

# Reformulating Agricultural Organophosphorus Pesticides to Reduce Global Suicide Rates: a Göttingen Minipig Model

*Michael Eddleston,<sup>1,2</sup> Jonathan M Street,<sup>1</sup> Ian Self,<sup>3</sup> Adrian Thompson,<sup>1</sup> Tim King,<sup>5</sup> Nicola Williams,<sup>6</sup> Gregorio Naredo,<sup>7</sup> Kosala Dissanayake,<sup>1</sup> Franz Worek,<sup>8</sup> Harald John,<sup>8</sup> Sionagh Smith,<sup>3,4</sup> Horst Thiermann,<sup>8</sup> John B Harris,<sup>9</sup> and R Eddie Clutton.<sup>3</sup>*

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Organophosphorus (OP) insecticide self-poisoning is responsible for about one-quarter of global suicides. Treatment classically focuses on the fact that OP compounds inhibit the enzyme acetylcholinesterase, causing overstimulation of cholinergic receptors in central and autonomic nervous systems and in the neuromuscular junction. Poisoned patients die from respiratory failure. However, drugs that reactivate the acetylcholinesterase enzyme have been found to provide little benefit to OP-poisoned humans.

Part of the reason may be that humans ingest formulated 'emulsifiable concentrate' (EC) pesticides, containing solvents and surfactants as well as the OP active ingredient (AI), rather than pure OP AI. The authors of this paper therefore studied the role of solvent co-formulants in OP toxicity, developing a novel Göttingen minipig model of agricultural OP poisoning with the widely used insecticide dimethoate. This species was selected based on the similarity of its cardiorespiratory physiology and drug metabolism with humans and on its size, which allows collection of multiple blood samples and the use of human monitors.

Göttingen minipigs under terminal anaesthesia were orally poisoned with a clinically relevant dose of the agricultural EC formulation of dimethoate, the dimethoate active ingredient (AI) alone, the solvents cyclohexanone and xylene, or a control. The severity of poisoning was recorded by monitoring the heart, lung and nerve function and by measuring the poisons' effects in the blood.

Poisoning with agricultural dimethoate EC40, but not saline control, caused respiratory arrest within 30 minutes, very low blood pressure, and nerve dysfunction, that was highly similar to human poisoning. Mean arterial lactate concentration rose to 15.6 [1.1] in poisoned pigs compared to 1.4 [0.4] in control pigs. By contrast, only moderate toxicity resulted from poisoning with dimethoate AI alone or the major solvent cyclohexanone, compared to dimethoate EC40. Combining dimethoate AI with cyclohexanone reproduced

severe poisoning. These results indicated that the solvent co-formulant cyclohexanone was essential for full toxicity. This has not previously been considered.

The main manufacturer of dimethoate, Cheminova, then provided an experimental formulation of dimethoate EC that did not contain cyclohexanone. This showed markedly less mammalian toxicity in this model than the usual agricultural formulation.

These results indicate that solvents play a crucial role in dimethoate toxicity. If companies were to reformulate agricultural dimethoate and other toxic OP insecticides, they would probably be much less toxic to humans. Safer formulations of dimethoate and other OP insecticides should rapidly reduce global suicide numbers. Further studies are required to determine how to change the formulations to increase human safety while maintaining agricultural efficacy.

<sup>1</sup> Clinical Pharmacology Unit and <sup>7</sup> Endocrinology Unit, University/BHF Centre for Cardiovascular Science, <sup>3</sup> Department of Anaesthesia, and <sup>4</sup> Veterinary Pathology Unit, Royal (Dick) School of Veterinary Sciences, and <sup>5</sup> Roslin Institute, University of Edinburgh, UK <sup>2</sup> National Poisons Information Service - Edinburgh, Royal Infirmary, Edinburgh, UK <sup>6</sup> Centre for Statistics in Medicine, Wolfson College, University of Oxford, UK <sup>8</sup> Bundeswehr Institute of Pharmacology and Toxicology, Munich, Germany <sup>9</sup> Medical Toxicology Centre and Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, UK