

# The Changing Field of Toxicology

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The science of toxicology is currently undergoing a transformation in medicine in the 1990s. The new toxicology is significantly different in its tenets to the high-dose, single agent toxicology of the past fifty years. The latter, while startlingly successful in the laboratory and in preventing death and injury from acute occupational exposure, has proven inadequate in describing the type of pathology or illness patterns seen in the population exposed to complex mixtures of potential toxins over long periods.

Molecular toxicology combines the fields of molecular biology, epidemiology, toxicology and clinical medicine, and uses diagnostic tools to assess early, reversible changes in organ function (as opposed to irreversible organ pathology). This approach has already yielded unexpected data about the potential toxicity of individual chemicals and complex mixtures of chemicals in the population, and holds the promise of revolutionising risk assessment and minimising damage from environmental contaminants.

An unexpected early finding is that long-term, low dose exposure to complex chemical mixtures may not lead to organ-specific damage, as high dose, single chemical exposure seems to do. Instead, the health problems which arise tend to depend on the genetics and biochemistry of the exposed individual. In particular, it depends on the capacity of their detoxification pathways and antioxidant protective systems (among others) to prevent such harm. Inadequate nutrition, stress, infection and genetic susceptibility are now implicated as secondary factors in increased health risks from toxic agents.

Toxicology (and the legal and public health policies which stem from it) has long focussed on cancer risk as the primary determinant of danger from chemical exposure. While clearly an important outcome, it represents only the minority of important adverse outcomes following toxic exposure. The permanent brain damage following chronic exposure to solvents, lead and pesticides, may prove to be our greatest short term price of chemical exposure. Diminished male fertility following in utero-exposure to xeno-oestrogens (chemicals which mimic oestrogen, but are derived externally and are not under biological regulation) may be of enormous significance in the final historical review of the damage caused by toxic agents in the twentieth century.

The uncomfortable fact is that toxins may act in totally different ways at low dose than they do at high dose. These varying actions at different

dosages may be the ultimate determinants of cancer risk. High level, acute pesticide or solvent exposure usually leads to direct damage to cellular membranes, and may also be mutagenic. Low level chronic toxicity, however, may be mediated through totally different pathways, such as by altering cellular function through hormonal mimicking effects.

Thus, our revered "dose-response" curves, which provide apparent reassurance that current exposure levels are "safe", may be meaningless. The data are derived from high-dose acute exposure to single agents in laboratory conditions. Extrapolation is used to derive so-called "no-effect levels" from LD-50s (a dose, which by definition, kills half of the test animals), without any allowance for differences between high dose and low dose exposure mechanisms. Nor does it allow for essential differences in basic biochemistry and metabolism between humans and the test animals.

Most test animals, for example, produce ascorbic acid in response to hepatic toxins, and this may act as a protective antioxidant, minimising damage from oxidation of membranes throughout the body. Humans and other primates, however, lack the final enzyme for production of the protective ascorbate, and require increased dietary intake to provide similar protection. If this is not forthcoming (attaining the tissue levels achieved by test animals may require intakes of many thousands of milligrams in adult primates), then the extrapolation upon which we make our assumptions may have no basis whatsoever. There is also a growing feeling that background chemical contamination from the general environment, the workplace and the home may have risks to health unforeseen by animal testing, and that those risks would be primarily borne by the foetus, developing infants, the sick and the aged. The developing foetus and children have rapidly dividing cells, a developing nervous system and poorly developed detoxification pathways. The sick and aged suffer intercurrent illness, reduced antioxidant and detoxification capacity and depressed immunology. To apply the exposure standards, which have been derived from animal studies and gross epidemiological surveys to these high risk groups has little basis in logic.

Exposure to chronic low dose environmental toxins has been shown to increase cancer risk from all causes in adults, and has been associated with Chronic Fatigue Syndrome, altered haematological parameters, altered reproductive

function in males (but not females), neuropsychological changes and abnormal psychiatric inventories in adults, permanent central nervous system damage, and altered immunological function in adults. While male fertility is generally decreased by exposure, immunology may be up-regulated or down-regulated depending on the agent in question. Neurological damage is most frequently associated with solvents, lead, and chemicals which interfere with neuro-esterases (especially organophosphate pesticides).

There are stages in life where cell division is naturally high, and these appear to coincide with the times of highest risk from mutagenic agents (see article - Cancer - An act in two parts).

The most critical time, clearly, is during foetal development, followed by early childhood, and followed again by puberty.

The extra risk for the developing foetus is in the development of the reproductive cells, the ova and sertoli cells. There is now some evidence that exposure to xeno-estrogens during the first and second trimester may lead to a decrease in sertoli cell numbers, and that this may lead to relative male infertility following puberty. If this is correct, then the apparent world-wide decrease in male fertility may be related less to current chemical exposure than to unregulated exposure during foetal development over the past two generations. If the decline in human fertility is real, and is as significant as has been recently suggested, the consequences may be infinitely more significant in evolutionary terms than increased cancer risk in susceptible individuals. Finding ourselves at a reproductive dead end over the next hundred years may well be a way of solving an overpopulation problem, but would be the ultimate irony in evolutionary terms. While the pests which we attempted to wipe out continue to thrive, the chemicals we used may yet be our own downfall through utterly unexpected mechanisms.

We should be cautious, therefore, not to extrapolate toxicity assessment outside the dosage range in which the testing is done. Rats tested for low-level exposure to dioxins (in the parts per trillion range) did not show increased tumour tendencies seen in the high dose exposure group, but did show a greatly increased incidence of endometriosis in the females when they were sacrificed. The high dose group, however, developed tumours but did not have the same increased incidence of endometriosis.

## Conclusion

Toxicology is becoming a far more complex specialty than it was five years ago, but that does not mean it is incomprehensible for primary care physicians. The most exciting prospects for clinicians in the coming decade will be the ability to assess patients with early reversible health changes due to such low level contamination, and the ability to determine the type and extent of damage done, as well as the likely contributing agents, in a given individual. This field, known technically as "molecular epidemiology", and more popularly as "functional medicine", uses new diagnostic tools to:

- identify specific biochemical and genetic risk factors in healthy individuals. These appear to predispose to increased susceptibility to toxic exposure in the future.
- identify early, reversible changes in specific organ function (neurological, immunological, reproductive, hepatic, etc) occurring as a result of toxic responses.

In the limit, a process known as 'metabolic profiling', first described in 1980, promises to provide a metabolic 'snapshot' of an individual's biochemistry, and this snapshot can serve as a baseline against which the effect of future toxic exposures, possibly occupational in nature, may be assessed.

The clinician already has access to a number of diagnostic tools to assess gross occupational and environmental contamination, and these remain useful to identify chemical-specific and organ specific risk. This type of risk, however, is simply the "tip of the iceberg", usually obvious and simple to identify.

The useful emerging technologies will allow the clinician to become actively involved in risk assessment and early intervention in the more common forms of population exposure to chemicals. Some diagnostic technologies, such as evoked response testing and assessment of metabolic pathways, are already available for those with an interest in the area, and will become more widely understood and available before the turn of the century.