsule Citrosept each and after 20 minutes and 3 hours respectively both experienced accelerating pain. One had a sensation of esophagospasm and the other felt nauseated and vomited. Both went to hospital and esophagitis was diagnosed. In two other cases a man and a woman used drops of Citroseed or Citrosept. The man administered two drops of Citrosept on an aching tooth and thereafter he immediately rinsed his mouth with water several times and went to bed. He soon woke up because of pain in his mouth. Within two hours he had a burning sensation in his tongue, pain and abundant salivation. He experienced speaking difficulties because of a swollen tongue. The mucous membranes abraded under and at the edge of his tongue. He did not see a doctor. The woman put 5 to 7 drops of Citroseed in her mouth, drank water and rinsed her mouth for some minutes. A few hours later her tongue was white and swollen and aching. She went to hospital. Her whole mouth was abraded and she had difficulty speaking. She had severe pain in her mouth. It was difficult for her to eat for one week. Pain under the tongue remained for two weeks. Conclusion: The Medical Products Agency in Sweden has now prohibited products with grapefruit seed extracts to be sold as pharmaceutical preparations. People using these products should be informed about the risk of developing mucous membrane lesions. The Citroseed and Citrosept drops should not be used in concentrated form.

103 A SUCCESSFUL INTRODUCTION OF ''MAGIC MUSHROOMS'' ON THE SWEDISH MARKET THROUGH THE INTERNET

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Objective: Over the last two years the number of questions to the Swedish Poisons Centre concerning ''magic mushrooms'' have shown a rising trend. A study to elucidate this phenomenon was therefore carried out. The mushrooms in question, Psilocybe and Panaeolus species contain the hallucinogenic substances psilocin and psilocybin. Psilocin and psilocybin have effects similar to those of LSD and have likewise a chemical structure closely related to serotonin. Another quite recently isolated substance, phenylethylamine, in *Psilocybe semilanceata* (Libery Cap) may contribute to the unpleasant reactions of Psilocybe mushroom intake. Methods: During a period of four months, June to September

1998, 40 inquiries concerning magic mushrooms were received and 21 of them could be followed up with a specially designed inquiry form. Information concerning place of purchase, the dose ingested, earlier experience of the drug etc. were noted. In cases where the Poisons Centre was consulted by a hospital, case reports were requested. Data from these reports together with data from case reports that were sent spontaneously to the Poisons Centre during 1998 were analyzed. Results: The users were mainly young men between 15 and 25 years. Half of them were "first-time users," a few had tried magic mushrooms once or twice before, the most experienced consumer ingested it for the 6th time. Most of these young men bought their mushrooms through the Internet, only four had gathered them in e.g. parks. The amount ingested varied considerably (1–12 g) but the average dose was 2 to 4 g dried weight. The mushroom intake often took place together with friends and often in combination with alcohol or other drugs. Signs of incipient addiction to drugs in general and social problems were often present. Only a few of the users were established drug addicts. Two persons experienced "flash-backs" 1–3 weeks after the ingestion and were therefore treated in hospital. A total of 15 case reports on hospitalized patients were sent to the centre. The most dominating symptoms were unpleasant hallucinations and anxiety. These symptoms were also the main reasons for seeking medical attention. Some patients showed violent behavior and in two cases police assistance was necessary. Conclusion: Intoxications with hallucinogenic mushrooms have increased in Sweden. Obviously, the main reason is the accessibility through the Internet. The influence of the legislation has, so far, been moderate. The somatic symptoms related to the use of these mushrooms seem to be mild. However, there is a risk of physical injury related to uncontrolled behavior during the acute stage of poisoning. Later "flash-backs" may lead to complications of a psychiatric nature.

104 SEVERE INTOXICATION WITH ACONITUM

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Background: The ingestion of rootstocks of Aconitum may cause severe life-threatening intoxications. The notable features of these intoxications are severe cardiac arrhythmias often refractory to standard treatment with antiarrhythmic agents. Case Report: A 35-year-old man ingested 3–4 rootstocks of *Aconitum napellus*. His initial symptoms were paresthesiae in his mouth, his hands and his feet, nausea and generalized weakness. The first ECG on admission revealed a sinus rhythm without any pathological alterations. About 4 hours after the Aconitum intake the patient developed frequent polymorphic ventricular ectopic beats followed by non-sustained polymorphic ventricular tachycardia and hypotension with a systolic blood pressure of 60 mm Hg. The Q-T interval was prolonged and had a Q-Tc value of 0.46 seconds. Treatment with 100 mg lidocaine was without any beneficial effect. After contact with our poison control centre we suggested the diagnosis of acquired long QT syndrome with torsade de pointes and recommended treatment with magnesium. The patient received 13.5 mmol magnesium as a bolus followed by an infusion of magnesium at a rate of 22.5 mmol/day. After the bolus of magnesium the arrhythmia disappeared completely and normal sinus rhythm was established. The magnesium infusion was continued for 24 hours. During this period and after the magnesium infusion was stopped no more arrhythmias occurred and the further course was uneventful. Five days after the intake of Aconitum the patient was discharged to a psychiatric facility. Discussion: *Aconitum napellus* contains aconitine which is a highly potent cardiotoxin. The fatal dose of aconitine in humans is reported to be 2 mg. The cardiotoxic effect is related to the binding of aconitine to a receptor within the sodium channel resulting in impaired closure of the sodium channel. This delays repolarization of the myocardial action potential and leads to Q-T prolongation and torsade de pointes. The treatment of choice for torsade de pointes includes cardioversion, magnesium infusion and increasing the heart rate by drug administration (isoprenaline, atropine) or rapid cardiac pacing with rates of 100 to 120 beats per minute. Conclusion: Aconitum related cardiotoxicity may be due to aconitine induced long Q-T syndrome and torsade de pointes and can be treated successfully by intravenous administration of magnesium.

105 A RETROSPECTIVE REVIEW OF CONTINUOUS QUALITY IMPROVEMENT AT THE ILLINOIS POISON CENTER

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Objective: To assess over six months the improvement in the documentation of cases and clinical recommendations following the implementation of a Continuous Quality Improvement (CQI) chart review via the DOTLAB® on-line data collection system. Methods: A randomized chart review process was initiated on a weekly basis for six months beginning in June 1998. In addition, all hospital based major effect calls were reviewed on a mandatory basis. In

December, a retrospective review of the number of CQI comments was performed. The Illinois Poison Center (IPC) uses the DOTLAB® computer system to record the case history including any reported physical exam findings and laboratory or radiological data and to document the recommendations made by IPC staff. The IPC medical director and a senior CSPI randomly reviewed 3% of all human exposure calls plus all hospital cases on a weekly basis. The DOTLAB® computer system also blinded the reviewers to the identity of the poison information specialists. After CQI was performed, copies of the charts were given to the participants involved. Copies were also placed in a folder in the poison center with educational comments for review by the entire staff. Each month from June to November was evaluated in terms of number of calls reviewed, number of calls deemed satisfactory by the reviewers, number with incomplete documentation, number with insufficient follow up and/or number with inappropriate management. Results: A total of 656 cases were reviewed. Nineteen cases had incomplete documentation, 15 cases had insufficient follow-up, 5 had inappropriate managements, and 2 required but did not receive immediate medical director review. The initial month of June had a 13% error rate (error rate is the total number of comments divided by the total number of calls), the months of July-Oct had a 6% error rate, and the month of November had a 3% error rate. There were no episodes of inappropriate management or failure to notify the medical toxicologist on call for seriously ill cases during the last three months surveyed. Conclusion: There was a definite improvement in the quality of our case management since implementing the CQI program. The improvements in quality were probably due to: (1) the more thorough and consistent CQI effort, (2) the timely notification of the poison information specialists of documentation problems, and (3) an increased awareness of all IPC staff of the common errors. The IPC administration believes the CQI program had a positive effect on case management and plans to continue the program indefinitely.

106 SHORT TERM THIONYL CHLORIDE EXPOSURE CAUSING DELAYED AIRWAY OBSTRUCTION

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Introduction: Thionyl chloride ($SOCl_2$) is a pale yellow liquid with suffocating odor. It is a common chlorating agent in laboratory use and essential for the production of lithium batteries. Only few cases have been reported on lung diseases following thionyl chloride (TCL) inhalation. In these cases pulmonary edema with short onset was observed. In one case a form of bronchiolitis obliterans was diagnosed. Case report: A 29-year-old healthy man with a smoking history of 20 cigarettes per day was admitted to our department after having inhaled TCL fumes during a laboratory accident. The accident occured when the patient added 100 mL of pure TCL to camphorsulphonacid without properly closing the reaction-vessel. The exposure caused skin burns and a burning sensation in the upper airways. He was treated by budenosid inhalation on the spot and during the first hours in hospital. Auscultation of the lungs remained normal and the patient was sent home the next day. The second day after the accident he returned to our hospital complaining of chest tightness and wheezing. Lung auscultation showed marked bronchospasm and his peak flow rate was reduced to 250 L/min (normal $>$ 400 L/min). Chest radiograph was without pathology. Lung function testing showed severe bronchoobstruction with no signs of restriction. Arterial blood gas examination exhibited a moderate hypoxemia. He was treated with 250 mg prednisolon IV, budenosid inhaler, fenoterol inhaler and theophyllin (2 $\times$ 350 mg orally). After three days glucocorticoids were reduced to 50 mg prednisolon orally. Within one week his lung function improved (PEF rate 440 L/min). Three weeks later after cessation of the theophyllin medication PEF rate deteriorated again which forced us to take up theophyllin medication again! After 6 weeks he was taken off all medication and he had recovered completely with a normal PEF of 460 L/min. Conclusion: To our knowledge bronchospasm with no signs of restriction represents a previously unreported complication of TCL inhalation. The potential danger of TCL inhalation lies within the lag period after which complications such as bronchoobstruction can develop. Therefore patients with TCL exposure should be kept under observation. Treatment with steroids and therapy with bronchodilators should be instituted.

107 LIVER TRANSPLANTATION (LTX) FOR GALERINA MARGINATA POISONING

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Introduction: *Galerina marginata* (marginate pholiota) is a mushroom with a dark cinnanon cap. It is 2 to 6 cm high and grows on rotten wood of conifers. It can be found till late in fall. It is easily mixed with a popular mushroom

(*Kuehneromyces mutabilis*) that grows on rotten wood of deciduous trees. *Galerina marginata* contains less amatoxins than Amanita virosa or *Amanita phalloides*, leading to milder forms of amanita poisoning. This is why we want to report on a case—probably the first case described—when after the ingestion of *Galerina marginata* liver transplant (LTX) had to be performed to save the patient. Case report: A 28-year-old female had, together with her friend, a mushroom meal (one pan full) at 20.00 h. The next morning at 6 o'clock she developed severe nausea, vomiting, diarrhea and headache. She went to her family doctor who identified the mushroom as a non-amanita species and sent the patient home on metoclopramide treatment. The symptoms did not improve and the patient went to the local hospital at 38 hours after the mushroom meal. There the transaminases were elevated around 300 U/L the bilirubin was 1.85 mg/dL and the thromboplastin-time was 50%. The patient was transferred to our department and arrived there 42 hours after the ingestion. The transaminases rose to over 1000 U/l, bilirubin went up to over 7 mg/dL. The thromboplastin time went down to 11%. Severe thrombocytopenia developed. Ammonia peaked at 166 µg/dL. The patient received late antidotal treatment with silibinin. Amatoxins in the urine were negative on admission to our department. Four days after the ingestion the patient developed Grade II encephalopathy. There was no improvement in the coagulation disorder and the bilirubin rose. The patient was put on high urgency for LTX on the fourth day after the ingestion and was successfully transplanted on day 6. Before the transplantation she had ascites, a pleural effusion and thrombocytopenia. Between day 5 and 6 human albumin dialysis was performed which improved the neurological state of the patient. Conclusion: This is the first report of such a severe amatoxin poisoning by the species of *Galerina marginata* that liver transplantation was needed. The criteria for LTX were the same as for other amanita poisoning: clotting disorder that didn't improve significantly after day 3, a rising bilirubin on day 5 and the onset of mild encephalopathy. Other signs of severity were thromocytopenia and the development of diffuse edema, ascites and a pleural effusion.