Substances are tested primarily by studies in animals where a $LD_{50}$ value for the substance is determined. The LD 50 the amount of toxin required per kg body weight to cause death in fifty percent of the animals.
[1]

The animals used in these studies are usually small rodents - mice and rats. The LD
50
depends on the species tested and how the chemical is administered. As rabbits, dogs, mice and rats may have significantly different LD
50
s for the same chemical results can only be indirectly related to humans.
[2]

Rates of absorption, binding and elimination of many chemicals in the body differ by up to one hundred times between small rodents and man.
[1,3,4]

Estimates of lethal doses in cases of suicide or accidental poisoning show that humans can be more susceptible than rats to some pesticides.
[2]

Thalidomide produced birth defects in humans at doses 100 times less than the dose needed in experimental animals.
[2]

"..Some species of laboratory animals can live happily all their life on seeds of a vetch that, when consumed by humans in amounts of a few 100 g a day, produces irreversible paralysis of the legs"
[5]

The $LD_{50}$ figures obtained from the animal studies are then adjusted for variations in body weight between rats and humans .[6] The mathematical models used to extrapolate results from rats to humans do not allow for the variations of the human immune system to repair cell damage. [6] In man, plasma levels of drugs such as imipramine, desipramine and chlorpromazine have shown a 12 times variation within the subjects tested, 12 hours after administration of these drugs.
[3]

Such variations also occur within the same species of laboratory animals and have been found to be due to age, sex, strain, litter, temperature and seasonal and social factors.
[4]

This variation means that the animals used in the toxicity studies are of uniform age, genetic strain and general health, although the people exposed to chemicals include the very young, the elderly, the sick and the particularly sensitive and unlike selected groups of rats, many people are suffering from
kidney failure, liver disease as well as inborn errors of metabolism.[2,4]

Incidentally the $LD_{50}$ values do not give any indication of debilitating, but non-lethal effects of toxins. Continuous headaches, rashes, sore throats or lowered immunity, which are often reported by exposed people, are not routinely reported by rats to their medical supervisors.[2]

Nor do these animal models assess the impact of chemicals on learning ability, attention span, emotional behaviour, IQ and many other related parameters.[4]

Scientific studies of chronic outcomes in animals are usually limited to cancers and some reproductive effects.[2]

There appears to be no appropriate animal model available for allergy testing.[2] In the Business Week Oct. 15, 1990, it was reported that scientists were working on genetically altered rodents that would better mimic human responses to foreign chemicals.[5]

Hopefully this will take longer than the expected 25 years.

Down to specifics, how do the various industries use the animal data? In the pharmaceutical industry the therapeutic index is defined as the ratio between the lethal dose (LD) and the therapeutically effect dose (ED).[7,8] These doses (concentrations) are based on animal and laboratory studies using germ cells and in cultures of micro-organisms.[7]

Toxicology studies are then performed to determine acute and chronic toxicity; effects passed onto the foetus; fertility effects' mutagenic effects and carcinogenicity prior to human clinical trials.[7]

In 1937, the newly developed sulfonamide drug, elixir of sulfanilamide, resulted in at least 73 deaths. Toxicity was found to be due not to the drug, but to the solvent diethlyene glycol in which it was marketed.[7] This incident led to the formation of the Federal Drug Agency (FDA) in 1937.[7,8]

In 1962 following the thalidomide tragedy, an amendment was made which gave the Department of Health and Human Resources control over the safety and effectiveness of new drugs as well as those marketed before passage of the amendment (1928-1962). The law also required, during initial stages, all possible drug interactions and the effects to be studied in vitro and in animals.[8] The pharmaceutical industry appreciated the increased toxicity of using two chemicals simultaneously almost 20 years ago when it was stated that before new drugs are made available or given, the interaction with other drugs given concurrently must be established.[1]

How effective were these new laws? In May 1979, the diuretic drug ticrynafen was approved in the USA. In January 1980, the drug was withdrawn because it was reported that 52 of 300,000 patients treated with the drug developed liver damage which resulted in a number of deaths.[7] In 1994, it was reported in the U.S.
*Health Freedom News*
, that 250 people die every day in the U.S. from legal prescriptions and that a 13 year study by the FDA showed that 67% of over the counter drugs are worthless, unsafe and ineffective but are still sold.
9

Why are they still on the market? Is it because 150 of the highest ranking officials of the U.S. FDA own stock in the drug companies that they are supposed to regulate?
9

or is it the $5,000 spent per medical doctor in the U.S. by drug companies to promote their goods?[10]

In the food industry, the $LD_{50}$ is used to estimate the Allowable Daily Intake (ADI) of food additives. The ADI of a particular chemical is worked out from protocols set up by the World Health Organisation (WHO) using data from animal studies and occasionally from human studies. It represents the amount of the chemical which is believed can be ingested on a daily basis without appreciable risk. It is set at 1/100 of the highest dose level which produces no observable toxic effect in the most sensitive test species. However, the ADI does not take into account the possible synergistic effect of other chemicals which may be ingested, or the chemical load which may be imposed on us by inhalation of our polluted atmosphere.
6

Most studies on the effect of food colouring agents assume a daily intake of approximately 25 mg, but a small proportion of the population is taking in excess of 350 mg where there may be a significant difference in toxicity.
4

Nor do these studies take into account that humans are frequently exposed to small amounts of many different chemical agents over a prolonged time.
4

Although many food colourings can be derived from vegetable matter, many colours and dyes are man made from coal and petroleum because they are easier and less expensive to produce.
11

The other measurement used in good additive code books is the Maximum Residue Limit (MRL). These limits are set on the basis of what would be expected with good agricultural practise. Both the ADI and MRL assure an 'average' or 'typical' diet for each country in which they are set.[6]

Many chemicals are known to interact with drugs, food additives and food components in the gastrointestinal tract. These interactions can cause increased absorption rate and toxicity of some chemicals. Antibiotics have been shown to enhance the absorption of artificial colouring agents and Vitamin C is known to increase the intestinal uptake of oestrogen from the contraceptive pill.[4]

This leads us onto the pesticide, insecticide, herbicide industry. In this industry the active constituents are tested one at a time, although there is considerable evidence to show that $LD_{50}$s can be affected by mixtures of chemicals such as are encountered in the workplace.[1,2]

In one study the toxicity of a mixture of two chemicals was 30 times greater than that predicted from the two individual LD

50

s

[1]

. As previously stated, only the active, principle chemical is tested in industrial and agricultural chemicals although these formulations often contain a mixture of chemicals such as pesticides, solvents, pentrants, detergents, emulsifiers, anti-caking agents etc.[1]

The Health Effect Laboratory of the US Environmental Protection Agency (EPA) has found that, due to the synergistic effects, the toxicity of a mixture of 34 chemicals was 20 to 30 times greater than the sum of the toxic effect of the individual chemicals in the mixture.[1]

Metabolised end product of insecticides and herbicides can be more toxic than the original substance.[1,4]

How far ranging is the combined effects of chemicals? Consider insecticides such as tetraethylpyrophosphate (TEPP), malathion and parathion as inhibitors of the enzyme cholinesterase. This enzyme is involved in the inactivation of natural compounds and drugs. Low levels of cholinesterase resulting from exposures to pesticides may result in prolonged responses to drugs such as local anaesthetics and muscle relaxants.[7] Rats given chlordane in corn oil prior to administration of the anti-tumour drug cyclophosphamine were found to have an increase mortality rate from 30% (in the control rats given cyclophosphamine alone) to > 70% in rats pretreated with chlordane.[1]

So where do the figures we do have for $LD_{50}$s come from? In Australia, we rely almost exclusively on the results of tests carried out overseas.

[2]

There are also significant gaps in the available toxicity data.
[2]

These tests are carried out by the people who manufacture and sell the chemical or drug.

Say no more!

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