

DRO

Deakin University's Research Repository

This is the published version:

Dawson, Andrew H., Eddleston, Michael, Senarathna, Lalith, Mohamed, Fahim, Gawarammana, Indika, Bowe, Steven J., Manuweera, Gamini and Buckley, Nicholas A. 2010, Acute human lethal toxicity of agricultural pesticides: a prospective cohort study, *PLoS medicine*, vol. 7, no. 10, Article Number : e1000357, pp. 1-10.

Available from Deakin Research Online:

<http://hdl.handle.net/10536/DRO/DU:30074321>

Reproduced with the kind permission of the copyright owner.

Copyright : 2010, The Authors

Acute Human Lethal Toxicity of Agricultural Pesticides: A Prospective Cohort Study

Andrew H. Dawson^{1,2,3,9*}, Michael Eddleston^{1,4,5,9}, Lalith Senarathna¹, Fahim Mohamed¹, Indika Gawarammana¹, Steven J. Bowe², Gamini Manuweera⁶, Nicholas A. Buckley^{1,3}

1 South Asian Clinical Toxicology Research Collaboration, Faculty of Medicine, University of Peradeniya, Peradeniya, Sri Lanka, **2** School of Medicine and Public Health, University of Newcastle, Newcastle, Australia, **3** Professorial Medicine Unit, POW Clinical School, University of New South Wales, Sydney, Australia, **4** National Poisons Information Service - Edinburgh, Royal Infirmary of Edinburgh, Edinburgh, United Kingdom, **5** Clinical Pharmacology Unit, Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, United Kingdom, **6** Office of the Pesticide Registrar, Government Department of Agriculture, Peradeniya, Sri Lanka

Abstract

Background: Agricultural pesticide poisoning is a major public health problem in the developing world, killing at least 250,000–370,000 people each year. Targeted pesticide restrictions in Sri Lanka over the last 20 years have reduced pesticide deaths by 50% without decreasing agricultural output. However, regulatory decisions have thus far not been based on the human toxicity of formulated agricultural pesticides but on the surrogate of rat toxicity using pure unformulated pesticides. We aimed to determine the relative human toxicity of formulated agricultural pesticides to improve the effectiveness of regulatory policy.

Methods and Findings: We examined the case fatality of different agricultural pesticides in a prospective cohort of patients presenting with pesticide self-poisoning to two clinical trial centers from April 2002 to November 2008. Identification of the pesticide ingested was based on history or positive identification of the container. A single pesticide was ingested by 9,302 patients. A specific pesticide was identified in 7,461 patients; 1,841 ingested an unknown pesticide. In a subset of 808 patients, the history of ingestion was confirmed by laboratory analysis in 95% of patients. There was a large variation in case fatality between pesticides—from 0% to 42%. This marked variation in lethality was observed for compounds within the same chemical and/or WHO toxicity classification of pesticides and for those used for similar agricultural indications.

Conclusion: The human data provided toxicity rankings for some pesticides that contrasted strongly with the WHO toxicity classification based on rat toxicity. Basing regulation on human toxicity will make pesticide poisoning less hazardous, preventing hundreds of thousands of deaths globally without compromising agricultural needs. Ongoing monitoring of patterns of use and clinical toxicity for new pesticides is needed to identify highly toxic pesticides in a timely manner.

Please see later in the article for the Editors' Summary.

Citation: Dawson AH, Eddleston M, Senarathna L, Mohamed F, Gawarammana I, et al. (2010) Acute Human Lethal Toxicity of Agricultural Pesticides: A Prospective Cohort Study. PLoS Med 7(10): e1000357. doi:10.1371/journal.pmed.1000357

Academic Editor: Mervyn Singer, University College London, United Kingdom

Received: March 23, 2009; **Accepted:** September 15, 2010; **Published:** October 26, 2010

Copyright: © 2010 Dawson et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Funding: This study was supported by the South Asian Clinical Toxicology Research Collaboration, which is funded by the Wellcome Trust/National Health and Medical Research Council International Collaborative Research Grant GR071669MA. The study sponsor had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Competing Interests: ME has received financial support to attend a scientific meeting of a study funded by Syngenta. NAB and AHD have received travel expenses from Syngenta (a manufacturer of paraquat and some other pesticides) to attend meetings of a scientific advisory group in relation to studies of new paraquat formulations.

Abbreviations: CI, confidence interval; EPA, Environmental Protection Agency; FAO, Food and Agriculture Organization; IQR, interquartile range; OP, organophosphorus; OR, odds ratio; WHO, World Health Organization.

* E-mail: adawson@sactrc.org

⁹ These authors contributed equally to this work

Introduction

Suicide and deliberate self-harm using pesticides is a major but under-recognised public health problem in the developing world. Each year 250,000–370,000 thousand people die from deliberate ingestion of pesticides [1,2]. These deaths are responsible for about a third of suicides globally [1]; the World Health Organization (WHO) now recognizes pesticide poisoning to be the single most important means of suicide worldwide [3].

Within the rural developing world, high levels of pesticide use with storage at home increases the risk of acute poisoning [4]. One strategy to reduce mortality is to restrict access to more toxic pesticides [5]. As a first line, countries should follow Food and Agriculture Organization (FAO) advice [6] and withdraw the most toxic WHO/US Environmental Protection Agency (EPA) class I pesticides (see Table 1 for description of toxicity classifications) from agricultural practice. Further efforts can range from educating farmers in the use of safer pesticides to imposing regulatory restrictions on the sale and distribution of the most toxic class II pesticides [7,8]. These strategies would be aided if countries developed pesticide policies that balanced agricultural and economic needs against the public health impact of acute and chronic human toxicity [9]. The development of such a policy should be iterative and based on evidence about which pesticides are major public health concerns [1].

Unfortunately, at present, regulatory decisions are based on a classification of pesticide toxicity that is largely based upon rat oral LD₅₀s. The scientific basis for extrapolating this classification to human poisoning with class II pesticides is weak. Rodents handle xenobiotics differently to humans [10]; as an example, they have greater capacity for metabolic detoxification of organophosphates [11]. And unlike human patients receiving intensive care, they do not receive any treatment in the toxicity studies. It is therefore not clear that a pesticide with low toxicity in rodents should be safe in humans and vice versa.

Information on the acute human toxicity of a wide range of pesticides is needed to complement the animal toxicity data. We therefore set up a prospective cohort of intentional pesticide-poisoned patients admitted to two Sri Lankan hospitals to study the relative toxicity of formulated pesticides in humans. Sri Lanka is an ideal location for this research. Ahead of the FAO recommendations, it has banned all WHO/EPA class I pesticides leaving just class II and III pesticides in agricultural use. Other Asian countries are slowly following suit—within a few years class I pesticides will no longer be used. Therefore, the current situation

in Sri Lanka represents the future situation in other Asia countries. Furthermore, because only class II and III pesticides are used in Sri Lanka, the great majority of deaths from pesticide poisoning occur in the secondary referral study hospitals [12,13]. Bias from prehospital deaths is minimized.

Methods

Ethics Statement

Ethics approval for this data collection has been obtained from Oxfordshire Clinical Research Ethics Committee, Oxford Tropical Medicine Ethics Committee, Colombo University Faculty of Medicine Ethics Committee, Sri Lankan Medical Association, University of Peradeniya, and the Australian National University.

Patients

This was a prospective observational cohort study of patients aged greater than 12 y with deliberate ingestion of a single pesticide who presented to two Sri Lankan rural referral hospitals for an agricultural provincial district of 1.1 million people. The poison ingested was determined from the history given by the patient or relatives, the hospital transfer letter, or from the pesticide bottle if it accompanied the patient. Patients who deliberately ingested more than one substance (except for alcohol) were excluded from this study. Patients were either direct admissions to the study hospital or transfers from smaller primary hospitals. Patient recruitment commenced on 31 March 2002 in Anuradhapura Hospital and 4 June 2002 in Polonnaruwa Hospital. Details of the referring hospital name were documented from 1 June 2006. Data analysis was performed on all patients who had been enrolled up until 17 November 2008.

All patients were enrolled into the cohort at admission by full-time study doctors employed as clinical research assistants. Clinical care followed a standard protocol that emphasized identifying patients poisoned by pesticides that would likely respond to antidotes, in particular organophosphorus (OP) and carbamate insecticides [14]. All patients were seen regularly at least every 4 h. Significant events (intubation, seizures, death) were recorded prospectively. Patients were also seen on a study ward round twice each day and their condition over the previous 12 h recorded. Patients remained under the care of the hospital consultant physicians. Decisions about medical treatment, intubation, and transfer of patients to intensive care were made solely by the hospital staff on the basis of the patient's clinical condition, and independently of the research team.

Statistics

Case fatality was defined as the proportion of deaths over admissions for any given pesticide. Odds ratios (ORs) and the 95% confidence intervals (CIs) of the proportions were calculated using the binomial exact method [15]. The binomial exact method will generate a one-sided CI (97.5% CI) when the proportion of deaths over admissions for a given pesticide is zero.

Logistic regression was used to calculate unadjusted and adjusted (for age and gender) ORs for death relative to the pesticide most commonly ingested (chlorpyrifos).

The potential effect of recently implemented pesticide bans was examined assuming proportional redistribution based upon existing distribution of poisoning across the class after excluding patients who had taken unidentified pesticides. Sensitivity analyses were undertaken by assuming complete redistribution to the next most toxic substitute and to the least toxic substitute.

Table 1. WHO classification of toxicity [18].

Class	Description	LD ₅₀ for the Rat (mg/kg Body Weight)			
		Oral		Dermal	
		Solids	Liquids	Solids	Liquids
Ia	Extremely hazardous	≤5	≤20	≤10	≤40
Ib	Highly hazardous	5–50	20–200	10–100	40–400
II	Moderately hazardous	50–500	200–2,000	100–1,000	400–4,000
III	Slightly hazardous	>500	>2,000	>1,000	>4,000

doi:10.1371/journal.pmed.1000357.t001

