NSW Public Health Bulletin

Volume 14, Number 8
August 2003

NSW HEALTH
Working as a Team

ISSN 1034 7674
State Health Publication PH 030221

QUANTITATIVE HEALTH RISK ASSESSMENT

GUEST EDITORIAL

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This issue of the *NSW Public Health Bulletin* focuses on the application of quantitative health risk assessment in public health decision-making. Over the last decade, these assessments have become a common currency for government, industry, and public health officials. Risk assessment, however, is not a value-free science. Underpinning the practice are notions of what health is, what risks are tolerable, what constitutes evidence, and the legitimacy of government intervention in the management of risk.

Some recent developments in the methodology of risk assessment, in particular the application of genetic science to risk assessment, give cause for optimism that the credibility and usefulness of risk assessments will improve. Some of these developments are summarised in the short history of quantitative health risk assessment presented in this editorial.

There is no doubt that, in good hands, risk assessments can contribute to good decisions about risk. There is also no doubt that these decisions are increasingly the subject of close scrutiny by a scientifically literate and sceptical public. The articles in this issue of the Bulletin attest to the utility of the intelligent application of risk assessment to common problems in public health practice. First, Andrew Langley discusses some of the philosophical underpinnings of the methods of health risk assessment. Geoff Richards gives a 'worked' example of the calculations made in a typical request for risk information. Community consultation is an integral part of all risk assessment, and Alison Rutherford describes an example of this often difficult negotiation. An intriguing application of risk assessment is found in Craig Dalton's article on selenium contamination in Lake Macquarie in the Hunter region. Finally, Cris Hickey and Christine Cowie examine applications of risk assessment methods in the derivation of standards for recreational water quality.

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QUANTITATIVE HEALTH RISK ASSESSMENT: A SHORT HISTORY

A quantitative approach to health risk assessment originated in the United States in the 1970s, in the context of the rising costs of environmental, food and drug legislation, and in the conviction that human cancers were largely attributable to chemical exposure.[1] In 1977, President Carter appointed an Inter-Agency Regulatory Liaison Group to coordinate regulatory activities in the environment, the workplace, product safety, and public health. A Risk Assessment Workgroup was charged with the responsibility for developing common criteria and approaches to the scientific aspects of risk assessment techniques. From the outset, there were fundamental objections to the use of quantitative risk assessment as a basis for decision making—it lacked a scientific foundation and it detracted from the efforts to reduce pollutants and contaminants using the best technology available.

The quantitative risk assessment approach was applied in five major areas: setting priorities; reviewing residual risk after application of best available technology; balancing risks with benefits; setting standard and target levels of risk; and estimating risks for specific populations.[2]

For carcinogens, there was a central controversy—the assumption that there was no threshold in the dose–response relationship for a carcinogen (that is, there is no safe minimum exposure and only a zero level of exposure is safe).[3] The first rigorous attempt to propose a non-zero level of exposure to a carcinogen was put forth by Mantel and Bryant in 1961.[4] They tackled the problem of extrapolating from high experimental doses in animal bioassays to the lower doses observed in human experience. Work on radiation exposure and leukaemia in atomic bomb survivors suggested that cancer risk could be extrapolated linearly from the 'no observed adverse effect level' (NOAEL) through zero with no apparent threshold. This approach was adopted as a default assumption in chemical risk assessment without strong evidence to support it.

To strengthen the scientific respectability of regulatory risk assessment, the National Research Council of the United States National Academy of Sciences published what is known as the 'Red Book', which defined four risk assessment disciplines: hazard identification, dose–response assessment, exposure assessment, and risk character-isation.[5]

Hazard identification

Hazard identification was a largely qualitative step aimed at evaluating the weight of evidence. Policies dictated that the most sensitive animal species be used for estimating the human response. Human epidemiologic data, though seldom available, was accorded the greatest 'weight'.

Dose–response assessment

Dose–response assessment evaluated the quantitative evidence from animal studies or, less commonly, epidemiologic studies to estimate risk of cancer as a function of exposure. Because environmental exposures are generally orders of magnitude less than those in either animal experiments or epidemiologic studies, extrapolation models were adopted to characterise risks for environmental exposures. A low dose linearity assumption was adopted as a default (that is, risks were assumed to decline to zero in a linear fashion from the lowest exposure known to cause health effect). Safety factors, usually in the range 10–100, were applied to account for the uncertainties of inter-species extrapolation and inter-individual variability.

Exposure assessment

Exposure assessment evaluated the character and level of exposure to substances in the population under consideration. This included the specific chemical forms, routes, and time course of exposure. Characterisation of the heterogeneity of exposure was by adopting conventions such as the maximally exposed individual (MEI) as an upper-bound exposure. The MEI was assumed to be exposed 24 hours per day for 70 years.

Risk characterisation

Risk characterisation is the quantification of risk based on information synthesised from hazard identification, dose–response assessment, and exposure assessment.

These four risk assessment disciplines have been applied to the assessment of non-carcinogenic chemicals over the last two decades.

NEW APPROACHES IN QUANTITATIVE HEALTH RISK ASSESSMENT

In each of these risk assessment disciplines, developments in genetics, toxicology, and statistical methods, have tried to address some of the more obvious problems of uncertainty and compounding conservatism. (Conservatism, in this sense, means that a standard is overly cautious; hence compounding conservatism is a situation where a series of cautious assumptions are used to derive a measure of risk, giving an ultra cautious result.)

Hazard assessment

Over the past two decades, research has recognised the importance of genetic and epigenetic (that is, processes that modify gene expression) mechanisms that determine responses to chemical hazards. These emerging genetic complexities will have a major effect on the simplifications inherent in current risk assessment practice.

Dose–response assessment

There have been great advances in the understanding of physiologically-based pharmacokinetic models in

toxicology. These advances enable a more accurate scaling of doses established in animal models to humans, by using the relevant determinants of pharmacokinetics such as tissue blood flow, tissue volume, and metabolic rate.

The 'benchmark dose' approach has been developed as an alternative to the 'no observed effect level' (NOAEL) approach, for both cancer and non-cancer health endpoints.[6] The benchmark dose corresponds to a pre-determined increase (usually five per cent) in the risk of an adverse health effect in a defined population. It has the advantages of taking into account the entire dose–response information, rather than a single dose. It is less influenced by the arbitrary choice of dose.

The International Program on Chemical Safety, as part of its Harmonization of Approaches to the Assessment of Risk of Exposure to Chemicals Program, has developed a guidance document for the use of chemical-specific adjustment factors for inter-species differences and human variability in dose–response assessment.

Exposure assessment

Developments in statistical modelling, and in particular the use of Monte Carlo modelling for incorporating exposure distributions into risk assessments, have been an important advance.

Risk characterisation

Improvements in hazard identification, dose–response assessment, and exposure assessment, have improved the way risk characterisation synthesises the quantification of risk.

Paustenbach has summarised some of the lessons learned in quantitative risk assessment and suggested areas for improvement in each of the four risk assessment disciplines (Table 1).[7]

A STRATEGY FOR IMPROVING THE QUALITY, CREDIBILITY, AND USEFULNESS OF QUANTITATIVE HEALTH RISK ASSESSMENT

Increased use of human data in health risk assessment

Much of the critique of risk assessment methodology revolves around the use of extrapolation of results from animals to humans. There is a clear need for better information on the effects of chemical hazards on human health.

In 1978, Saracci laid out a strategy for environmental epidemiology,[8] which called for:

- improvements in exposure assessment—there have been great advances in the availability and utility of biologic markers of previous human exposure;

TABLE 1

IMPROVING RISK ASSESSMENT: LESSONS LEARNED

Hazard Assessment	Dose–Response Assessment	Exposure Assessment	Risk Characterisation
Do not consider all animal carcinogens (equally) as a serious hazard	Present upper bound of risk plus best estimate of bounds.	Don't put too much emphasis on risk estimates for maximally exposed individuals.	Understand that one in a million increased risk is rarely a significant public health hazard.
Consider weight of evidence	Consider estimates from several low dose models.	Evaluate the uptake (absorbed dose) for both 50% and 95% persons.	Do not interpret low dose modelling results as an actual increase in risk (rather than a plausible upper bound).
	Consider reality check using epidemiological data.	Do not use repeatedly conservative or worst case assumptions. Use Monte Carlo techniques whenever possible.	Consider background levels of exposure when characterising incremental risk.
	Adjust for biological differences among species using physiologically based pharmacokinetic (PBPK) models.	Ensure a proper statistical analysis of environmental data, including a sensitivity analysis.	Do not assume the solution is remediation, destruction or substitution.
	Use low dose models to rank carcinogens rather than using models to predict cancer rate.	Understand the role of environmental fate when estimating exposure.	Put estimates of risk into perspective. Characterise risk using Monte Carlo analysis.
	Understand the fragility and sturdiness of low dose models.	Consider using biological monitoring to confirm exposure estimates.	Conduct uncertainty and sensitivity analyses.
		Consider all indirect pathways of exposure.	

Source: Paustenbach D. *The Practice of Health Risk Assessment in the United States.*[7]

- tackling the problems of the combined effects of multiple exposures—the disaggregation of the effects of dose–response, interactive effects, and induction periods, is a formidable task;
- integration of experimental and epidemiological evidence, which will require a more intense collaboration between toxicologists, environmental scientists, and epidemiologists.

A set of principles for evaluating epidemiologic data for use in risk assessment, known as the London Principles,[9] have been proposed and are summarised in Table 2.

Characterising individual susceptibility

An emerging issue in environmental epidemiology, and in both clinical and regulatory toxicology, is that of variation in susceptibility. This concept is not new. It constitutes the 'host' in the old paradigm of epidemiology that divided causes of disease into environment, host, and agent. It has, however, taken on a new dimension with the rapid developments in the characterisation of the human genome.[10]

Chemical toxicants have the potential to cause alterations at different organisational levels of a cell or tissue:[11]

- genome: the chromosomal information;
- transcriptome: the messenger RNA from actively transcribed genes;
- proteome: the entire protein complement of a biological sample;
- metabonome: the constituent metabolite in a biological sample.

Rapidly evolving technologies are enabling the characterisation of idiosyncratic responses to chemical toxicants; these include genomics, pharmocogenetics or toxicogenetics, functional genomics, and proteomics.

Genomics are the techniques for characterising the DNA sequence of the genome. The investigation of variable, or polymorphic regions of genes in an attempt to characterise idiosyncrasies in response to chemical insults is called *pharmocogenetics* or *toxicogenetics*. *Functional genomics* refers to a host of technologies that enables the functions of genes to be investigated. *Proteomics* is the characterisation of protein modifications that may lead to changes in the activity of gene products.

The application of these emerging technologies could assist risk assessment by:

- enhancing the ability to extrapolate accurately between animals and humans;
- enabling a more detailed understanding of molecular mechanisms of toxicity.

There is considerable optimism that these technologies can greatly enhance our understanding of the risks to health posed by chemicals in the environment.[12]

Prioritising health risk assessment: National and international practice

Chemicals used in food production, household products, textiles, medicines, and automobiles, underpin modern life. Global production of industrial chemicals has increased from one million tonnes in 1930 to 400 million tonnes today. The number of chemicals marketed in

TABLE 2

THE LONDON PRINCIPLES FOR EVALUATING EPIDEMIOLOGIC DATA IN REGULATORY RISK ASSESSMENT

Principles for Evaluating an Epidemiologic Report for Cause–Effect Relationship	
A1	The population studied should be pertinent to the risk assessment at hand, and it should be representative of a well-defined underlying cohort or population at risk.
A2	Study procedures should be described in sufficient detail, or available from the study's written protocol, to determine whether appropriate methods were used in the design and conduct of the investigation.
A3	The measures of exposure(s) or exposure surrogates should be: • conceptually relevant to the risk assessment being conducted; • based on principles that are biologically sound in light of present knowledge; • properly quantitated to assess dose-response relationships.
A4	Study outcomes (endpoints) should be clearly defined, properly measured, and ascertained in an unbiased manner.
A5	The analysis of the study's data should provide both point and interval estimates of the exposure's effect, including adjustment for confounding, assessment of interaction (for example, effect of multiple exposures or differential susceptibility), and an evaluation of the possible influence of study bias.
A6	The reporting of the study should clearly identify both its strengths and limitations, and the interpretation of its findings should reflect not only an honest consideration of those factors, but also its relationship to the current state of knowledge in the area. The overall study quality should be sufficiently high that it would be judged publishable in a peer-reviewed scientific journal.

Source: Federal Focus Inc. *Principles for Evaluating Epidemiological Data in Regulatory Risk Assessment*.[9]

volumes above 10 kg reported in 1981 was 102,806, of which 30,000 are marketed in volumes greater than one tonne per annum.

National and international chemical policies must ensure high levels of protection of human health for present and future generations. Adoption of the 'precautionary principle' is fundamental to achieving this objective. That is, whenever scientific evidence is available that a substance may have an adverse effect on human health and the environment, but there is still uncertainty as to the nature and magnitude of that effect, then decision-making must be precautionary.

The European Union and other countries have made a distinction between new and existing chemicals, in constructing mandatory regulatory requirements for the assessments of chemicals. Existing chemicals are subject to lesser scrutiny and account for over 99 per cent of the total number of chemicals. Some 140 of these substances have been listed as priority chemicals requiring comprehensive assessment.

The European Union White Paper outlines a strategy for a future chemicals policy.[13] It proposes a scheme that classifies and prioritises the vast list of existing chemicals—the REACH (Registration, Evaluation and Authorisation of Chemicals) Program. Registration of basic information is required for each of the 30,000 existing and new chemicals with production volumes greater than one tonne per annum. Evaluation of the registered information is required for all substances exceeding a production volume of 100 tonnes per annum. Authorisation of substances with certain hazardous properties that give rise to high levels of concern requires that authorisation be given before a substance can be used. Substances of concern include those that are carcinogenic, mutagenic, or toxic to reproduction, or substances with POP (persistent organic pollutants) characteristics.

This screening and risk classification does include some assessment of likelihood of human exposure, although production volume is used as the most convenient proxy for this measure. Some exemptions for assessment can be granted, if it can be demonstrated that human exposure is unlikely.

In Australia, the National Industrial Chemicals Notification and Assessment Scheme compiles detailed assessments of priority chemicals. Priorities are assessed by a consideration of published information on toxicity, volume of use, assumed frequency of exposure, and severity of health or environmental effects.[14]

CONCLUSION

Of public health, the historian Christopher Hamlin has said: 'What masquerades as an obscure offshoot of medicine or a marginal division of civil engineering is really a vast and unexamined part of our culture.'[15] Over the last two decades, quantitative risk assessment has, more or less by stealth, become a part of the culture of Australian risk management.

In June 2002, the enHealth council published Guidelines for Assessing Human Health Risks from Environmental Hazards.[6] This publication presents, for the first time, a considered national approach to health risk assessment practice, which will hopefully lead to a more consistent and critical application of this important technology.

REFERENCES

1. Landy MK, Roberts MJ, Thomas SR. Chapter 6—Forging a Cancer Policy: The Interagency Regulatory Liaison Group. *The Environmental Protection Agency: From Nixon to Clinton*. Oxford: Oxford University Press, 1994.
2. Anderson EL and the Carcinogen Assessment Group of the United States Environmental Protection Authority. *Risk Analysis* 1983; 3: 277.
3. Hrudey SE. Quantitative Cancer Risk Assessment: Pitfalls and Progress in Risk Assessment and Risk Management. Hester RE and RM Harrison RM (editors). *Issues in Environmental Science and Technology Number 9*. Cambridge: Royal Society of Chemistry, 1998.
4. Mantel N, Bryant WR. *J Natl Cancer Inst* 1961; 27: 455.
5. National Research Council. *Risk Assessment in the Federal Government: Managing the Process*. Washington DC: National Academy Press, 1983.
6. Environmental Health Risk Assessment, 2002. enHealth Council online at http://enhealth.nphp.gov.au/council/pubs/pdf/envhazards.pdf.
7. Paustenbach D. The Practice of Health Risk Assessment in the United States. *Human and Ecological Risk Assessment* 1995; 1(1): 29–75.
8. Saracci R. Epidemiological Strategies and Environmental Factors. *Int J Epidemiol* 1978; 7: 101–111.
9. Federal Focus Inc. Principles for Evaluating Epidemiological Data in Regulatory Risk Assessment. Washington DC: Federal Focus Inc., 1996.
10. Hertz Picciotto I. *Environmental Epidemiology in Modern Epidemiology*. Rothman KR, Greenland S (editors). Rven: Lippincott, 1998.
11. Pennie B, Ahr HJ, Braun C, Bars R, Jacob E. *Genomics, Transcript Profiling and Metabonomics: An Introduction*. European Centre for Ecotoxicology and Toxicology of Chemicals Document No 42.
12. Olden K, Guthrie, J. Genomics: Implications for Toxicology. *Mutation Research* 2001; 473: 3–10.
13. Commission of European Communities. White Paper: Strategy for a Future Chemicals Policy. Brussels: Commission of European Communities, 2001.
14. National Industrial Chemical Notification and Assessment Scheme. *Notifiers Handbook: Section 3—Priority Existing Chemicals Assessments* online at http://www.nicnas.gov.au/publications/pdf/handbook/chapter9.pdf.
15. Hamlin C. *Public Health and Social Justice in the Age of Chadwick: Britain, 1800–1854*. Cambridge: Cambridge University Press, 1997.