Available online at www.sciencedirect.com
ScienceDirect
Regulatory Toxicology and Pharmacology 51 (2008) S1–S5
Regulatory Toxicology and Pharmacology
www.elsevier.com/locate/yrtph

The naphthalene state of the science symposium: Objectives, organization, structure, and charge

Richard B. Belzer [a,*,1], James S. Bus [b,1], Ercole L. Cavalieri [c,1], Steven C. Lewis [d,1], D. Warner North [e,1], Richard C. Pleus [f,1]

[a] *Scientific Peer Review Program, Regulatory Checkbook, P.O. Box 319, Mt. Vernon, VA 22121, USA*
[b] *External Technology, Toxicology and Environmental Research and Consulting Group, Dow Chemical, and Department of Pharmacology & Toxicology, Michigan State University, USA*
[c] *Eppley Institute for Research in Cancer and Allied Diseases & Center for Environmental Health and Toxicology, University of Nebraska Medical Center, USA*
[d] *Integrative Policy and Sciences, Inc., and Robert Wood Johnson Medical School, University of Medicine and Dentistry of New Jersey, USA*
[e] *Northworks, Inc., and Department of Management Science and Engineering, Stanford University, USA*
[f] *Intertox, Inc., and Department of Pharmacology, University of Nebraska Medical Center, USA*

Received 12 July 2007
Available online 21 November 2007

Abstract

This report provides a summary of the objectives, organization, structure and charge for the naphthalene state of the science symposium (NS^3), Monterey, CA, October 9–12, 2006. A 1-day preliminary conference was held followed by a 3-day state of the science symposium covering four topics judged by the Planning Committee to be crucial for developing valid and reliable scientific estimates of low-dose human cancer risk from naphthalene. The Planning Committee reviewed the relevant scientific literature to identify singularly knowledgeable researchers and a pool of scientists qualified to serve as expert panelists. In two cases, independent scientists were commissioned to develop comprehensive reviews of the relevant science in a specific area for which no leading researcher could be identified. Researchers and expert panelists alike were screened for conflicts of interest. All policy issues related to risk assessment practices and risk management were scrupulously excluded. NS^3 was novel in several ways and provides an innovative model for the effective use of peer review to identify scientific uncertainties and propose research strategies for reducing or eliminating them prior to the conduct of risk assessment.

Keywords: Peer review; Peer review organization; Peer review objectives; Peer review structure; Peer review charge; Risk assessment; Information quality; Naphthalene

1. Introduction

Human health risk assessment has historically contained a mix of science and judgment (NRC, 1983), but the application of judgment has stirred repeated controversy because the boundaries between science and judgment have not always been clear (OMB, 1990; NRC, 1994). Peer review, the primary quality assurance tool used in scholarly settings, has been applied by some federal government agencies (EPA, 2000, 2006) and recently extended to the entire Executive branch (OMB, 2005). The purpose is to maximize the quality of scientific information disseminated by the government and used for decision-making (OMB, 2002).

In federal practice, peer review typically occurs late in the risk assessment process when scientific and policy issues have become intertwined. The peer review model set forth and applied here is novel because it is designed to be

* Corresponding author. Fax: +1 202 478 1626.
E-mail address: Belzer@regulatorycheckbook.org (R.B. Belzer).
[1] Planning Committee member.

0273-2300/$ - see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.yrtph.2007.10.017

implemented at a much earlier stage, preferably prior to the development and dissemination of human health risk assessment.

The goal of human cancer risk assessment is to assess human cancer risk. That is, risk assessment is an input to risk management decision-making by individuals authorized by statute to make choices on behalf of the public. Risk management decisions also take account of other scientific and technical information, such as economics and engineering, and public values and preferences (NRC, 1983, 1994). In part because scientific knowledge is always incomplete and uncertain, however, cancer risk assessment historically has contained numerous inference guidelines (NRC, 1983) or default values (NRC, 1994) to accommodate uncertainty, which are regarded as "public health-protective policy" (i.e., risk management-driven) but replaced with scientific information as it becomes available (EPA, 2005). The goals of the symposium were to (1) determine whether adequate scientific information existed to replace certain defaults now; (2) identify uncertainties that could be significantly reduced or resolved by scientific research; and (3) obtain expert scientific judgment concerning uncertainties that probably could not be resolved by scientific inquiry.

2. Objectives

This alternative peer review model is appealing in cases where scientific uncertainty is great, and the resolution of uncertainty by carefully targeted research has significant potential social value. Naphthalene was selected because it met these criteria. A recent whole animal bioassay suggested the possibility that exposure could be tumorigenic (NTP, 2000; Abdo et al., 2001). This study led to one final (OEHHA, 2004a,b) and one external review draft (EPA, 2004) risk assessment that included quantitative predictions of low-dose human cancer risk, and an IARC monograph (2002) classifying naphthalene as a Group 2B carcinogen ("possibly carcinogenic to humans").

The symposium had three objectives. First, multiple expert panels were convened to review the relevant primary scientific literature and develop a consensus view of the state of the science in each area. Secondary and other derivative scientific literature was generally excluded, but expert panels retained (and frequently exercised) the right to consider any scientific information they wished. To ensure that the symposium retained a scientific focus, policy-related literature was excluded and expert panels were actively discouraged from bringing it in. The Planning Committee encountered no resistance to that effort.

Second, expert panels were asked to identify gaps in scientific knowledge, discern which of these gaps were crucial to resolve for estimating low-dose human cancer risk, and propose targeted research projects that could be performed in a timely manner to significantly reduce or eliminate these scientific uncertainties.

Third, expert panels were asked to confront scientific uncertainties that could not be resolved through targeted research and provide thoughtful science- (not policy-) based judgments. The Planning Committee hoped to apply the lessons from experiments such as those by Evans et al. (1994) and the advice given by the National Research Council in its recent review of dioxin (NRC, 2006) concerning the acknowledgment and incorporation of uncertainty into risk assessment.

The symposium explicitly excluded from its set of objectives all policy matters related to the management of human cancer risk.

3. Organization

The Planning Committee was constructed to have expertise in multiple areas including toxicology, pharmacology, and decision sciences. One member of the committee, Dr. William O. Berndt, professor emeritus and former chairman of the Department of Pharmacology at the University of Nebraska Medical Center, died before the symposium was held. The participation of a senior Environmental Protection Agency scientist was sought but had to be dropped to accommodate EPA grant restrictions, which prohibit federal employees from serving. Regulatory Checkbook and the University of Nebraska Medical Center collaborated as co-organizers of the symposium, with additional non-financial sponsorship from the Society for Risk Analysis.

4. Structure

The Planning Committee reviewed the literature and identified the top four scientific issues to be addressed:

(a) Whole animal bioassays conducted on behalf of the National Toxicology Program.
(b) Human exposure, epidemiology, and cancer incidence.
(c) Cytotoxicity as a mode of action for observed carcinogenesis in animals.
(d) Genotoxicity as a mode of action for observed carcinogenesis in animals.

The selection of cancer extrapolation models was excluded in the ground that it was not a strictly scientific enterprise.

For each issue, a module was constructed consisting of one or more extended scientific presentations delivered by recognized research experts in the field. Where such experts could not be identified, the Planning Committee commissioned scientists recognized in the subject matter to prepare and deliver research papers (Price and Jayjock, 2008; Brusick, 2008).

To ensure fidelity to established peer review guidelines (OMB, 2005) and credibility within the larger scientific community, the Planning Committee sought expert panelists who met the following criteria: (1) widely recognized expertise in the underlying scientific sub-discipline, with

or without extensive familiarity with naphthalene; (2) a prior research publication history that would be unlikely to impair the ability to fairly review competing or novel scientific views; (3) acceptance of the symposium structure and organization; and (4) willingness to limit review to scientific matters and to refrain from infusing scientific debate with policy considerations. In addition, the Planning Committee decided to err on the side of having too many expert panelists rather than too few, in the belief that a multiplicity of voices and perspectives would be the most effective instrument for diluting any particular expert panelist's inherent biases.

The NS^3 structure is unique, novel and valuable as a peer review tool for several reasons. First, NS^3 relied on primary researchers instead of secondary research interpreters as the leading source of scientific information. Conventional government peer review practice places secondary interpreters between primary researchers and peer reviewers. This creates manifold opportunities for confusion, misunderstanding, and the introduction of information of a non-scientific nature into scientific peer review.

Second, the role of peer reviewers at NS^3 was fundamentally different. Conventional government peer review is an evaluation of the completeness and adequacy of a secondary scientific synthesis. Expert panelists at NS^3 were not asked to evaluate completeness or adequacy of a single document, but instead to synthesize relevant scientific knowledge and identify promising avenues for research that could inform risk assessment.

Third, a conventional government peer review panel might have (say) 15 members responsible for evaluating all material scientific aspects of a draft risk assessment, but only two or three members might be qualified to examine a particular detailed area. In contrast, NS^3 focused on just the four most salient scientific issues and assembled no less than four and as many as eight qualified experts for each issue. Whereas spreading expertise too thinly can dilute the effectiveness of conventional government peer review, the NS^3 model ensures that critical scientific issues are addressed by a significantly larger number of qualified experts. This approach significantly increases intellectual diversity in peer review and better assures that scientific credibility is maintained.

Fourth, NS^3 explicitly and transparently restricted its review to scientific matters and refrained from debating policy judgments. The line distinguishing science from policy is not well defined (NRC, 1983, 1994), but excursions across it are increasingly easy to discern and formally discouraged as a matter of government policy (OMB, 2002).

Fifth, NS^3 explicitly provided extensive opportunities for public interaction with both research speakers and expert panelists. Conventional government peer review severely restricts public participation, and often regards public contact with peer reviewers as unethical. At NS^3, for every hour devoted to presentations by distinguished research scientists, approximately an hour was made available for open public discussion. Session moderators were empowered and encouraged to permit all nature of relevant scientific discussion but prevent these discussions from straying into policy matters.

5. Selection and compensation

The Planning Committee selected research speakers and expert panelists in a collaborative process. Actual procedures for recruitment varied somewhat, but in general, they received formal letters of invitation either from the University of Nebraska or Regulatory Checkbook. Three invited research speakers declined; one decline proved to be non-essential, and the other two declines led to the commissioned paper by Brusick (2008), which after the fact the Planning Committee concluded should have been part of the original design. All expert panelists and commissioned speakers were vetted to identify and disclose conflicts of interest such as, but not limited to, a financial relationship to one of the sponsors. One research speaker (Abdo) was a retired government employee judged by the Planning Committee to have essential knowledge about relevant primary research. One research speaker employed by EPA was invited but declined; prospective expert panelists employed by EPA and California EPA also were invited but declined.

All research speakers, expert panelists, and facilitators were offered honoraria for their service; for various reasons, some declined. All were offered reimbursement of their travel expenses; for various reasons, some declined. Authors of the commissioned papers (Brusick, 2008; Price and Jayjock, 2008) were also compensated, and Brusick was compensated for converting the Module D report into publishable form.

6. Charge

Each panel was given roughly the same charge, albeit tailored slightly where necessary to accommodate differences in subject matter.

(a) Knowledge and uncertainty:
- What scientific statements can be made with a high degree of confidence?
- What scientific statements cannot be made with a high degree of confidence?

(b) Of those scientific statements that cannot be made with a high degree of confidence, which are quintessential uncertainties for human cancer risk assessment?

(c) Considering quintessential scientific uncertainties:
- What specific research projects could be undertaken promptly and cost-effectively that would resolve them?
- How should results from such studies be interpreted?

(d) What constitutes best scientific judgment about quintessential scientific uncertainties that cannot be addressed by science promptly and cost-effectively?

Fig. 1 was developed to focus research speaker presentations, public discussion, and expert panel deliberations. Panel (a) established at the outset that only science would be discussed. The primary responsibility of the research speakers was to synthesize relevant scientific knowledge and guide expert panelists to distinguish between knowledge and uncertainty, as shown in Panel (b). Expert panelists then sifted through the uncertainties to distinguish those that were quintessential from those which were not, as shown in Panel (c). Finally, as shown in Panel (d), they were asked to propose targeted, cost-effective research projects that could be completed in a timely manner to address those quintessential uncertainties resolvable through science.

An expert in decision sciences facilitated each expert panel. In addition to moderating discussion and debate, they had substantive responsibility for assisting the subject matter experts in distinguishing among types of uncertainty so that quintessential uncertainties could be identified and research projects devised. A commonly used strategy was to ask experts to explain how the data would resolve uncertainty assuming that they had it in hand today.

In many cases, the expert panels struggled to orient their thinking along these lines. As research scientists, all had a great deal of experience proposing and evaluating research projects, but the criteria normally used to evaluate intellectual merit are different from those which the Planning Committee asked be applied. Few expert panelists had prior experience with the application of value-of-information principles for ranking such proposals. The NS^3 process yielded many valuable insights on specific research. Nevertheless, there remains considerable room for improvement in devising more effective strategies for eliciting expert scientific judgment in ways that target scarce research resources to resolve the most pressing scientific uncertainties.

7. Sponsorship funding

Sponsorship NS^3 was funded in part by grants to the University of Nebraska Medical Center by the U.S. Environmental Protection Agency (Grant No. 83330401-0) and the Electric Power Research Institute; to Regulatory Checkbook by the Naphthalene Council, Inc., and the American Petroleum Institute on behalf of an ad hoc industry coalition consisting of the Association of Railroads, the American Coke and Coal Chemicals Institute, the American Petroleum Institute, the Asphalt Institute, and the National Petrochemical Refiners Association; and by unrestricted grants to Regulatory Checkbook, a

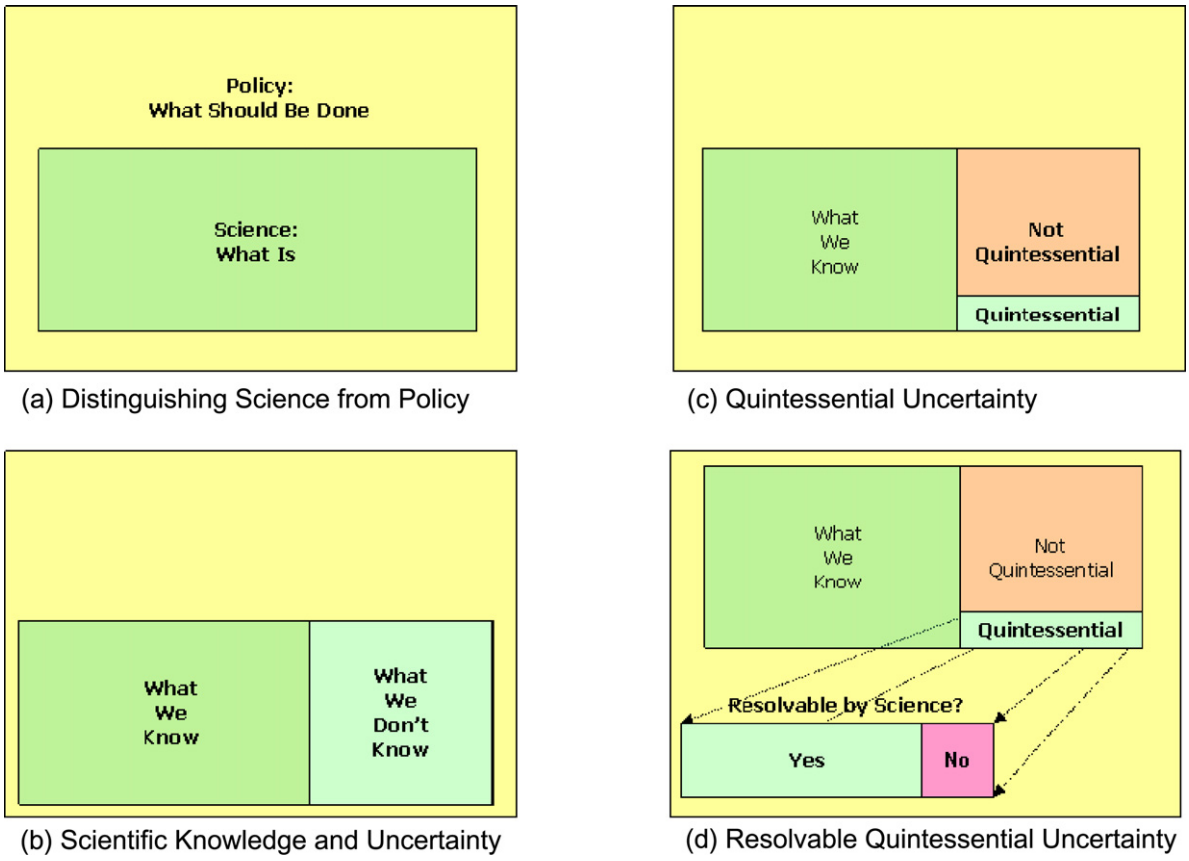

Fig. 1. The NS^3 model for identifying and resolving scientific uncertainty.

501(c)(3) non-profit organization. The Society for Risk Analysis was a non-financial sponsor.

Under the terms of the restricted grants, the Planning Committee retained total substantive and managerial control over the content, structure, and charge; the selection of research speakers and the commissioning of research papers by Price and Jayjock (2008) and Brusick (2008); the selection of expert panelists; the submission of final reports; and the provision of compensation including honoraria to research speakers, expert panelists, and facilitators. While the Planning Committee welcomed input from all, and received valuable advice from EPA and industry sponsors, at no time did the Planning Committee cede control to any sponsor. The Planning Committee alone had sole responsibility for executing NS^3, but the expert panelists and facilitators are responsible for the content of the commissioned papers (Price and Jayjock, 2008; Brusick, 2008) and module papers (North et al., 2008; Griego et al., 2008; Bogen et al., 2008; Brusick et al., 2008). In two of the four modules (North et al., 2008; Brusick et al., 2008), research speakers were invited by the expert panelists to contribute to the development of the expert panel report; accordingly, they are listed as co-authors.

Conflict of interest disclosure statement

The authors declare that they have no conflicts of interest.

Acknowledgments

This article was developed in part under EPA Assistance Agreement No. 83330401-0 awarded by the U.S. Environmental Protection Agency. It has not been formally reviewed by the EPA. The views expressed in this document are solely those of the authors and the EPA does not endorse any products or commercial services mentioned in this publication.

Additional grant support was provided by the Electric Power Research Institute, the American Petroleum Institute, the Naphthalene Council, Inc., the Association of Railroads, the American Coke and Coal Chemicals Institute, the Asphalt Institute, and the National Petrochemical Refiners Association. It has not been reviewed by any of these sponsors, and does not necessarily represent their views.

Finally, Regulatory Checkbook, the 501(c) (3) nonprofit organization that coordinated the project, also provided funding from unrestricted support and retained earnings.

References

Abdo, K.M., Grumbein, S., Chou, B.J., Herbert, R., 2001. Toxicity and carcinogenicity in F344 rats following 2 years of whole-body exposure to naphthalene vapors. Inhalation Toxicol. 13 (10), 931–950.

Bogen, K.T., Benson, J.M., Clewell, H.J., Dahl, A.R., Krishnan, K., Morris, J.B., Omiecinski, C.J., Yost, G.S., 2008. Naphthalene metabolism in relation to target tissue anatomy, physiology, cytotoxicity and tumorigenic mechanism of action. Regul. Toxicol. Pharmacol. 51 (Suppl. 1), S27–S36.

Brusick, D.J., Small, M.S., Cavalieri, E.L., Chakravarti, D., Ding, X., Longfellow, D.G., Nakamura, J., Rogan, E.G., Swenberg, J.A., 2008. Possible genotoxic modes of action for naphthalene. Regul. Toxicol. Pharmacol. 51 (Suppl. 1), S43–S50.

Brusick, D.J., 2008. A critical assessment of the genetic toxicity of naphthalene. Regul. Toxicol. Pharmacol. 51 (Suppl. 1), S37–S42.

California Office of Human Health Hazard Assessment (OEHHA), 2004a. Long-term Health Effects of Exposure to Naphthalene. OEHHA, online at http://www.oehha.ca.gov/air/hot_spots/pdf/naphth080304.pdf.

California Office of Human Health Hazard Assessment (OEHHA), 2004b. Adoption of Unit Risk Value for Naphthalene. OEHHA, online at http://www.oehha.ca.gov/air/hot_spots/pdf/naphthmemo.pdf.

Environmental Protection Agency (EPA), 2000. Peer Review Handbook, second ed. EPA 100-B-00-001, Environmental Protection Agency.

Environmental Protection Agency (EPA), 2004. Toxicological Review of Naphthalene (CAS No. 91-20-3) In Support of Summary Information on the Integrated Risk Information System (IRIS). NCEA-S-1707, June 2004, External review draft. U.S. EPA Office of Research and Development, Washington, DC.

Environmental Protection Agency (EPA), 2005. Guidelines for Carcinogen Risk Assessment. EPA/630/P-03/001F.

Environmental Protection Agency (EPA), 2006. Peer Review Handbook, third ed. EPA/100/B-06/002.

Evans, J.S., Gray, G.M., Sielken, R.L., Smith, A.E., Valdez-Florez, C., Graham, J.D., 1994. Use of probabilistic expert judgment in uncertainty analysis of carcinogenic potency. Regul. Toxicol. Pharmacol. 20, 15–36.

Griego, F.Y., Bogen, K.T., Price, P.S., Weed, D.L., 2008. Exposure, epidemiology and human cancer incidence of naphthalene. Regul. Toxicol. Pharmacol. 51 (Suppl. 1), S22–S26.

International Agency for Research on Cancer (IARC), 2002. Traditional Herbal Medicines, Some Mycotoxins, Naphthalene and Styrene. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, vol. 82. IARC, Lyon, France.

National Research Council (NRC), 1983. Risk Assessment in the Federal Government: Managing the Process. National Academy Press, Washington, DC.

National Research Council (NRC), 1994. Science and Judgment in Risk Assessment. National Academy Press, Washington, DC.

National Research Council (NRC), 2006. Health Risks from Dioxin and Relate Compounds: Evaluation of the EPA Reassessment. Academy Press, Washington, DC.

National Toxicology Program (NTP), 2000. Toxicology and Carcinogenesis Study of Naphthalene in F344/N Rats (Inhalation Studies). Technical Report Series No. 500. National Toxicology Program, Research Triangle Park, NC.

North, D.W., Abdo, K.M., Benson, J.M., Dahl, A.R., Morris, J.B., Renne, R., Witschi, H., 2008. A review of whole animal bioassays of the carcinogenic potential of naphthalene. Regul. Toxicol. Pharmacol. 51 (Suppl. 1), S6–S14.

Office of Management and Budget (OMB), 1990. Current regulatory issues in risk assessment and risk management. In: Regulatory Program of the United States Government, April 1, 1990–March 31, 1991.

Office of Management and Budget (OMB), 2002. Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by Federal Agencies; Notice; Republication. Fed. Reg. 67, 8452–8460.

Office of Management and Budget (OMB), 2005. Final Information Quality Bulletin for Peer Review. Fed. Reg. 70, 2664–2677.

Price, P.S., Jayjock, M.A., 2008. Available data on naphthalene exposures: strenghts and limitations. Regul. Toxicol. Pharmacol. 51 (Suppl. 1), S15–S21.