A risky business

Toxicology

Toxicology research should urgently appraise its performance and join mainstream biomedical science.

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Several key advances in biology and medicine in the past were brought about by studies of poisons. The elucidation of the mechanism of carbon monoxide toxicity by Claude Bernard, which led to the understanding of the function of haemoglobin, is a classic example. However, Jean-Pierre Changeux and colleagues, who used α-bungarotoxin to purify acetylcholine receptors, and William Catterall, who isolated sodium channels using scorpion toxin, probably did not consider themselves to be toxicologists. Has modern toxicology actually provided new fundamental concepts? Surprisingly, with a few notable exceptions, it has not — it is nowadays regarded as an applied science that is devoted to minimizing environmental health risks posed by chemicals, mainly through risk assessment.

At the same time, there is an emerging crisis of confidence in toxicology as an applied science that can effectively predict risk, as illustrated by the debate about servicemen exposed to depleted uranium from weapons during the Kosovo conflict in 1999. Although there is no evidence for radiological or chemical carcinogenic risk at any conceivable level of exposure, the wide perception of this issue has been very different. Predictions based solely upon epidemiological projections without solid scientific bases are often misleading. Examples include the debates over genetically modified foods, dioxins, measles vaccinations, and prion diseases in cattle and sheep. In the case of prion diseases, there is a remarkably uncertain and contradictory range of theoretical predictions for the size of any future epidemic of variant Creutzfeld–Jakob disease in humans.

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Lymphocytes (pink) attack cancer cells (dull red). How should toxicologists best tackle the problem of assessing the risks of carcinogen exposure?

There are surely various reasons for this failure of trust, but we wish to discuss one in particular. Perhaps because of the immense scope of research into the mechanisms by which individual compounds act, basic research has, over the past two decades, become irrelevant to many toxicologists. A discipline that mostly depends on others for fresh fundamental knowledge, and is slow in acquiring it, will also be slow in its progress and weak in its conclusions. Prejudice, ideology and irrationality will undoubtedly grow. For instance, few among the public appreciate the fact that hazard and risk are different concepts. Hazard defines the potential of a compound to cause harm and is therefore associated with virtually any molecule, whereas a risk of adverse health effects relates to the level of exposure and to individual susceptibility to that molecule. Such misunderstanding may account for the generous public funds that have been allocated to the study of dioxin toxicity, despite the lack of evidence for effects on human health at current environmental exposures.

The exciting research opportunities that have arisen from recent spectacular developments in biology mean that we may finally have something to nail down and test. It is becoming increasingly clear that many forms of toxicity involve a handful of evolutionarily conserved responses to injury — for example, the heat-shock response or the mechanism of apoptosis. Understanding stereotypical reactions may help to identify the risks posed by a wide range of products, including genetically modified crops, new foods, chemicals and waste materials.

How can toxicological research remain a central discipline for risk assessment? To take cancer as an example, the molecular classification of some forms of the disease by monitoring gene expression suggests a general strategy to assess the risk associated with exposure to potential carcinogens. Tumour subtypes induced in animals by chemicals could be identified by developing algorithms to cluster cancers according to gene expression, assessing the significance of such aggregations and comparing them to those found in common human cancers. Thus, the rationale for current mutagenicity and carcinogenicity tests could be confirmed or refuted.

Tumour-cell genomes are invariably altered at multiple sites, and progressive genetic instability is closely associated with many cancers. Assessment of large gene rearrangements or genetic instabilities is likely to be very significant in these cancers. Comparisons of gene expression at different levels of carcinogen exposure should clarify the role of exposure for both cancer-associated and non-cancer-linked effects. Ultimately, comparing these patterns with those of common cancers could help to define whether animal carcinogens also pose a hazard to humans.

In a wider context, it seems possible to conceive a 'matrix' approach to the prediction of health risks, using information derived from commonality between disease states that are not induced by chemicals and those elicited by toxicants, and the differences between exposed and unexposed individuals.

Toxicology is being shaped by worldwide political agendas, triggered by the public's desire for swift and precautionary solutions to the possible health effects of environmental chemicals. The resulting feedback loop has impoverished the discipline, because its growth has largely been driven by the demand for protocols for regulatory actions. We believe that incorporating toxicology into the mainstream of fundamental biomedical research, keeping it less directly applied to issues of social and political concern, will contribute to a climate in which scientific knowledge is more 'socially robust', and its practitioners will accordingly be more trusted by the public. The assessment of toxicological risks ploughs a difficult furrow between scientific uncertainty and social responsibility. However, the approach we envision will hone the rules of hazard identification to deeper and more fundamental principles, while contributing to the development of basic biomedical knowledge. ■

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FURTHER READING

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