

Human testing – industry lobbying may increase exposure

After pressure from industry the United States Environmental Protection Agency recently published new rules on human pesticide testing ending a moratorium on the use of such studies. Brian Hill reviews recent developments and considers their ethical implications.

Consider the following two examples of studies involving intentional dosing of human subjects:

(1) Researchers place the pesticide chlorpyrifos on people's skin. The amount absorbed through their skin is compared with the amount absorbed in studies placing chlorpyrifos on rats' skin¹.

(2) Volunteers on a college campus are paid to have predetermined concentrations of the fumigant methyl isothiocyanate (MITC) blown into their eyes. Subjective and objective thresholds for irritation are determined².

Is it ethical to conduct such studies? If so, what general principles should guide them?

General ethical principles

The Nuremberg 'Directives for Human Experimentation' codify ten principles for answering such ethical questions. It was created for the United States prosecution in the case against German physicians involved in human experimentation during World War II³.

Detailed requirements for informed consent are the first principle in the Nuremberg Code. The second principle is that the study results must be for the 'good of society, unprocurable by other methods or means.' The sixth principle strengthens the second by demanding that risk to human subjects can only be taken to solve

problems of 'humanitarian importance.' Other principles of the Nuremberg Code discuss protocols for conducting experiments, and conditions under which the experiments must be terminated.

Two questions raised then are whether refining regulatory limits for pesticides is a problem of humanitarian importance, and whether progress is unprocurable by other means.

Uncertainty factors

Traditionally, regulatory limits for pesticides have been set to limit toxicity to humans and the environment. The toxicity effects in humans are estimated from tests in laboratory animals, on epidemiological studies of the effects of occupational exposure, on mathematical modeling of exposure, and on other techniques.

Regulators use measurements of toxicity in laboratory animals to estimate toxicity in humans. Gross physical differences (for example, in body weight and respiratory rate) are commonly incorporated into such extrapolations. However, unknown differences in the metabolism of animals and humans, and even between different people, make precise extrapolations impossible. Therefore, regulators apply 'uncertainty factors' when estimating the maximum levels of pesticides that people can be exposed to without harm. The amount of a pesticide which causes no observed effect in a laboratory animal is often divided by ten to set the upper level of exposure allowed in humans.

The use of human subjects could refine extrapolations from animal data potentially eliminating the need for the 10-fold safety factor and allowing less protective limits to be set. But are such studies ethical?

A new era of human testing

Intentional dosing of human subjects with pesticides has been carried out by agrochemical companies for decades. However, the consideration of such studies has been infrequent and controversial. In 1998 the United States Environmental Protection Agency (US EPA) expressed concern that pesticide manufacturers were engaging in human studies to avoid the more protective limits established by animal studies. They

placed a moratorium on the use of such data.

In February of 2006, under the Administration of United States President George W. Bush, the US EPA ended this moratorium, by publishing rules⁴ for such testing⁵. These rules now allow studies like those described in the first section of this article and were effective from 7 April, 2006.

Since the US EPA cites and claims compliance with the Nuremberg Code, the Bush Administration is in effect saying that refining regulatory standards for pesticides is a problem of humanitarian importance. Although the rules only apply to pesticides, from this logic it presumably follows that the Bush Administration believes that refinement of essentially any health or safety standard is a problem of humanitarian importance, and that it would be acceptable to take deliberate risks with human subjects to measure any factor related to the harmful effects the health or safety standard is designed to prevent.

The US EPA human testing rule included provisions for a Human Studies Review Board (HSRB) to review both proposed and completed human studies. Their first several months of work involves reviewing the backlog of already completed studies that were submitted during the moratorium on consideration of human studies.

The use of human subjects could refine extrapolations from animal data potentially eliminating the need for the 10-fold safety factor and allowing less protective limits to be set.

Jennifer Sass, Senior Scientist at the Natural Resource Defense Council (NRDC) and Shelley Davis, Deputy Director at the Farmworker Justice Fund (FJF), both based in Washington DC, are the only representatives from the public interest community. While they have argued against use of most of the studies that have been reviewed by the HSRB, so far most of the completed studies that the board has considered have in fact been approved.

The standard for approval of all studies conducted prior to April 2006 unfortunately places the burden of proof on the HSRB to demonstrate 'clear and convincing evidence that the conduct of the research was fundamentally unethical,' for example, if 'the research was intended to seriously harm participants.' However, even this remarkably low ethical bar is almost impossible to verify, since evidence of fundamental flaws can only rarely be garnered from the sparse and inadequate documentation that accompanies each study. Fortunately, the rule is much stronger for approval of new studies.

The UK situation

The European Union's European Chemical Bureau procedures currently do not describe intentional dosing of human subjects as a method for determining human toxicity of pesticides and so do not place any requirement on registrants to produce human testing data⁶. However, human testing results may be considered if available. For example, the UK's Pesticides Safety Directorate will accept studies on human volunteers provided that they are conducted according to ethical safeguards designed to ensure that the volunteers are at minimal risk and are aware of any risk involved⁶. A number of these studies have been carried out at the Inveresk Clinical Laboratory in Edinburgh, Scotland.

The death of strychnine

The EU withdrawal of strychnine marks its end as a method of mole control. While this has got to be applauded there is no guarantee that the main alternative, lethal traps, will be more humane. **Chris Davies** examines the issues and calls on ministers to review laws and draw up new guidance and training.

Few of us will ever see a mole yet many will see the small mounds of earth left as these elusive animals tunnel under the ground catching worms and insects. Some find mole hills unsightly. Others find the tunnels they create damaging to their land and go to great lengths to stop moles. Moles living on grassland such as golf courses or horse gallops are a particular target.

Up to now professional pest controllers have been able to apply for government licences to use strychnine to control moles with 3,000 users currently licensed. But while strychnine is effective it causes a slow and agonizing death, and potentially

puts other animals at risk.

However, change is afoot. European Union (EU) directive 91/414/EEC is midway through an ambitious programme to review all pesticides used within Member States. This requires manufacturers to provide health and safety data to support the continued registration of their products. Strychnine was to be reviewed in the fourth part ('fourth review programme') of this programme but manufacturers have failed to provide such data. Despite last ditch appeals by users, from 1 September 2006 it will no longer be legal to use.

While an end to the use of strychnine is

(continued from page 6)

Good news for manufacturers

The US EPA does not require that tests on human subjects be conducted when registering a pesticide. Rather, the rule simply allows the agency to consider studies involving intentional dosing. Most studies done to register a new pesticide are performed or sponsored by the registrant (generally the manufacturer) and registrants generally consider the 'uncertainty factor', applied when extrapolating from animals to humans, to be unnecessarily protective. By performing experiments on humans and submitting them to the USEPA, registrants hope to reduce or eliminate this factor. This would increase the amount considered 'safe' for humans and higher pesticide use rates would be allowed.

Responses

Most people are surprised that under many circumstances intentional human dosing studies are now considered ethical by the US EPA. The Pesticide Action Network, in concert with other environmental health and justice organisations is responding to the new rules in multiple ways. One way is to expose the problems with the US EPA's ethical guidelines when they were being prepared. Now that the rules have been finalized by the Bush administration, there is a judicial review underway. Significant loopholes have been identified⁶.

A complementary approach is to strengthen ethical guidelines used by other regulatory agencies. For example, in the State of California, there is a regulatory process that is independent of the US EPA (this is not the case for most US states). PAN North America is a co-sponsor of legislation designed to prevent intentional dosing involving people from being used in

California's regulatory process.

Ultimately, testing pesticides on people will come to haunt pesticide manufacturers as a public relations problem, much as deliberate attempts to market cigarettes to children now haunts cigarette manufacturers. We can do everyone involved a favour by pursuing all possible mechanisms for strengthening ethical standards for pesticide testing.

References

1. Ross JH, Driver CH, Cochran RC, Thongsinthasak T, Krieger RI, *Could Pesticide Toxicology Studies be More Relevant to Occupational Risk Assessment?*, *Annals of Occupational Hygiene*, 45, S5-S17, 2001, http://annhyg.oxfordjournals.org/cgi/reprint/45/suppl_1/S5.pdf
2. US EPA Data Evaluation Record, TXR#0051475, www.epa.gov/osa/hsrb/files/mitc_der.pdf
3. *Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10*, Vol. 2, pp. 181-182. Washington, D.C.: U.S. Government Printing Office, 1949, www.nihtraining.com/ohsr/site/guidelines/nuremberg.html
4. US EPA, *Protections for Subjects in Human Research*, www.epa.gov/oppfead1/guidance/human-studies-finalrule.pdf
5. The Bush Administration's announcement of the guidelines highlighted that they were banning consideration of studies involving intentional dosing of pregnant women and children (this aspect of the guideline was specifically required by amendments to budgetary legislation passed in August, 2005).
6. PAN North America, *Groups Sue EPA for Approving Unethical and Illegal Human Pesticide Testing*, 23 February 2006, www.panna.org/resources/newsroom/humanTestingSuit20060223.dv.html
7. European Chemicals Bureau, *Toxicology and Chemical Substances, Annex V (5), Part B, Methods for the determination of toxicity*, <http://ecb.jrc.it/testing-methods/>
8. Letter from Caroline Kennedy, Pesticides Safety Directorate, 25 May 2005.

Brian R. Hill, PhD, Staff Scientist, PAN North America; bhill@panna.org



Chris Davies examining mole hills

Photo: Avril Manderson

welcome one serious concern remains. The main alternatives to poisoning are 'kill traps'. Although well-designed and properly-used traps cause much less suffering than strychnine, many mole-catchers fear an increase in the use of poor quality traps by untrained operators: badly made traps can maim, leaving the mole to slowly bleed to death. If traps are to take over from strychnine the government should ensure they are humane and used by trained catchers.

At present regulations for mole traps are limited. The withdrawal of strychnine should be used as an opportunity to implement new training and guidance that is urgently needed to guarantee humane mole control. The Minister for Rural Affairs should review the laws regulating trapping. A first step towards better practices would be to classify moles as mammals and not vermin. Under current law this would require traps to be checked every 24 hours.

The EU Health Commissioner Markos Kyprianou has refuted claims by some mole-catchers that moles may be a threat to health and says the Commission is not aware of any scientific evidence indicating that the presence of moles in soil poses specific health risks for other animals or humans. In some European countries moles are a protected species.

Moles can actually be gardeners' friends: they eat slugs and many harmful insect larvae such as cockchafer and carrotfly. Their tunnels also help to drain and aerate heavy soils and the fine soil of mole-hills was traditionally for potting compost. Landowners should think twice about extermination. Moles need to be controlled where their presence poses a danger to safety, for example on airstrips or horse gallops. But it is time to realise we cannot simply exterminate a creature because it pushes up a few daisies.

Chris Davies, Liberal Democrat MEP for North West England