

Animal Aid
mad science
Awards
2002



'Safety' Tests - *A Danger to Human Health*



'Safety' testing on animals is the theme of Animal Aid's 2002 Mad Science Awards. As in previous years, the winning research teams stand charged with conducting demonstrably pointless and grotesque experiments on animals.



Introduction

Some 443,000 animals were used in British laboratories for 'safety' tests in 2001 - thereby accounting for nearly a fifth of all animals consumed.

The tests are supposed to assess the safety of new products for consumers. Such products include insecticides (experiment 11), herbicides (exp. 3), plasticisers (exps 5 and 9) and other industrial materials (exp. 6), food components (exps 8 and 10) and, of course, pharmaceuticals.

Toxicity tests usually involve force-feeding animals by gavage (a long tube pushed right down to the stomach – a very unpleasant experience) or injection, or both. In other 'procedures' the animals are forced to inhale vapour by sealing them in an inhalation chamber, as in experiment 6. Various doses are tried out, in order to find the highest level that can be used without poisoning the animals. This dose is known as the 'No Adverse Effect Level' (NOAEL). Higher doses (often thousands of times more than any conceivable human exposure) are also given so as to establish what the poisonous effects would be. They include vomiting, haemorrhage, tremor, weight loss, liver damage and tumours.

Apart from the suffering involved, these tests are scientifically worthless and have long been recognised as such even by many in the industry. A former Director of (then) Huntingdon Research Centre pointed out that animal studies predict drug side-effects for people only 5-25% of the time!¹ This means we would get better predictions by tossing a coin – the same conclusion reached by pharmaceuticals giant Pfizer 20 years ago.² It is acknowledged by



experts that it is not even possible to predict carcinogenicity in mice using data from rats – and that wildly different results are produced by different strains of rat or mouse, or even by different labs conducting identical tests on identical strains.³

The consequences are obvious. Hazardous chemicals are being passed as 'safe' on the basis of tests on animals, thereby giving consumers a false sense of security and causing them to be exposed to dangerous substances without due protection. Two glaring examples of this are cigarette smoke and cholesterol – neither of which is bad for people, according to animal tests! In fact, French scientific organisation, Pro Anima, estimates that one million EU citizens die prematurely every year because of toxins in their food or environment, which have been passed as safe by animal tests.⁴

There are many reasons why animal tests are so deficient when it comes to predicting the impact of chemicals on people. One is that conditions such as cancer, certain allergies and neurological disorders take years of exposure before they emerge, making the initial cause very difficult to identify. It is clearly impossible to assess these effects in animals, as their life span is so much shorter than our own. Toxicologists try to mitigate this by using enormous doses, but that is a serious error. Even water will kill in doses of thousands of litres, though one litre is evidently beneficial. But even if they lived as long as us, animals are genetically and biochemically different – they absorb, metabolise and excrete chemicals differently and, therefore, cannot predict how a chemical will affect people. Yet this is the very basis of animal use in toxicity tests!

Ralph Heywood, former Director of Huntingdon Research Centre, says the concept was developed in the late 1950s, and was flawed even then.⁵ Christopher Portier, director of the Environmental Toxicology Program at the US National Institute of Environmental Health Sciences, adds that modern 'biologically-based' concepts are more accurate, though researchers will have to convince regulatory agencies, like the US Food and Drug Administration (FDA), to accept the analyses in lieu of animal data.⁶ The FDA has at least one reason to favour his suggestion, Portier says. While animal-based bioassays take a minimum of five years and several million dollars, databases promise a quick, inexpensive way to screen carcinogens. More than a decade ago, the editor of Science magazine commented: 'Carcinogen tests that use rodents are an obsolescent relic of the ignorance of past decades'⁷ – yet still the government requires them.

Unsurprisingly, when pressed to make a scientific case for the tests, not even the Department of Health can muster a plausible body of evidence. The House of Lords Select Committee has just completed its inquiry into Animals in Scientific Procedures. As part of its evidence-gathering, the committee asked the DoH to provide published scientific papers that support the validity of toxicity tests on animals. Nine of the papers they came up with actually make a better case against the validity of animal toxicology than for it! (*For a full analysis see www.vernoncoleman.com*)

One of the papers⁸ actually lists several reasons why data obtained from animals is usually not predictive of human effects. One difficulty is that 'the life span of humans is from 4.4 to 66 times that of common test species. Thus, there is generally a much longer time available for many toxicities to be expressed or developed in people than in test animals.' A second paper⁹ describes

an experiment in which, 'The doses necessary to cause the hepatic [liver] effects in rats were therefore approximately 2000-fold those that produced similar toxicity in human patients'. The same author goes on to note '...adverse effects of drugs in humans, not easily predicted by animal studies, include nausea, headache, dizziness, tinnitus, vision disturbances and hypersensitivity and skin reactions'. Yet these are the very symptoms most commonly experienced as side effects.

Another¹⁰ notes – devastatingly – that, 'Two reviews addressed those drug cases where the clinical (human) toxicity was so severe as to lead to withdrawal from marketing in the approximate period 1960 – 1990...In one report only 4 of 24 cases were predictable from animal data; in the other report, only 6 of 114 clinical toxicities had animal correlates'. No wonder that adverse drug reactions are now the fourth leading cause of death in the west, behind only heart disease, cancer and stroke!¹¹



Testing the safety of new pharmaceuticals accounted for 61 % of all toxicity tests on animals in the UK during 2001 – or 277,000 animals. Regulators require testing in one rodent species and one non-rodent 'second' species -

which has usually been dogs or macaque monkeys. Over the past few years, however, there has been an increasing trend to use marmosets. An enlightening paper¹² published last year by the Association of the British Pharmaceutical Industry (ABPI) explains the reasons why.

The authors make a valiant attempt to pretend that the choice of marmosets is rooted in science, but it is abundantly clear that the real reasons are considerations of cost, practicality and minimum inconvenience for researchers. Marmosets weigh around 400g and are thus comparatively cheap to dose with valuable test compounds. Their small size also makes them easy to incarcerate in small metabolism cages or in inhalation chambers.

There is the added attraction of quite a long life span (though short by human standards). This means that they can be used in chronic toxicity studies – up to 7 years so far. Marmosets are, furthermore, easy to breed in captivity, allowing drug companies, or their contract testing firms, to keep in-house colonies and avoid the controversy associated with importing macaques or other monkeys from abroad. Their use also seems – so far – to have attracted less controversy than that of companion animals such as dogs.

Dogs remain popular because they are docile, easy to handle, and have been used so extensively that there is a vast amount of data on them. Ferrets would be more popular if they weren't so awkward to inject or take blood samples from. Minipigs are increasingly popular, note the authors, particularly because they breed so prolifically. But they can grow as heavy as 30kg – making them over 15 times more expensive than marmosets to dose with valuable test chemicals.

As more firms opt for marmosets, their use is likely to accelerate exponentially as a result of there being more data for comparisons. Regulators (the Medicines Control Agency in the UK) accept marmoset toxicity data happily, without querying their use. This is despite Home Office regulations stating that the use of primates is permissible only when there is no alternative animal 'model'. But whatever animal species is chosen, it is impossible to know whether it is a good 'model' for humans until we discover how humans react to the substance in question – by which point the animal data is clearly unnecessary!

With regard to pharmaceuticals, the evidence is clear: 80% of new drugs fail after Phase 1 clinical trials, showing just how ineffective the preceding

animal tests were. The same scientifically bogus procedure is used to get new industrial, agricultural and household products to market – thus putting human health and safety in jeopardy. On the basis of such tests, manufacturers are able falsely to imply their products are safe at a particular dose, when proper testing might prove them to be otherwise. When it comes to products such as household cleaners, we know that they are corrosive by nature and should be used with care; no amount of animal testing will ever make it safe to drink disinfectant or to use floor cleaner as toothpaste. The public's health must be protected in other ways, such as through the use of child-proof lids and bitter-tasting additives.

In the light of the above, this year's Animal Aid Mad Science Awards go to a representative sample of commercial and academic centres conducting scientifically flawed experiments on animals. Ultimate responsibility for the conduct of such studies rests with the government for requiring them. But drug and chemical companies are also to blame. They know that faster, cheaper, and reliable non-animal methods already exist, but using animals has become an easy habit, which they can hide behind when taken to court by someone damaged through the toxic effects of one of their products.

Non-animal testing methods include sophisticated *in vitro* systems using cell, tissue and organ cultures, as well as powerful computer modelling programmes capable of simulating *human* metabolism of the substance in question. It is up to the regulatory authorities to accept non-animal methods as valid, so that inferior (and never validated!) animal tests will no longer be accepted. Clearly, a system responsible for so many deaths should be outlawed.

Report researched and written by Kathy Archibald BSc Hons Genetics

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- 1 R Heywood in *Animal Toxicity Studies: their Relevance for Man*; (Eds CE Lumley and SR Walker) Quay Publishing, 1990
 - 2 D Salsburg; *Fundamental and Applied Toxicology* 1983; **3**: 63-67
 - 3 JC Crabbe *et al*, *Science* 4th June 1999 **284** (5420): 1670-73
 - 4 www.proanima.asso.fr (accessed June 2002)
 - 5 *New Scientist*, 2nd May 1992: 31-33
 - 6 A Mandavilli, *BioMedNet News* 30th April 2002 www.bmn.com
 - 7 P Abelson, *Science* 21st Sept 1990 p1357
 - 8 Gad SC, 1990. Model Selection in Toxicology: Principles and Practice, *Journal of the Am. Coll. of Toxicol.*, **3**, 291-302
 - 9 Morton DM, 1998. Importance of Species Selection in Drug Toxicity Testing, *Toxicology Letters*, 102-103. 545-550
 - 10 Olsen H *et al*, 2000. Concordance of the Toxicity of Pharmaceuticals in Humans and Animals, *Regulatory Toxicology and Pharmacology*, **32**, 56-57
 - 11 Lazarou J, Pomeranz BH, Corey PN, Incidence of Adverse Drug Reactions in hospitalised patients: a meta-analysis of prospective studies. *Journal of the American Medical Association* 1998; **279** (15), 1200-1205
 - 12 Smith D, Trennerly P, Farningham D, Klapwijk J, The selection of marmoset monkeys (*Callithrix jacchus*) in pharmaceutical toxicology. (AstraZeneca and Glaxo SmithKline), *Lab Anim* 2001 **35** (2):117-30

Summaries

1. 'Gulf War Syndrome' experiments on guinea pigs, Ministry of Defence, Porton Down

Researchers at Porton Down injected guinea pigs with ten different vaccines over a short period, in an attempt to simulate the 'worst-case' scenario potentially responsible for the mysterious illnesses in many Gulf War veterans. Before their medley of injections – which included yellow fever, plague, polio, typhoid, anthrax and cholera – the guinea pigs were administered a nerve-agent pre-treatment by means of mini-pumps. These were surgically implanted for 28 days and then surgically removed before the main experiment started. Most of the vaccines were injected, at various sites all over the body, but the polio vaccine was given by gavage (force-fed by stomach tube).

Over the next ten weeks, blood samples were taken from the guinea pigs' ears a total of eleven times, before they were killed. The study concluded that the combination of vaccines did not produce any 'significant effects'. Even though they did cause raised temperatures and swollen limbs, these effects were dismissed as 'local discomfort'.

It is already known that plague vaccine can cause malaise, headache, fever, and hardening of the injection site in people. The effects of the nerve-agent pre-treatment have already been studied in a number of animal species, including marmosets, and found to vary widely between species.

Studies have been conducted in Gulf War veterans themselves but, regardless, these researchers are now repeating this guinea pig study in marmosets – presumably because the veterans' complaints cannot be believed unless they are confirmed in animals.

Biological consequences of multiple vaccine and pyridostigmine pretreatment in the guinea pig. Griffiths GD, Hornby RJ, Stevens DJ, Scott LA, Upshall DG (Porton Down, Wiltshire) *Journal of Applied Toxicology*, 2001, **21(1)**:59-68

2. Testing IUD's in guinea pigs, University of Brighton

In an experiment to test preventive measures for

pelvic infections associated with intra-uterine contraceptive devices (IUDs), young female guinea pigs were housed in wire-bottomed cages, which are known to cause problems for their feet. They were injected into the stomach (known to be distressing) and then the back, to anaesthetise them; then their abdomens were opened to insert a hollow nylon fibre containing the anti-microbial agent, chlorhexidine, into their uterus. Five days later they were killed for analysis.

It was found that high doses of chlorhexidine were toxic to the animals' endometrium, but the researchers concluded that this would not be a problem for women, in whom the dose would be lower, and the drug likely to be dissipated.

As part of the same experiment, female rats were mated and killed so that their embryos could be tested with chlorhexidine to see if it is a 'teratogen', ie. if it affects their development. It did, but the researchers decided it is 'merely' toxic, rather than teratogenic.

The authors conclude that chlorhexidine is a 'safe' way to reduce infection due to IUD-insertion, but forget to mention that their data is relevant only to guinea pigs and rats – not to women.

Cytotoxicity and teratogenicity of chlorhexidine diacetate released from hollow nylon fibres. Ostad SN, Gard PR (University of Brighton) *J Pharm Pharmacol* 2000, **52(7)**:779-84

3. Herbicide (MCPA) toxicity in dogs, Covance Laboratories, North Yorkshire

At Covance contract testing labs, four beagles were dosed with the herbicide, MCPA, and incarcerated in close-confinement metabolism cages for five days. Blood was taken from them 11 times. Urine and faeces were analysed for herbicide residues. The same experiment was conducted on 20 rats as a comparison; they were force-fed the weed killer by stomach tube. It was already known that there is a 6.5-fold difference in NOAEL (No Adverse Effect Level) between rats and dogs, with dogs being much more sensitive to the toxic effects.

This experiment was intended to determine the reason for this difference. The study found marked differences in the rates and routes of excretion of MCPA, with rats eliminating the herbicide much more quickly than dogs. Many previous experiments with similar compounds have shown that dogs are much slower to eliminate them than mice, rats, monkeys or people. The authors conclude that this study, along with many others, demonstrates that dogs are not appropriate for assessing the toxicity to man of this class of compound. Yet they have been used for precisely this purpose for many years. Not only does this mean that all the dogs' lives have been wasted, but also that safety information for people has been based on incorrect evidence.

Absorption, metabolism and excretion of MCPA in rat and dog. GJ Lappin, TD Hardwick, R Stow, GH Pigott, RB Van (Covance Laboratories, North Yorkshire) *Xenobiotica* 2002, **32(2)**: 153-63

4. Vomiting ferrets, St. George's Hospital Medical School, London

In an experiment funded by the Pfizer drug company, 18 ferrets were injected with loperamide, an opiate that induces vomiting. Some of them were pre-treated with an anti-emetic. Retching (up to 85 times), vomiting (up to 10 times), gagging, mouth scratching, intense licking and 'wet-dog shaking' episodes were counted for the following two hours. All the animals were then killed and their brains analysed, in an attempt to locate the 'vomiting centre'. The authors suggest their findings may have relevance 'in the clinic', though exactly what relevance ferret vomiting and retching has for people is not explained.

The effect of the NK1 receptor antagonist CP-99,994 on emesis and c-fos protein induction by loperamide in the ferret. Zaman S, Woods AJ, Watson JW, Reynolds DJ, Andrews PL. (St. George's Hospital Medical School, London) *Neuropharmacology* 2000, **39(2)**: 316-23

5. PVC poisoning in rats, Huntingdon Life Sciences, Cambridgeshire

Researchers at Huntingdon Life Sciences, on behalf of Shell and BP, fed two different plasticiser constituents of PVC to rats over two generations, to see if their reproduction or

offspring were affected. The phthalate plasticisers are used in cable, flooring, roofing and fabric coating products. In 1999, the UK became (reluctantly) the ninth EU country to ban phthalates from teething toys for babies – because of fears that they are linked to cancer and infertility. Approximately **7,000 rats** were used. All of them were killed by carbon dioxide asphyxiation, except very young pups, who were killed by injection into the stomach. The offspring were killed before they were sexually mature, so any effects on sexual maturation could not be detected, even though this was one of the aims of the study.

The study concluded that the chemicals do not affect fertility in the rat, even though they cause significant reduction in weight gain in male rats. All the male animals' livers were severely affected, but the researchers point out that it is well known that such liver pathology in rodents would not occur in people and can thus be ignored as meaningless. One of the chemicals also caused severe testicular atrophy and, in some rats, 'mating success' dropped significantly. The authors established a NOAEL (No Adverse Effect Level) of 0.5% for both chemicals, which will be used as the basis for setting safe exposure levels for people, even though it has no relevance for humans.

Two-generation reproduction toxicity studies of di-(C(7)-C(9) alkyl) phthalate and di-(C(9)-C(11) alkyl) phthalate in the rat. Willoughby CR, Fulcher SM, Creasy DM, Heath JA, Priston RAJ, Moore NP (Huntingdon Life Sciences, Cambridgeshire) *Reprod Toxicol*, 2000, **14(5)**:427-50

6. Glass fibre and asbestos inhalation in rats, Institute of Occupational Medicine, Edinburgh

In a series of experiments to test the link between the absorption of glass fibre and the development of cancer, rats were confined in inhalation chambers and exposed to a glass microfibre – seven hours a day, five days a week, for up to a year. Then they were kept for a further year to monitor any recovery. Other rats were injected into the stomach with the fibres. 'Control' rats were kept in wire-bottomed cages for their natural life span to provide data on background tumour levels. 145 rats were used altogether. They were killed by carbon dioxide asphyxiation and their lungs examined for damage and remaining fibres. Animals suffered inflammation and fibrosis of the lungs,

mesotheliomas and other tumours – known from human sufferers to be distressing and debilitating conditions. The authors acknowledge that the intra-peritoneal (into the stomach) test has been criticised for being scientifically invalid but, no matter, it is accepted as a testing protocol by the EC. Results from this experiment were compared with earlier experiments using asbestos and another glass fibre. There were marked differences between them in tumorigenic (cancer-causing) potential, which the authors felt would probably be reversed in people because of their much longer life span!

Sponsored by the UK Mineral Wool Association, the European Ceramic Fibre Industry Association, Cape plc, BBA plc and Health & Safety Executive.

Pathogenicity of a special-purpose glass microfiber (E glass) relative to another glass microfiber and amosite asbestos. Cullen RT, Searl A, Buchanan D, Davis JM, Miller BG, Jones AD (Institute of Occupational Medicine, Edinburgh) *Inhal Toxicol* 2000, **12(10)**:959-77

7. Fragrance safety. TNO Bibra International, Ltd., Carshalton, Surrey)

Rats were dosed by gavage (stomach tube) with various amounts of coumarin – a fragrance ingredient in cosmetics. Further rats were used beforehand to establish lethal and 'maximum tolerated' doses, even though these were already known from the literature. All the animals were killed and their livers examined for tumours and DNA damage. It was concluded that coumarin does not damage rat DNA, and is thus safe for human use! One of the authors (Lake) reached the same conclusion three years earlier, even while acknowledging that coumarin toxicity varies enormously between species.

Coumarin has been used for many years in cosmetics, alcoholic drinks and tobacco, and was once used as a food flavouring. It has been studied in numerous species of animal for many years – sometimes producing liver tumours, depending on species used and the method of dosing. It has also been studied in human liver slices – the only substrate of real interest.

Not only did this pointless study kill more than 70 rats – it was conducted to test a cosmetic ingredient. Animal testing for such purposes has not been licensed in this country since 1998.

Funded by the Research Institute for Fragrance Materials, Inc, USA and Rhone-Poulenc Inc, USA.

Lack of effect of coumarin on unscheduled DNA synthesis

in the in vivo rat hepatocyte DNA repair assay. Edwards AJ, Price RJ, Renwick AB, Lake BG (TNO Bibra International, Ltd., Carshalton, Surrey) *Food Chem Toxicol* 2000, **38(5)**:403-9

8. Shea nut cooking oil, Unilever Research, Sharnbrook, Bedfordshire

Five hundred rats were housed individually – contrary to welfare guidelines – for two years, in suspended wire-mesh cages. They were fed palm oil (as a control), sheanut oil, or shea oleine (a by-product), to assess carcinogenicity (cancer-causing potential). Blood samples were taken by cardiac puncture before the animals were killed. The study did not comply with Good Laboratory Practice standards.

Several unexplained pathologies were found, relating to the heart, lungs and liver. But it was concluded that none of these effects was due to toxicity of shea oleine. The study shows shea oleine in the diet to be of comparable safety to other edible oils as far as rats are concerned. As far as people are concerned, who knows?

An assessment of the carcinogenic potential of shea oleine in the rat. Carthew, P, Baldrick, Hepburn PA (Unilever Research, Sharnbrook, Bedfordshire) *Food Chem Toxicol* 2001, **39(9)**:923-30

9. Inhaling plastics fumes, Zeneca Central Toxicology Laboratory, Macclesfield, Cheshire

Approximately 200 rats were exposed to varying concentrations of methyl methacrylate, an industrial plastics ingredient, for up to 28 days. They were then studied for up to 36 weeks. Substantial damage was caused to their nasal passages (revealed by dissecting their heads) but rapid recovery was shown to occur in animals left to recover from exposure before being killed.

The authors freely acknowledge the marked species differences in nasal toxicity between hamsters, rats and man - resulting from the self-evident biological differences. Previous data show that people are unlikely to develop the nasal lesions seen in rats, even if they were exposed to such high concentrations, which is extremely unlikely! Clearly, the only reason for conducting the experiment was that it was commissioned and sponsored by the European Chemical Industry Association (CEFIC) and the Methacrylate Producers' Association.

Presumably, the trade bodies got the 'reassuring' results on toxicity that they paid for.

Methyl methacrylate toxicity in rat nasal epithelium: investigation of the time course of lesion development and recovery from short term vapour inhalation. Hext PM, Pinto PJ, Gaskell BA (Zeneca Central Toxicology Laboratory, Cheshire) *Toxicology* 2001, **156(2-3)**: 119-28

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10. Cholesterol-lowering margarine, Unilever Research, Sharnbrook, Bedfordshire

Thirty-five young rats were housed individually in tiny, barren metabolism cages and dosed by gavage (force-fed by stomach tube) with various sterols. Four days later they were killed, frozen, and sliced up for analysis. The conclusion of the experiment was that cholesterol is well absorbed from the gut and distributed throughout the tissues. The authors acknowledge that cholesterol absorption in animals and man has already been widely studied. They neglect to mention that cholesterol metabolism varies enormously between species, meaning that results from animals are not relevant for people. In fact, this is the very reason why health warnings over high cholesterol diets were delayed for so many years - because cholesterol consumption does not lead to coronary artery disease in animals. As with cigarette smoke, this delay led to incalculable numbers of avoidable deaths - all thanks to misinformation from animal studies.

The safety evaluation of phytosterol esters. Part 6. The comparative absorption and tissue distribution of phytosterols in the rat. Sanders DJ, Minter HJ, Howes D, Hepburn PA (Unilever Research, Sharnbrook, Bedfordshire) *Food Chem Toxicol* 2000, **38 (6)**: 485-91

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11. Do insecticides 'feminise' male rats?, AstraZeneca Central Toxicology Laboratory, Macclesfield, and Dept Biological Sciences, Brunel University, Uxbridge, Middlesex

Eighty male rats were dosed by gavage (stomach tube) for 20 days with the insecticide Fenitrothion, or the synthetic oestrogen, DES, as a 'control'. (DES is a known endocrine disruptor - meaning that it interferes with the body's hormones. These damaging effects were not discovered until after it was prescribed to millions of pregnant women, thanks to misinformation from animal tests).

In addition to the gavage-dosed male rats, 20 additional rats were castrated surgically and

dosed for 10 days. Forty female mice were also used to test for oestrogenic activity.

The tests were aimed at understanding the impact of an insecticide on the male hormones. The results were inconclusive because the insecticide was toxic to the animals and it was difficult to isolate reproductive effects from overall poisoning effects, which included tremors.

Many more animals will inevitably be consumed to establish whether this insecticide disrupts their androgen (male hormone) receptors, even though it has been shown in *vitro* to disrupt the human androgen receptor - clearly the only one of genuine interest.

The current controversy over 'endocrine disruptors' is huge. Massive numbers of animals are being used to test potentially 'gender-bending' chemicals, with the results serving only to create further controversy and confusion. The biggest problems in this field are the inconsistent results from animals and the argument over establishing 'safe' doses. The question of dose (ie. what might be a safe level of exposure) is central. But the reproductive disturbances in animals are only achieved by doses hundreds or thousands of times any conceivable human exposure - making a mockery of the data. It is clearly essential to develop sensitive systems to detect what may be a very serious problem for humanity. It should be equally clear that animals can have no part in providing such a screen. In fact, a highly sensitive and accurate recombinant yeast oestrogen screen is already available. It has clearly demonstrated the powerful 'cocktail effect'* - i.e. that endocrine disruptors (present in pesticides, paints, cleaning products, cosmetics and most foods) act together to produce significant effects, even though they are only present individually at very low doses (well below their NOAEL - no adverse effects level). Potential gender-benders are everywhere. Toxicologists are calling the issue 'the next tobacco'. As with tobacco, the most dangerous thing we can possibly do here is to rely on animals for answers.

(*Something from "nothing" - eight weak estrogenic chemicals combined at concentrations below NOECs produce significant mixture effects. Silva E, Rajapakse N, Kortenkamp A. *Environmental Science and Technology* 2002, **36 (8)**: 1751-56)

Possible androgenic/anti-androgenic activity of the insecticide fenitrothion. Sohoni, P *et al.* (AstraZeneca Central Toxicology Laboratory, Macclesfield, and the Dept Biological Sciences, Brunel University, Uxbridge, Middlesex), *Journal of Applied Toxicol* 2001, **21**, 173-178



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